

PHOTOINDUCED REGIO-/STEREOSELECTIVE C- C/C-X BOND FORMATION

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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,

Grandparents and Brothers

CERTIFICATE

This is to certify that the thesis entitled, “**Photoinduced Regio-/Stereoselective C-C/C-X Bond Formation**”, being submitted by **Mr. Shashank Singh** 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. Shashank Singh** 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 illustrated and incorporated 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 Regio-/Stereoselective C-C/C-X Bond Formation**” is divided into five chapters which are mainly focused with development of chemical reactions by illuminating the intricacies of visible light, unlocking the secret of photoinduced reaction in performing unconventional reactions. Chapter one describes the importance of visible light, photocatalysis for selective C-C and C-X bond formation. In chapter two describes the efficient application of naturally abundant carboxylic acid in alkylation. Chapter three realizes the importance of visible light for synthesizing C-Se bond formation. Chapter four describes an unconventional site-selective trifluoromethylation/perfluoroalkylation *via* visible light. Finally, chapter five, realizes the concept of diastereoselective and enantioselective photoinduced alkylation.

Chapter 1: Discloses the brief concept of photochemistry to understand the molecular dynamics. In addition, chirality and its role in day-to-day life, emphasis on asymmetric catalysis *via* photoinduction has been described. Moreover, achiral photocatalysis induced *via* single bifunctional catalysis or dual catalysis and its proof of concept has been elaborated along with their photophysical properties.

Chapter 2: Herein, we have unraveled a metal-free, photochemical protocol for C-4 alkylation of 2-iminochromene has been reported by employing naturally abundant chemical feedstock aliphatic carboxylic acid. Importantly, our catalytic system efficiently tolerates range of carboxylic acids including bioactive acids such as gemfibrozil, etc. The developed protocol yields selective C-4 alkylation under photo redox condition to access C-4 alkylated 2-iminochromene in high yields. We believe that this protocol amplifies the potential of organic photo-redox catalytic processes for C-4 alkylation of imines, providing an opportunity for further investigation of the core.

Chapter 3: Discloses a visible light mediated novel metal-free, oxidant free phosphoric acid catalysed method for the synthesis of selenyl NHCbz-Tryptamine/3-methyl indole. This protocol for direct C-2 selenation strategy, under environmental benign conditions by reaction of tryptamine/3-methyl indole and diphenylselenide, allows access to a wide range of 2-aryl selenyl NHCbz-tryptamines/3-methyl indole. An experimental investigation using UV-Vis, cyclic voltammetry, and controlled experiments sheds insight into the plausible mechanism.

Chapter 4: Unconventional regioselective trifluoromethylation/perfluoroalkylation for aromatic C-H bond in presence of multifarious reactive sites has been described, this chapter has been further divided into two subchapters.

Chapter 4a: The task of reinventing and installing trifluoromethyl group via radical pathway has attracted attention recently. However, functionalization of C-H bonds of benzocore of alkylidene malononitrile is still a challenge. In this study we have developed facile visible light-driven- metal free *para* selective trifluoromethylation/perfluoroalkylation of aryl/alkylidene malononitriles. The dual pronged strategy appears to be critical for achieving desirable reactivity and selectivity for broad range of substrates including drugs stapled substrates.

Chapter 4b: Herein, a highly regioselective photocatalyzed protocol for aromatic C-7 selective C-H trifluoromethylation/perfluoroalkylation of coumarins is presented. The reaction undergoes a radical type of nucleophilic substitution instead of a radical type electrophilic substitution owing to the benzocore activation as a result of lowering the LUMO. The reaction was found to be extremely general and versatile as demonstrated by its applicability to a wide range of substrates giving exclusive C-7 trifluoromethylated product.

Chapter 5: In this chapter, we have disclosed the work which encompasses a stereoselective alkylation, with the focus on diastereoselective photoinduced alkylation (chapter 5a) and enantioselective alkylation (chapter 5b).

Chapter 5a: Herein, we have developed a mild, metal-free, diastereoselective protocol for the synthesis of C-4 alkylated coumarins. The incorporation of (-) Phenyl-menthol, is the key for diastereoselective addition. Furthermore, the protocol is compatible for range of carboxylic acid including secondary and tertiary derived NHPI esters. We believe that the developed methodology offers a powerful approach for post-synthetic modification route for generating various new chiral class of highly functionalized small molecules.

