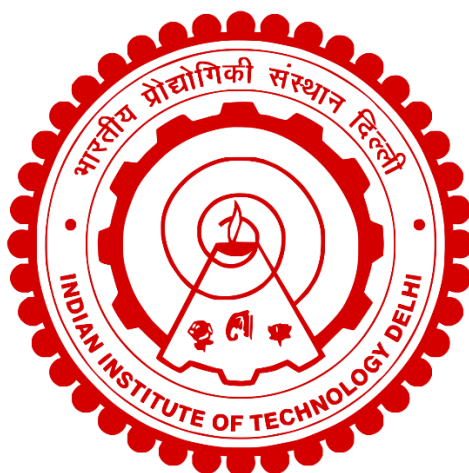


DEVELOPMENT OF FLUORINE-RETENTIVE APPROACHES TO SYNTHESIZE FLUORO- TETHERED OXINDOLES

RUCHI SHARMA



**DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY, DELHI**

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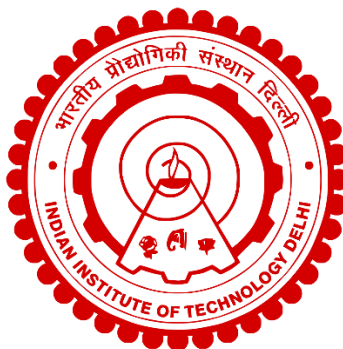
RUCHI SHARMA

Submitted

In fulfilment of the requirements of the degree of

Doctor of Philosophy

to the



**DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY, DELHI**

September 2025

Dedicated to my beloved Parents

Certificate

This is to certify that the thesis entitled “**Development of Fluorine-Retentive Approaches to Synthesize Fluoro-Tethered Oxindoles**” submitted by **Ms. Ruchi Sharma (Entry Number: 2019CYZ8542)** to the **Indian Institute of Technology Delhi** for the award of the degree of **Doctor of Philosophy** is a documented record of the research work conducted by her. **Ms. Ruchi Sharma** has worked under my supervision and has met all the necessary requirements for submitting her PhD thesis. To my knowledge, her work meets the requisite standard and is worthy of consideration for the award of the degree.

The work embodied in this thesis has not been submitted, in part or full, to other universities or institutes to award any degree or diploma to the best of my knowledge.

Prof. M. Ramu Yadav

Thesis Supervisor

Department of Chemistry

Indian Institute of Technology Delhi

Hauz Khas, New Delhi-110016

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Ruchi Sharma

Abstract

The thesis entitled “**Development of Fluorine-Retentive Approaches to Synthesize Fluoro-Tethered Oxindoles**” represents novel synthetic methodologies to achieve fluorine-tethered oxindoles using fluorinated building blocks. The thesis is divided into five chapters and a brief description of each chapter is given below.

Chapter 1: This chapter illustrates the unique properties of fluorine and the importance of oxindole in medicinal chemistry. Furthermore, the methodologies to generate fluorine-retentive approaches are discussed along with previous methods of fluorine incorporation in organic molecules. Based on these aspects, the scope and objectives of the thesis are mentioned.

Chapter 2: This chapter describes a ligand-free Pd-catalyzed double Heck cyclization using *N*-(*o*-bromoaryl) acrylamides and fluoro/trifluoromethyl acrylates to furnish monofluoro/trifluoromethyl-containing 3,3-disubstituted oxindoles bearing a quaternary carbon center in a stereoselective manner. Overcoming previous limitations, using commercially available fluorinated olefins is an intriguing method to avoid pre-functionalization, thereby reducing time and energy. Furthermore, the transformation is achieved without the need for external ligands and inert conditions, avoiding any fluorine loss, making the strategy more attractive and cost-effective.

Chapter 3: In the previous chapter, an external fluorinated building block afforded fluorinated oxindoles, comprising of fluorinated group at a distant position from the oxindole core. Further, we envisioned incorporating the fluorinated group onto the main core of oxindoles. In accomplishing this, *N*-aryl-2-(trifluoromethyl) acrylamide (TFMAM) was employed to afford 3,3-disubstituted oxindoles with a CF₃ group at the C3 position through intramolecular cyclization. Broad substrate scope with good functional group tolerance is achieved without

using any external ligand. The current cascade reaction can generate significant molecular complexity in a single streamlined step, minimizing the consumption of solvents, reagents, time, and energy.

Chapter 4: After establishing thorough understanding of double Heck/Heck-Suzuki cascade reactions with fluorinated arylacrylamides, the thesis takes a strategic shift towards a more sustainable, and cost-effective approach. This chapter investigates the photochemical carbohalogenation reaction of sterically challenging *tri*- and *tetra*-substituted olefins, which remains underdeveloped. Moreover, photochemical processes involving *gem*-difluorinated olefins are often accompanied by fluorine loss, limiting the atom economy of the process. Overcoming these challenges, a simple excited Ni-catalysis, activated by blue light, effectively facilitates the intramolecular carbohalogenation of *mono*-fluoro, *gem*-difluoro, and trifluoromethyl tethered acryl amides to their corresponding halo-fluoroalkyl oxindoles. The resulting compounds feature a functionalizable CF₂-X/CH₂-X/CFHI moiety, which opens avenues for conversion into valuable synthetic intermediates.

