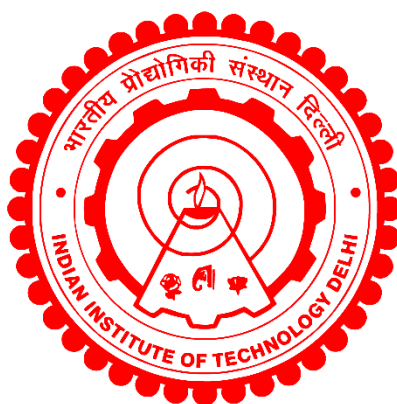


FUNCTIONALIZATION OF C(sp²)-H BONDS FOR THE SYNTHESIS OF VALUE-ADDED MOLECULES

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by

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Department of Chemistry

Submitted

*in fulfillment of the requirements of the degree of **Doctor of Philosophy***

to the



INDIAN INSTITUTE OF TECHNOLOGY DELHI

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Dedicated
To
My Family and Teachers

CERTIFICATE

This is to certify that the thesis entitled “***Functionalization of C(sp²)-H Bonds for the Synthesis of Value-added Molecules***” being submitted by **Ms. Neha Dagar** to the *Indian Institute of Technology Delhi*, for the award of the degree of **Doctor of Philosophy**, is a record of bonafide research work carried out by her. **Ms. Neha Dagar** has worked under my supervision and guidance and has fulfilled all the requirements for the submission of a Ph.D. thesis, which to my knowledge has reached the requisite standard and is worthy of consideration for the award of a Ph.D. degree.

The work embodied in this thesis has not been submitted, in part or full, to another university or institute for the award of any degree or diploma.

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ABSTRACT

The thesis titled “**Functionalization of C(sp²)–H Bonds for the Synthesis of Value-added Molecules**” is focused on the development of new synthetic routes to achieve C(sp²)–H functionalization. The aim of this thesis was to demonstrate the C(sp²)–H functionalization from readily available starting materials using inexpensive catalytic system. Furthermore, we have utilized visible-light mediated photoredox catalysis to achieve acylation and alkylation to access useful and interesting value-added molecular scaffolds. This further allows direct C(sp²)–H functionalization at room temperatures without the use of expensive transition metal reagents and stoichiometric amount of strong bases. In addition to this, introduction of electro-organic synthesis allows cyclization using electricity as greenest and sustainable replacement to sacrificial oxidants enabling reactions to be conducted at room temperature under milder conditions. The thesis also features the late-stage functionalization of various value-added molecules.

Chapter 1 gives a layout on direct catalytic transformations of C–H bonds in organic molecules to different functionalities as a straightforward and powerful strategy for the synthesis of complex molecular scaffolds. Therefore, development of more atom and step-economical methodologies for direct C(sp²)–H functionalization with readily available starting materials that can be applied to broad class of substrates is highly desirable for important contribution to the field of organic synthesis and late-stage functionalization.

In addition to this, from the viewpoint of green and sustainable chemistry, the recognition of environmentally benign strategies with successful utilization of renewable resources, such as electricity and light are required to expand the sustainable chemical industry. Modulating photocatalytic/electrocatalytic conditions, therefore makes it possible to avoid usage of harsh oxidants, pre-functionalization, and precious metal catalysts therefore allowing reactions to be conducted under milder conditions and obviating the production of undesirable waste. Therefore, this chapter focuses on the direct C(sp²)–H functionalization from readily available starting materials and how the utilization of photocatalytic and electrocatalytic conditions allows transformations to be conducted under milder conditions, thereby enhancing the functional group tolerance of the reactions.

Chapter 2 describes a mild and practical copper catalyzed-TBHP promoted esterification of aldehydes in the presence of alkyl halides and alcohols has been developed. This strategy relies on naturally abundant aldehydes as acyl precursors which can further couple with readily available alkyl halides/alcohols to transform into esters. Preliminary mechanistic investigation

reveals that aldehyde in the presence of *tert*-butoxy radical transforms into acyl radical. This protocol exhibits a broad substrate scope along with wide functional group compatibility and is applicable to a wide range of aldehydes, including challenging aliphatic aldehydes to undergo the C(sp²)-H bond scission to furnish the desired esters in good to excellent yields.