Chapter 5b: Herein, we report the copper catalysed enantioselective deaminative alkylation with glycine derivatives. Key for success was the chiral phosphine-Cu complex formed in-situ which not only acts as a photocatalyst but also plays a pivotal role in inducing stereoselectivity. Experimental and spectroscopic mechanistic studies provide key insight for the plausible mechanism and stereo induction. These findings open avenues for the development of chiral unnatural amino acids thus offering a de-nova strategy for enantioenriched sp^3 - sp^3 linkage via deaminative strategy.

सार

"फोटोइंड्यूस्ड रेजियो-/स्टीरियोसेलेक्टिव सी-सी/सी-एक्स बॉन्ड फॉर्मेशन" शीर्षक शोध प्रबंध को पांच अध्यायों में विभाजित किया गया है, जो मुख्य रूप से दृश्य प्रकाश की जटिलताओं को उजागर करके रासायनिक प्रतिक्रियाओं के विकास पर केंद्रित हैं, जो अपरंपरागत प्रतिक्रियाओं के निर्माण में फोटोप्रेरित प्रतिक्रिया के रहस्य को उजागर करते हैं। अध्याय एक, चयनात्मक सी-सी और सी-एक्स बंधन निर्माण के लिए दृश्य प्रकाश, फोटोकैटलिसिस के महत्व का वर्णन करता है। अध्याय दो में एल्किलेशन में प्राकृतिक रूप से प्रचुर मात्रा में कार्बोक्जिलिक एसिड के कुशल अनुप्रयोग का वर्णन किया गया है। अध्याय तीन में सी-एसई बांड निर्माण को संश्लेषित करने के लिए दृश्य प्रकाश के महत्व पर प्रकाश डाला गया है। अध्याय चार, दृश्य प्रकाश के माध्यम से एक अपरंपरागत साइट-चयनात्मक ट्राइफ्लोरोमेथाइलेशन/ परफ्लूरोएल्काइलेशन का वर्णन करता है। अंत में, अध्याय पांच, डायस्टेरियोसेलेक्टिव और एनेंटियोसेलेक्टिव फोटोप्रेरित एल्किलेशन की अवधारणा को स्पष्ट करता है।]

अध्याय 1: आणविक गतिशीलता को समझने के लिए फोटोकैमिस्ट्री की संक्षिप्त अवधारणा का खुलासा करता है। इसके अलावा, काइरैलिटी और दैनिक जीवन में इसकी भूमिका, फोटोइंडक्शन के माध्यम से असममित उत्प्रेरण पर जोर का वर्णन किया गया है। इसके अलावा, एकल द्विकार्यात्मक कटैलिसीस या दोहरे कैटलिसिस के माध्यम से प्रेरित अकायरल फोटोकैटलिसिस और इसकी अवधारणा के प्रमाण को उनके फोटोफिजिकल गुणों सहित विस्तार से वर्णित किया गया है।

अध्याय 2: इसमें, हमने प्राकृतिक रूप से प्रचुर मात्रा में रासायनिक फीडस्टॉक एलिफैटिक कार्बोक्जिलिक एसिड को नियोजित करके 2-इमिनोक्रोमीन के सी-4 एल्किलेशन के लिए एक धातु-मुक्त, फोटोकैमिकल प्रोटोकॉल का खुलासा किया है। महत्वपूर्ण बात यह है कि हमारी उत्प्रेरक प्रणाली बायोएक्टिव एसिड जैसे जेमफाइब्रोज़िल आदि सहित कार्बोक्जिलिक एसिड की रेंज को कुशलता से सहन करती है। विकसित प्रोटोकॉल उच्च पैदावार में सी-4 एल्काइलेटेड 2-इमिनोक्रोमीन तक पहुंचने के लिए फोटो रेडॉक्स स्थिति के तहत चयनात्मक सी-4 एल्किलेशन उत्पन्न करता है। हमारा मानना है कि यह प्रोटोकॉल इमाइन्स के सी-4 एल्किलेशन के लिए कार्बनिक फोटो-रेडॉक्स उत्प्रेरक प्रक्रियाओं की क्षमता को बढ़ाता है, जिससे कोर की आगे की जांच का अवसर मिलता है।

