PHOTOINDUCED REGIOSELECTIVE C-C BOND FORMATION AND TRANSITION METAL CATALYZED C-H ACTIVATION

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by

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Dedicated to my beloved Parents

CERTIFICATE

This is to certify that the thesis entitled, **"Photoinduced Regioselective C−C Bond Formation and Transition Metal Catalyzed C-H Activation"**, being submitted by **Mr. Krishna Nand Tripathi** 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 Nand Tripathi 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 “Photoinduced regioselective C−C bond formation and transition metal-catalyzed C-H activation” deals with the development of chemical reactions for the synthesis of heterocyclic molecules *via* a relatively greener approach. Visible light catalyzed selective construction of carbon−carbon bond has started to garner huge attention from chemists recently. The attractiveness of such selective photoreactions is attributed to the synthetic utility for the development of new reactions. We have developed regioselective C−C bond formation in heterocyclic compounds, which leads to the construction of analogues to biologically active molecules.

This dissertation comprises of five chapters. In the **first chapter**, the importance of photoredox catalysis, photophysical and electrochemical process and types of photocatalysts with emphasis on photoredox catalysis has been described. In the second part of the introduction chapter, discussions on various types of oxidative coupling reactions employed in C−C bond formation with the main emphasis on the dehydrogenative coupling of aromatic compounds is presented.

C**hapter two** describes a metal-free and mild, photoinduced decarboxylative alkylation of coumarins at C4-position. Photoinduced single electron transfer has been initiated by utilizing the visible-light absorptivity of Eosin Y for a reductive generation of alkyl radicals from *N*-(acyloxy)-phthalimide esters. Depending on the nature of *N*-(acyloxy)-phthalimide esters (primary, secondary, and tertiary carboxylic acid derived), several saturated and unsaturated C4-alkylated coumarins were synthesized. To showcase the utility of the transformation for diversifying carboxylic acids containing natural-products and drugs, also have been used for the synthesis of coumarins derivative.

In **chapter three** development of Eosin Y catalyzed, photoinduced deaminative C4-position alkylation of coumarins *via* C-N bond activation has been reported. We have attempted to explore the reactivity of the radical intermediates generated by photocatalytic deaminative alkylpyridinium salts with 3-substituted coumarins and its analogues. Various secondary and benzylic amines derived pyridinium salts provided several exclusive unsaturated C-4 alkylated coumarins. Further, control experiments studies supported a radical based mechanism for the selective deaminative alkylation.

Chapter four deals with visible light-mediated regioselective functionalization of coumarins. This methodology offered selective functionalization of the benzo ring rather than a heterocyclic ring of coumarins. Several tertiary carboxylic acids derived *N*-(acyloxy)phthalimide (NHPI) afforded exclusive C7-alkylated coumarins. Other carboxylic acid-containing drug derivative NHPI also provided corresponding coumarin products. All synthesized coumarin derivatives in this chapter are analogous to biological and pharmaceutical molecules.

In the **fifth chapter**, a transition metal-catalyzed regioselective, intramolecular, dehydrogenative cross-coupling reactions at the C5 and C2 position of pyrrole derivatives have been described for the synthesis of polyheterocyclic arenes, which is further divided into three subchapters.

In **chapter 5a**, we have disclosed a Cu-catalyzed, intramolecular dehydrogenative cross-coupling in 3-substituted and 3',4'-disubstituted pyrrole-azole systems. The site-selective C2-H activation of unsymmetrically substituted pyrroles in presence of C5 position has been successfully achieved in moderate to good yields for direct access to six- and seven-membered annulated pyrroles, which is an important scaffold, considering the wide biological activity of nitrogen-containing heterocycles.

C**hapter 5b** described the synthesis of polycyclic pyrrole-azole structures possessing fused six-membered and seven-membered rings *via* ligand-enabled, Pd-catalyzed, site-selective, intramolecular cross-couplings of *N*-substituted pyrrole-azoles. C5-H activation in the presence of a reactive C2-H remains a challenge that needs to be addressed and this was targeted to be resolved through the present approach by specifically generating the cyclized products with high selectivity. The featured methodology provides a novel disconnection for the synthesis of pyrrole containing alkaloids and medicinal compounds.

Chapter 5c deals a highly efficient and regioselective palladium-catalyzed annulation protocol for a series of linear and terminally substituted 1,2 and 1,3-diheteroaryl alkanes to corresponding polyheterocyclic arenes. Intramolecular oxidative coupling involving double C(sp^2)-*H* bond functionalization provides feasible access to a bi-heteroaryl system annulated into a six-membered ring. The methodology is not only restricted to six-membered annulations but also extended to the synthesis of the seven-membered ring with bi-heteroaryl core.