Chapter 5: In conclusion, fluorine-retentive methodologies have been explored to synthesize a diverse range of fluoro/difluoro/trifluoromethyl tethered oxindoles. Commercially available fluorinated building blocks have been utilized to achieve important transformations in a streamlined manner. Alongside, the limitations of these approaches have also been studied which opens a good avenue for future research aspect. The resulting products may have a substantial impact on drug discovery due to diverse substitutions and novel structural developments in organofluorine chemistry.

सारांश

यह शोध प्रबंध, "फ्लोरीन-रिटेंटिव दृष्टिकोणों का विकास करके फ्लूरो-संयोजित ऑक्सिंडोल्स का संश्लेषण", नवीन संश्लेषण पद्धतियों को प्रस्तुत करता है, जिनके माध्यम से फ्लोरीन युक्त बिल्डिंग ब्लॉक्स का उपयोग करके फ्लूरो-संयोजित ऑक्सिंडोल्स प्राप्त किए गए हैं। यह शोध प्रबंध पाँच अध्यायों में विभाजित है, जिनका संक्षिप्त विवरण नीचे दिया गया है।

अध्याय 1: इस अध्याय में फ्लोरीन के विशिष्ट गुणों और औषधीय रसायन विज्ञान में ऑक्सिंडोल की भूमिका पर चर्चा की गई है। इसके अलावा, फ्लोरीन-रिटेंटिव दृष्टिकोण विकसित करने की विभिन्न पद्धतियों के साथ-साथ जैविक अणुओं में फ्लोरीन सम्मिलन की पूर्ववर्ती विधियों का उल्लेख किया गया है। इन्हीं पहलुओं के आधार पर, इस शोध के उद्देश्य और इसकी परिधि को परिभाषित किया गया है।

अध्याय 2: यह अध्याय एक लिगैंड-मुक्त पैलेडियम-उत्प्रेरित डबल हेक चक्रीयकरण (Heck cyclization) प्रक्रिया का वर्णन करता है, जिसमें *N*-(*o*-ब्रोमो) एरिलक्रायलामाइड्स और फ्लूरो/ट्राइफ्लूरोमिथाइल एक्रिलेट्स का उपयोग किया गया है। इसके माध्यम से मोनोफ्लूरो/ट्राइफ्लूरोमिथाइल युक्त 3,3-डिस्थापित ऑक्सिंडोल्स का संश्लेषण स्टीरियो-चयनात्मक रूप से किया गया है, जिसमें चतुर्धात्विक कार्बन केंद्र मौजूद है। यह विधि पूर्ववर्ती सीमाओं को पार करते हुए व्यावसायिक रूप से उपलब्ध फ्लोरीनयुक्त ओलेफिन्स के प्रत्यक्ष उपयोग को सक्षम बनाती है, जिससे पूर्व-कार्यात्मककरण की आवश्यकता समाप्त हो जाती है और समय तथा ऊर्जा की बचत होती है। इसके अलावा, यह प्रक्रिया बाहरी लिगैंड्स और निष्क्रिय परिस्थितियों के बिना पूरी होती है, जिससे फ्लोरीन हानि को रोका जा सकता है, और यह दृष्टिकोण अधिक आकर्षक एवं लागत-प्रभावी बनता है।

अध्याय 3: पिछले अध्याय में, एक बाहरी फ्लोरीनयुक्त बिल्डिंग ब्लॉक का उपयोग करके फ्लोरीनयुक्त ऑक्सिंडोल्स प्राप्त किए गए थे, जिनमें फ्लोरीनयुक्त समूह ऑक्सिंडोल कोर से एक निश्चित दूरी पर स्थित था। आगे, हमने फ्लोरीनयुक्त समूह को सीधे ऑक्सिंडोल के मुख्य कोर पर शामिल करने की योजना बनाई। इस उद्देश्य को प्राप्त करने के लिए, *N*-एरिल-2-(ट्राइफ्लूरोमिथाइल)एक्रिलामाइड (TFMAM) को अपनाया गया, जिससे C3 स्थिति पर CF₃ समूह युक्त 3,3-डिस्थापित ऑक्सिंडोल्स आंतर-अणुकारी चक्रीयकरण (intramolecular cyclization) के माध्यम से प्राप्त किए गए। इस पद्धति में एक व्यापक सबस्ट्रेट स्कोप और अच्छी फंक्शनल ग्रुप सहनशीलता प्राप्त हुई है, और यह बिना किसी बाहरी लिगैंड के संभव हुआ है। वर्तमान कैस्केड अभिक्रिया एक ही चरण में महत्वपूर्ण आणविक जटिलता उत्पन्न कर सकती है, जिससे विलायकों, अभिकर्मकों, समय और ऊर्जा की खपत कम हो जाती है।