Chapter 3 describes an organo-photocatalyzed carboacylation reaction that offers a springboard for direct access to a wide range of acylated oxindoles derivatives. The modular one-pot method uses feedstock aldehydes and alcohols as acyl surrogates and commercially available Eosin Y as the photoredox catalyst, making it simple and affordable to introduce structural diversity. Several biologically relevant skeletons have been easily synthesized under mild conditions in the presence of visible-light irradiation by fostering a radical acylation/cyclization cascade. The proposed reaction mechanism was further illuminated by a number of spectroscopic studies. We have applied this protocol for the late-stage functionalization of pharmaceuticals and blockbuster drugs.

Chapter 4 describes the dual role of cerium to promote photoinduced ligand to metal charge transfer (LMCT)-process for the generation of the alkyl radical and subsequent Lewis acid catalysis to construct stereodefined C-C bonds. This paradigm utilized ubiquitous carboxylic acids as alkyl radical surrogates and offers excellent diastereoselectivity for the formation of C-4 alkylated coumarins in good to excellent yield. UV-Vis spectroscopy studies in combination with *in-situ* FTIR spectroscopy are consistent with the proposed mechanism, supporting the participation of Ce^{IV}-carboxylate complex in photoinduced LMCT and its subsequent homolysis to generate alkyl radical through the exclusion of CO₂. Furthermore, this mild and atom economical catalytic manifolds allow the late-stage modification of pharmaceuticals.

Chapter 5 describes a mild and versatile cerium mediated decarboxylative strategy for sequential alkylation/cyclization for the synthesis of biologically important functionalized oxindoles and benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones via photoinduced-LMCT. This operationally simple procedure relies on inexpensive and feedstock carboxylic acids as alkyl radical surrogates and aerial molecular oxygen as the terminal oxidant. This mild and atom economical protocol showed viability with a wide range of alkyl carboxylic acids (1° to 3° acids) as coupling partners and also allows the late-stage modification of pharmaceutically important acids. Mechanistic studies revealed the reaction to follow a radical pathway, while the decarboxylative event was studied by *in situ* FTIR.

Chapter 6 describes a milder and metal-free approach for the construction of naphthofuran-2-

carboxaldehyde derivatives by utilizing the synergy of electrochemical oxidation and organo-selenium catalysis at room temperature. The compatibility of various functional groups and scalability of this protocol demonstrate the practicality of the electrochemical strategy. The synthetic utility of this strategy is furthermore demonstrated by synthesizing diversified molecules through downstream transformations.

Chapter 7 gives the overall conclusions of the entire work carried out in the present study and future outline.

सारांश

"मूल्य वर्धित अणुओं के संश्लेषण के लिए रेडिकल $C(sp^2)-H$ बॉन्ड फंक्शनलाइजेशन" शीर्षक वाली थीसिस $C(sp^2)-H$ कार्यात्मकता प्राप्त करने के लिए नए सिंथेटिक मार्गों के विकास पर केंद्रित है। इस थीसिस का उद्देश्य सस्ती उत्प्रेरक प्रणाली का उपयोग करके आसानी से उपलब्ध प्रारंभिक सामग्री से $C(sp^2)-H$ कार्यात्मककरण का प्रदर्शन करना था। इसके अलावा, हमने उपयोगी और दिलचस्प मूल्य वर्धित आणविक मचानों तक पहुंचने के लिए एसाइलेशन और अल्काइलेशन प्राप्त करने के लिए दृश्य-प्रकाश मध्यस्थता फोटोरेडॉक्स कटैलिसिस का उपयोग किया है। यह आगे महंगे संक्रमण धातु अभिकर्मकों और मजबूत ठिकानों की स्टोइकोमेट्रिक मात्रा के उपयोग के बिना कमरे के तापमान पर प्रत्यक्ष $C(sp^2)-H$ कार्यात्मककरण की अनुमति देता है। इसके अलावा, इलेक्ट्रो-ऑर्गेनिक संश्लेषण की शुरूआत बिजली का उपयोग करके बलि ऑक्सीडेंट के लिए सबसे हरे और टिकाऊ प्रतिस्थापन के रूप में चक्रीकरण की अनुमति देती है, जिससे प्रतिक्रियाओं को हल्के परिस्थितियों में कमरे के तापमान पर आयोजित किया जा सकता है। थीसिस में विभिन्न मूल्य वर्धित अणुओं के देर से चरण के कार्यात्मककरण की भी सुविधा है।