सार

थिसिस "फोटोइंड्यूज्ड रिजियोसेलेक्टिव सी-सी बॉन्ड गठन और संक्रमण धातु-उत्प्रेरित सी-एच सक्रियण" नामक एक अपेक्षाकृत हरियाली दृष्टिकोण के माध्यम से हेटेरोसायक्लिक अणुओं के संश्लेषण के लिए रासायनिक प्रतिक्रियाओं के विकास से संबंधित है। कार्बन-कार्बन बॉन्ड के दर्शनीय प्रकाश उत्प्रेरित चयनात्मक निर्माण ने हाल ही में केमिस्टों से भारी ध्यान आकर्षित करना शुरू कर दिया है। इस तरह के चयनात्मक फोटोरिएक्शन के आकर्षण को नई प्रतिक्रियाओं के विकास के लिए सिंथेटिक उपयोगिता के लिए जिम्मेदार ठहराया जाता है। हमने हेट्रोसाइक्लिक यौगिकों में रिजियोसेलेक्टिव सी-सी बॉन्ड गठन विकसित किया है, जो जैविक रूप से सक्रिय अणुओं के लिए एनालॉग्स के निर्माण की ओर जाता है ।

इस शोध प्रबंध में पाँच अध्याय शामिल हैं। पहले अध्याय में, फोटोरिडॉक्स कैटेलिसिस के आधार पर, फोटोरिडॉक्स कैटेलिसिस, फोटोफिजिकल और इलेक्ट्रोकेमिकल प्रक्रिया और फोटोकैटलिस्ट्स के प्रकारों के महत्व का वर्णन किया गया है। परिचय अध्याय के दूसरे भाग में, सुगंधित यौगिकों के निर्जलीकरणीय युग्मन पर मुख्य जोर देने के साथ सी-सी बंध गठन में कार्यरत विभिन्न प्रकार के ऑक्सीडेटिव युग्मन प्रतिक्रियाओं पर चर्चा प्रस्तुत की गई है।

अध्याय दो में सी ४-स्थित कूमेरिन के एक धातु-मुक्त और सौम्य, फोटोइंड्यूज्ड डीकार्बाक्सिलेटिव एल्काइलेशन का वर्णन किया गया है। एन-(एसाइक्लॉक्सी)-थैलिडामाइड एस्टर से एल्काइल रेडिकल की एक रिडक्टिव जेनरेशन के लिए इओसिन वाई के दृश्य-प्रकाश अवशोषण का उपयोग करके फोटोइंडिटेड सिंगल इलेक्ट्रॉन ट्रांसफर किया गया है। एन-(एसाइक्लॉक्सी)-थैलिडामाइड एस्टर (प्राथमिक, द्वितीयक, और तृतीयक कार्बोक्जिलिक एसिड व्युत्पन्न) की प्रकृति के आधार पर, कई संतृप्त और असंतृप्त सी ४-अल्केलाइज्ड कूमेरिन को संश्लेषित किया गया है। प्राकृतिक-उत्पादों और दवाओं से युक्त कार्बोक्जिलिक एसिड में विविधता लाने के लिए परिवर्तन की उपयोगिता को दर्शाने के लिए, कूमेरिन व्युत्पन्न के संश्लेषण के लिए भी उपयोग किया गया है।

अध्याय तीन में इओसिन वाई उत्प्रेरित, सी-एन बांड सक्रियण के माध्यम से फोटोइंड्यूज्ड डीएमिनेटिव कूमेरिन के सी ४-स्थिति अल्काइलेशन की सूचना दी गई है। हमने ३-स्थानापन्न युग्मकों और इसके एनालॉग्स के साथ फोटोकैटलिटिक डीएमिनेटिव अल्काइलीपीरिडिनियम लवण

द्वारा उत्पन्न मध्यवर्ती की प्रतिक्रिया का पता लगाने का प्रयास किया है। विभिन्न माध्यमिक और बेन्ज़ाइल एमीन व्युत्पन्न पिरिडिनियम लवण कई विशिष्ट असंतृप्त सी-४ अल्काइलेटेड कूमेरिन प्रदान करते हैं। इसके अलावा, नियंत्रण प्रयोगों के अध्ययन ने चयनात्मक डीएमिनेटिव अल्काइलेशन के लिए एक रेडिकल आधारित तंत्र का समर्थन किया।