अध्याय 4: डबल हेक/हेक-सुजुकी कैस्केड अभिक्रियाओं के साथ फ्लोरीनयुक्त एरिलक्रायलामाइड्स पर विस्तृत अध्ययन स्थापित करने के बाद, यह शोध अधिक सतत और लागत-प्रभावी दृष्टिकोण की ओर रणनीतिक बदलाव करता है। इस अध्याय में, स्टेरिक रूप से चुनौतीपूर्ण ट्राइ- और टेट्रा-विस्थापित ओलेफिन्स की फोटोकैमिकल कार्बोहैलोजनेशन अभिक्रिया का अध्ययन किया गया है, जो अब तक सीमित रूप से विकसित हुई है। इसके अतिरिक्त, gem-डिफ्लूरोयुक्त ओलेफिन्स से संबंधित फोटोकैमिकल प्रक्रियाएँ अक्सर फ्लोरीन हानि के साथ होती हैं, जिससे इस प्रक्रिया की परमाणु अर्थव्यवस्था प्रभावित होती है। इन चुनौतियों को पार करने के लिए, एक सरल उत्तेजित निकल (Ni) उत्प्रेरण प्रणाली, जो नीली रोशनी द्वारा सक्रिय होती है, को विकसित किया गया है। यह प्रणाली मोनो-फ्लूरो, gem-डिफ्लूरो, और ट्राइफ्लूरोमिथाइल-संयोजित एक्रिलामाइड्स के आंतर-अणुकारी कार्बोहैलोजनेशन को प्रभावी रूप से सक्षम बनाती है। इस प्रक्रिया से प्राप्त यौगिकों में $\text{CF}_2\text{-X/CH}_2\text{-X/CFHI}$ जैसी कार्यात्मक समूह संरचनाएँ होती हैं, जो आगे संशोधित होकर महत्वपूर्ण संश्लेषण मध्यवर्तियों में परिवर्तित की जा सकती हैं।

अध्याय 5: निष्कर्ष इस शोध प्रबंध में फ्लोरीन-रिटेंटिव पद्धतियों का उपयोग करके विविध प्रकार के फ्लूरो/डिफ्लूरो/ट्राइफ्लूरोमिथाइल-संयोजित ऑक्सिंडोल्स का संश्लेषण किया गया है। इसमें व्यावसायिक रूप से उपलब्ध फ्लोरीनयुक्त बिल्डिंग ब्लॉक्स का उपयोग किया गया है, जिससे विभिन्न जैविक रूप से महत्वपूर्ण संरचनाएँ सरलीकृत एवं प्रभावी रूप से प्राप्त की जा सकें। इसके साथ ही, इन विधियों की सीमाओं का भी विश्लेषण किया गया है, जो आगे के अनुसंधान के लिए संभावनाओं के द्वार खोलता है। इस शोध से प्राप्त उत्पादों की औषधीय खोज में महत्वपूर्ण भूमिका हो सकती है, क्योंकि इनमें विविध प्रतिस्थापन और ऑर्गेनोफ्लोरीन रसायन विज्ञान में नवीन संरचनात्मक विकास की संभावना मौजूद है।

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List of Symbols and Abbreviations

Å	Angstrom
°	degree
°C	degree centigrade
α	alpha
β	beta
δ	(delta) chemical shift
μ	mu
<i>o</i>	ortho
%	percentage
Ar	aryl
AIBN	azo bis-isobutyronitrile
ATP	adenosine triphosphate
Ac	acetyl
bs	broad singlet
bd	broad doublet
Bn	benzyl
Bu	butyl
Calcd.	calculated
d	doublet
dd	doublet of doublets
dt	doublet of triplets
ddd	doublet of doublets of doublets
dddd	doublet of doublets of doublets of doublets
dq	doublet of quartets
dr	diastereomeric ratio
deg	degree
DCM	dichloromethane
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
DMAP	4-dimethylaminopyridine
DABCO	1,4-diaza bicyclo[2.2.2]octane
DFT	density functional theory
EWG	electron withdrawing group
EDG	electron donating group

EtOAc	ethyl acetate
Et	ethyl
<i>gem</i>	geminal
HRMS	high-resolution mass spectrometry
<i>i</i>Pr	isopropyl
K	Kelvin
Me	methyl
MeOH	methanol
MS	molecular sieves
mg	milligram
M	molarity
mmol	millimole
mol	mole
MHz	mega hertz
m	multiplet
nm	nanometer
NPs	nanoparticles
NMR	nuclear magnetic resonance
NHPI	<i>N</i> -hydroxyphthalimide
NMP	<i>N</i> -methyl-2-pyrrolidone
NBS	<i>N</i> -bromosuccinimide
Ph	phenyl
ppm	parts per million
q	quartet
qd	quartet of doublets
R_f	retention factor
SET	single electron transfer
t	triplet
td	triplet of doublets
t_R	retention time
Ts	tosyl
<i>t</i>Bu	tertiary butyl
THF	tetrahydrofuran
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TLC	thin layer chromatography