अध्याय 1 जटिल आणविक मचानों के संश्लेषण के लिए एक सीधी और शक्तिशाली रणनीति के रूप में विभिन्न कार्यात्मकताओं के लिए कार्बनिक अणुओं में सी-एच बांड के प्रत्यक्ष उत्प्रेरक परिवर्तनों पर एक लेआउट देता है। इसलिए, आसानी से उपलब्ध प्रारंभिक सामग्रियों के साथ प्रत्यक्ष $C(sp^2)-H$ कार्यात्मककरण के लिए अधिक परमाणु और कदम-किफायती तरीकों का विकास जो सबस्ट्रेट के व्यापक वर्ग पर लागू किया जा सकता है, कार्बनिक संश्लेषण और देर से चरण कार्यात्मककरण के क्षेत्र में महत्वपूर्ण योगदान के लिए अत्यधिक वांछनीय है।

इसके अलावा, हरे और टिकाऊ रसायन विज्ञान के दृष्टिकोण से, टिकाऊ रासायनिक उद्योग का विस्तार करने के लिए बिजली और प्रकाश जैसे नवीकरणीय संसाधनों के सफल उपयोग के साथ पर्यावरणीय रूप से सौम्य रणनीतियों की मान्यता आवश्यक है। इलेक्ट्रोकेटलिटिक स्थितियों को संशोधित करना, इसलिए कठोर ऑक्सीडेंट, पूर्व-कार्यात्मककरण और कीमती धातु उत्प्रेरक के उपयोग से बचना संभव बनाता है, इसलिए प्रतिक्रियाओं को हल्के परिस्थितियों में आयोजित करने और अवांछनीय कचरे के उत्पादन को रोकने की अनुमति देता है। इसलिए, यह अध्याय आसानी से उपलब्ध प्रारंभिक सामग्रियों से प्रत्यक्ष $C(sp^2)-H$ कार्यात्मककरण पर केंद्रित है और फोटोकेटलिटिक और इलेक्ट्रोकेटलिटिक स्थितियों का उपयोग कैसे हल्के परिस्थितियों में परिवर्तनों को आयोजित करने की अनुमति देता है, जिससे प्रतिक्रियाओं की कार्यात्मक समूह सहिष्णुता बढ़ जाती है।

अध्याय 2 में एल्काइल हलाइड्स और अल्कोहल की उपस्थिति में एल्डिहाइड के हल्के और व्यावहारिक

तांबे उत्प्रेरित-टीबीएचपी प्रचारित एस्टरीफिकेशन का वर्णन किया गया है। यह रणनीति एसाइल अग्रदूतों के रूप में स्वाभाविक रूप से प्रचुर मात्रा में एल्लिहाइड पर निर्भर करती है जो एस्टर में बदलने के लिए आसानी से उपलब्ध एल्काइल हलाइड्स / अल्कोहल के साथ आगे बढ़ सकती है। प्रारंभिक यंत्रवत जांच से पता चलता है कि टर्ट-ब्यूटॉक्सी रेडिकल की उपस्थिति में एल्लिहाइड एसाइल रेडिकल में बदल जाता है। यह प्रोटोकॉल व्यापक कार्यात्मक समूह संगतता के साथ एक व्यापक सबस्ट्रेट गुंजाइश प्रदर्शित करता है और उत्कृष्ट पैदावार के लिए वांछित एस्टर प्रस्तुत करने के लिए $C(sp^2)-H$ बॉन्ड कैची से गुजरने के लिए स्निग्ध एल्लिहाइड को चुनौती देने सहित एल्लिहाइड की एक विस्तृत श्रृंखला पर लागू होता है।