अध्याय 3: सेलेनिल एनएचसीबीज़-ट्रिप्टामाइन/3-मिथाइल इंडोल के संश्लेषण के लिए एक दृश्य प्रकाश मध्यस्थता उपन्यास धातु मुक्त, ऑक्सीडेंट मुक्त फॉस्फोरिक एसिड उत्प्रेरित विधि का खुलासा करता है। ट्रिप्टामाइन/3-मिथाइल इंडोल और डिफेनिलसेलेनाइड की प्रतिक्रिया द्वारा पर्यावरणीय सौम्य परिस्थितियों में प्रत्यक्ष सी-2 सेलेनेशन रणनीति के लिए यह प्रोटोकॉल, 2-एरिल सेलेनिल एनएचसीबीज़-ट्रिप्टामाइन/3-मिथाइल इंडोल की एक विस्तृत श्रृंखला तक पहुंच की अनुमति देता है। यूवी-विज़, चक्रीय वोल्तामेट्री और नियंत्रित प्रयोगों का उपयोग करके एक प्रयोगात्मक जांच प्रशंसनीय तंत्र पर अंतर्दृष्टि प्रदान करती है।

अध्याय 4: विविध प्रतिक्रियाशील साइटों की उपस्थिति में सुगंधित सी-एच बांड के लिए अपरंपरागत रीजियोसेलेक्टिव ट्राइफ्लोरोमेथाइलेशन/परफ्लूरोअल्केएशन का वर्णन किया गया है, इस अध्याय को आगे दो उपअध्यायों में विभाजित किया गया है।

अध्याय 4a: रेडिकल पाथवे के माध्यम से ट्राइफ्लोरोमेथाइल समूह को फिर से स्थापित करने और स्थापित करने के कार्य ने हाल ही में ध्यान आकर्षित किया है। हालाँकि, एल्काइलिडीन मैलोनोनिट्राइल के बेंज़ोकोर के सी-एच बांड का क्रियाशीलता अभी भी एक चुनौती है। इस अध्ययन में हमने एरिल/एल्काइलिडीन मैलोनोनिट्राइल्स का सुस्पष्ट दृश्यमान प्रकाश-चालित-धातु मुक्त पैरा चयनात्मक ट्राइफ्लोरोमेथाइलेशन/परफ्लूरोअल्केएशन विकसित किया है। दवाओं के स्टेपल सबस्ट्रेट सहित सबस्ट्रेट्स की विस्तृत श्रृंखला के लिए वांछनीय प्रतिक्रियाशीलता और चयनात्मकता प्राप्त करने के लिए दोहरी आयामी रणनीति महत्वपूर्ण प्रतीत होती है।

अध्याय 4b: इसमें, कूमारिन के C-7 चयनात्मक C-H ट्राइफ्लोरोमेथाइलेशन/परफ्लूरोएल्काइलेशन के लिए एक अत्यधिक रीजियोसेलेक्टिव फोटोकैटलिस्ट प्रोटोकॉल प्रस्तुत किया गया है। LUMO को कम करने के परिणामस्वरूप बेंज़ोकोर सक्रियण के कारण प्रतिक्रिया एक रेडिकल प्रकार के इलेक्ट्रोफिलिक प्रतिस्थापन के बजाय एक रेडिकल प्रकार के न्यूक्लियोफिलिक प्रतिस्थापन से गुजरती है। यह प्रतिक्रिया बेहद सामान्य और बहुमुखी पाई गई, जैसा कि विशेष सी-7 ट्राइफ्लोरोमेथिलेटेड उत्पाद देने वाले सबस्ट्रेट्स की एक विस्तृत श्रृंखला के लिए इसकी प्रयोज्यता से प्रदर्शित होता है।

अध्याय 5: इस अध्याय में, हमने उस कार्य का खुलासा किया है जिसमें डायस्टेरियोसेलेक्टिव फोटोप्रेरित एल्किलेशन (अध्याय 5 ए) और एनेंटियोसेलेक्टिव एल्किलेशन (अध्याय 5 बी) पर ध्यान केंद्रित करते हुए एक स्टीरियोसेलेक्टिव एल्किलेशन शामिल है।