अध्याय चार में कूमेरिन के दृश्य प्रकाश की मध्यस्थता वाले प्रतिगामी कार्यात्मककरण के बारे में बताया गया है। इस पद्धति ने युग्मकों के विषमकोणीय वलय के बजाय बेन्जो वलय के चयनात्मक क्रियाकलाप की पेशकश की। कई तृतीयक कार्बोक्जिलिक एसिड व्युत्पन्न एन-(एसाइक्लॉक्सी)-थैलिडामाइड (एनएचपीआई) अनन्य सी७-अल्कायलेटेड कूमेरिन प्रदान करते हैं। अन्य कार्बोक्जिलिक एसिड युक्त दवा व्युत्पन्न एनएचपीआई भी इसी प्रकार के कूमेरिन उत्पादों को प्रदान करता है। इस अध्याय में सभी संश्लेषित कूमेरिन यौगिक जैविक और दवा के अणुओं के अनुरूप हैं।

पांचवें अध्याय में, एक संक्रमण धातु-उत्प्रेरित प्रतिगामी, इंट्रामोलीक्युलर, पायरोल डेरिवेटिव के सी५ और सी२ की स्थिति पर निर्जलीकरण संबंधी क्रॉस-कपलिंग प्रतिक्रियाओं से पॉलीहेट्रोसाइक्लिक एरीनो के संश्लेषण को वर्णित किया गया है, जिसे आगे तीन उपचरों में विभाजित किया गया है।

अध्याय ५अ में, हमने ३-प्रतिस्थापित और ३', ४'- द्विप्रतिस्थापित पायरोल-एज़ोल सिस्टम में एक कापर -उत्प्रेरित, इंट्रामोलीक्युलर डिहाइड्रोजनेटिव क्रॉस-कपलिंग का खुलासा किया है। सी-५ की उपस्थिति में साइट-चयनात्मक सी२-एच सक्रियण असममित पायरोल में अच्छी पैदावार के साथ सफलतापूर्वक प्राप्त किया गया है जो कि सीधा ६ और सात-सदस्यीय पायरोल चक्र युक्त पिरामिड प्रदान करता है, और व्यापक जैविक गतिविधि को देखते हुए एक नाइट्रोजन युक्त हेट्रोसायकल की महत्वपूर्ण पाड़ है।

अध्याय 5 बी में पॉलीसाइक्लिक पिरामिड-एजोल संरचनाओं के संश्लेषण का वर्णन किया गया है जिसमें लिगैंड-सक्षम, पैलेडियम-उत्प्रेरित, साइट-चयनात्मक, एन-प्रतिस्थापित पाइरोल-एज़ोल्स की इंट्रामालिक्युलर क्रॉस-कपलिंग के माध्यम से छह-सदस्यीय और सात-सदस्यीय छल्ले प्राप्त होते हैं। प्रतिक्रियाशील सी२-एच की उपस्थिति में सी५-एच सक्रियण एक चुनौती है जिसे संबोधित करने की आवश्यकता है और इसे विशेष रूप से उच्च चयनात्मकता के साथ चक्रीय

उत्पादों को उत्पन्न करके वर्तमान दृष्टिकोण के माध्यम से हल करने का लक्ष्य रखा गया था। चित्रित कार्यप्रणाली अल्कलॉइड और औषधीय यौगिकों वाले पिरामिड के संश्लेषण के लिए यह एक नवीन वियोग प्रदान करता है।

अध्याय ५सी मे रैखिक और अन्तिम छोर रूप से प्रतिस्थापित १,२ और १,३-डायथेरोयेरल अल्केन्स की एक श्रृंखला के लिए एक अत्यधिक कुशल और प्रतिगामी पैलेडियम-उत्प्रेरित कुंडलीकरण प्रोटोकॉल संबंधित पालीहेट्रोसायक्लिक एरीन्स को प्रदान करता है। इंट्रामोल्युलर ऑक्सीडेटिव युग्मन जिसमें डबल सी (एसपी२)-एच बॉन्ड कार्यतरूव्यवस्था शामिल है, एक छह-सदस्यीय रिंग में घोषित द्विहेट्रोएरिल सिस्टम के लिए संभव पहुंच प्रदान करता है। कार्यप्रणाली केवल छह-सदस्यीय घोषणाओं तक ही सीमित नहीं है, बल्कि द्विहेट्रोसायक्लिक कोर के साथ सात-सदस्यीय चक्र के संश्लेषण तक विस्तारित है।

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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
$Cu(OAc)_2$	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
TFFA	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