अध्याय 3 एक ऑर्गेनो-फोटोकैटलाइज्ड कार्बोएसाइलेशन प्रतिक्रिया का वर्णन करता है जो एसिलेटेड ऑक्सिडोल्स डेरिवेटिव की एक विस्तृत श्रृंखला तक सीधी पहुंच के लिए एक स्प्रिंगबोर्ड प्रदान करता है। मॉड्यूलर वन-पॉट विधि फीडस्टॉक एल्लिहाइड और अल्कोहल को एसाइल सरोगेट्स के रूप में और व्यावसायिक रूप से उपलब्ध ईओसिन वाई को फोटोरेडॉक्स उत्प्रेरक के रूप में उपयोग करती है, जिससे संरचनात्मक विविधता को पेश करना सरल और सस्ती हो जाता है। कई जैविक रूप से प्रासंगिक कंकालों को आसानी से एक कट्टरपंथी एसाइलेशन / चक्रीकरण कैस्केड को बढ़ावा देकर दृश्य-प्रकाश विकिरण की उपस्थिति में हल्के परिस्थितियों में संश्लेषित किया गया है। प्रस्तावित प्रतिक्रिया तंत्र को कई स्पेक्ट्रोस्कोपिक अध्ययनों द्वारा आगे रोशन किया गया था। हमने फार्मास्यूटिकल्स और ब्लॉकबस्टर दवाओं के देर से चरण के कार्यात्मककरण के लिए इस प्रोटोकॉल को लागू किया है।

अध्याय 4 में फोटोइंज्यूस्ड लिगेंड को मेटल चार्ज ट्रांसफर (एलएमसीटी) को बढ़ावा देने के लिए सेरियम की दोहरी भूमिका का वर्णन किया गया है - स्टीरियोडिफाईंड सी-सी बॉन्ड बनाने के लिए एल्काइल रेडिकल और बाद में लुईस एसिड कटैलिसिस की पीढ़ी के लिए प्रक्रिया। इस प्रतिमान ने सर्वव्यापी कार्बोकिजलिक एसिड का उपयोग एल्काइल रेडिकल सरोगेट्स के रूप में किया और उत्कृष्ट उपज के लिए अच्छे में C-4 अल्काइलेटेड कौमारिन के गठन के लिए उत्कृष्ट डायस्टेरोसेलेक्टिविटी प्रदान करता है। *इन-सीटू एफटीआईआर स्पेक्ट्रोस्कोपी के संयोजन में यूवी-विज़* स्पेक्ट्रोस्कोपी अध्ययन प्रस्तावित तंत्र के अनुरूप हैं, जो CO_2 के बहिष्करण के माध्यम से एल्काइल रेडियल उत्पन्न करने के लिए फोटोइंज्यूस्ड एलएमसीटी और इसके बाद के होमोलिसिस में Ce^{IV} -कार्बोक्सिलेट कॉम्प्लेक्स की भागीदारी का समर्थन करते हैं। इसके अलावा, यह हल्के और परमाणु किफायती उत्प्रेरक कई गुना फार्मास्यूटिकल्स के देर से चरण संशोधन की अनुमति देते हैं।

अध्याय 5 जैविक रूप से महत्वपूर्ण कार्यात्मक ऑक्सिडोल्स और बेजिमिडाज़ो [2,1-ए] आइसोक्विनोलिन -6 (5 एच) के संश्लेषण के लिए अनुक्रमिक क्षारीकरण / चक्रीकरण के लिए एक हल्के और बहुमुखी सेरियम मध्यस्थता वाले डीकार्बोक्जिलेटिव रणनीति का वर्णन करता है। यह परिचालन सरल प्रक्रिया

सस्ती और फीडस्टॉक कार्बोक्जिलिक एसिड पर एल्काइल रेडिकल सरोगेट्स और टर्मिनल ऑक्सीडेंट के रूप में हवाई आणविक ऑक्सीजन पर निर्भर करती है। इस हल्के और परमाणु किफायती प्रोटोकॉल युग्मन भागीदारों के रूप में एल्काइल कार्बोक्जिलिक एसिड (1° से 3° एसिड) की एक विस्तृत श्रृंखला के साथ व्यवहार्यता से पता चला और यह भी औषधीय महत्वपूर्ण एसिड के देर से चरण संशोधन की अनुमति देता है। यंत्रवत अध्ययनों ने एक कट्टरपंथी मार्ग का पालन करने की प्रतिक्रिया का खुलासा किया, जबकि डीकार्बोक्सिलेटिव घटना का अध्ययन सीटू एफटीआईआर द्वारा किया गया था।

अध्याय 6 कमरे के तापमान पर इलेक्ट्रोकेमिकल ऑक्सीकरण और ऑर्गेनो-सेलेनियम कटैलिसिस के तालमेल का उपयोग करके नेफथोफ्यूरन-2-कार्बोक्साइडिहाइड डेरिवेटिव के निर्माण के लिए एक मामूली और धातु-मुक्त दृष्टिकोण का वर्णन करता है। विभिन्न कार्यात्मक समूहों की संगतता और इस प्रोटोकॉल की मापनीयता विद्युत रासायनिक रणनीति की व्यावहारिकता को प्रदर्शित करती है। इस रणनीति की सिंथेटिक उपयोगिता इसके अलावा डाउनस्ट्रीम परिवर्तनों के माध्यम से विविध अणुओं को संश्लेषित करके प्रदर्शित की जाती है।

अध्याय 7 वर्तमान में किए गए पूरे कार्य के समग्र निष्कर्ष देता है अध्ययन और भविष्य की रूपरेखा।

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LIST OF ABBREVIATIONS

CDC	cross-dehydrogenative coupling
TM	transition metal
PC	photoredox catalyst
4CzIPN	1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene
GC	gas chromatography
TLC	thin layer chromatography
KMnO ₄	potassium permanganate
δ	chemical shift
¹ H NMR	Proton nuclear magnetic resonance
¹³ C NMR	Carbon nuclear magnetic resonance
Hz	Hertz
ppm	parts per million
HRMS	High-resolution mass spectra
ESI-TOF	electrospray ionization time-of-flight
HAT	hydrogen-atom transfer
TBAI	tetrabutylammonium iodide
DCE	dichloroethane
^t BuOH	tertiary butanol
TBHP	<i>tert</i> -butyl hydroperoxide
TBPB	<i>tert</i> -butyl peroxybenzoate
DTBP	di- <i>tert</i> -butyl peroxide
TEMPO	2,2,6,6-tetramethylpiperidin-1-yl-oxidanyl
BHT	2,6-di- <i>tert</i> -butyl-4-methylphenol
EY	Eosin Y
OH ⁻	hydroxide anion
^t BuO [•]	<i>tert</i> -butoxyl radical
^t BuOO [•]	<i>tert</i> -butyl peroxy radical
SET	single-electron transfer
BDE	bond-dissociation energy
ΔH_{HA}	Hydrogen Atom Affinities
LMCT	ligand-to-metal charge transfer

LSF	late-stage functionalization
GC–MS	gas chromatography–mass spectrometry
FTIR	Fourier transform infrared
H ₂ O ₂	hydrogen peroxide
KI	potassium iodide
DG	directing group
AIBN	azobisisobutyronitrile
NHC	<i>N</i> -heterocyclic carbenes
MeCN	acetonitrile
EtOAc	ethyl acetate
H ₂	hydrogen