अध्याय 5a: इसमें, हमने सी-4 एल्काइलेटेड कूमारिन के संश्लेषण के लिए एक हल्का, धातु-मुक्त, डायस्टेरियोसेलेक्टिव प्रोटोकॉल विकसित किया है। (-) फिनाइल-मेथॉल का समावेश, डायस्टेरियोसेलेक्टिव जोड़ की कुंजी है। इसके अलावा, प्रोटोकॉल माध्यमिक और तृतीयक व्युत्पन्न एनएचपीआई एस्टर सहित कार्बोक्जिलिक एसिड की श्रृंखला के लिए संगत है। हमारा मानना है कि विकसित पद्धति अत्यधिक कार्यात्मक छोटे अणुओं के विभिन्न नए कार्बन वर्ग उत्पन्न करने के लिए पोस्ट-सिंथेटिक संशोधन मार्ग के लिए एक शक्तिशाली दृष्टिकोण प्रदान करती है।

अध्याय 5b: इसमें, हम ग्लाइसिन डेरिवेटिव के साथ कॉपर उत्प्रेरित एनेंटियोसेलेक्टिव डेमिनेटिव एल्किलेशन की रिपोर्ट करते हैं। सफलता की कुंजी इन-सीटू में निर्मित कार्बन फॉस्फीन-सीयू कॉम्प्लेक्स थी जो न केवल एक फोटोकैटलिस्ट के रूप में कार्य करता है बल्कि स्टीरियोसेलेक्टिविटी को प्रेरित करने में भी महत्वपूर्ण भूमिका निभाता

है। प्रायोगिक और स्पेक्ट्रोस्कोपिक यंत्रवत अध्ययन प्रशंसनीय तंत्र और स्टीरियो इंडक्शन के लिए महत्वपूर्ण अंतर्दृष्टि प्रदान करते हैं। ये निष्कर्ष कायरल अप्राकृतिक अमीनो एसिड के विकास के लिए रास्ते खोलते हैं और इस प्रकार डेमिनेटिव रणनीति के माध्यम से एनेंटियोएनरिचड एसपी₃-एसपी₃ लिंकेज के लिए डी-नोवा रणनीति की पेशकश करते हैं।

TABLE OF CONTENT

Certificate	i
Acknowledgements	ii
Abstract	iv
Contents	ix
List of Figures	xiv
List of Tables	xvii
List of Schemes	xviii
List of Abbreviations	xxiii
Chapter 1. Introduction	
1.1. Prologue	2
1.2. Photochemistry – Importance of visible light	2
1.3. Photophysical and electrochemical background consideration of photocatalyst	4
1.3.1 Photophysical processes	4
1.3.2 Photophysical properties of photoredox catalyst	5
1.3.2.1 λ_{max} - Importance and application	
1.3.2.2 Fluorescence: (τ_f : Lifetime of fluorescence), and ϕ : Quantum yield	
1.3.2.3 ϕ_{ISC} : Quantum yield of intersystem crossing	
1.3.3 Electrochemistry: Redox potential of states: Feasibility of electron transfer	6
1.3.3.1 Photoinduced electron transfer kinetics	
1.4. Photoredox catalysis	7
1.4.1.1 Hydrogen atom transfer	7
1.4.1.2 Electron-donor complex	9
1.4.1.3 Single electron transfer	9
1.4.1.3.1 Reductive quenching cycle	
1.4.1.3.2 Oxidative quenching cycle	
1.5. Transition metal-based photoredox catalysts	11
1.5.1 Photochemistry of tris(2,2'-bipyridine) Ruthenium [Ru(bpy) ₃ ²⁺]	11
1.5.2 Photochemistry of copper-based complexes	12
1.5.2.1. Photochemistry of copper (I) complexes	12
1.5.2.2. Photochemistry of copper (II) complexes	13
1.5.2.3. Cooperative photoredox copper dual catalysis	14
1.5.2.4 Enantioselective dual photoredox copper catalysis/ bifunctional copper catalysis	15
1.5.2.4.1. Importance and role of chirality	15
1.5.2.4.2. Chiral induction	16
1.5.2.4.3. Chiral pool	16
1.5.2.4.4. Chiral auxiliary	16
1.5.2.4.5. Asymmetric catalysis- Transition metal catalyzed	17
1.6. Organic photoredox catalysts	20

1.6.1.	DCA	20
1.6.2.	Benzophenone	21
1.6.3.	Quinones	21
1.6.4.	Acridinium dyes	23
1.6.5.	Cyanobenzene derived photocatalyst	24
1.6.6.	Pyryliums and thiapyryliums	25
1.6.7.	Xanthene dye	26
1.6.7.1	Eosin Y	27
1.7.	Overview of the thesis	28
1.7.1	Visible light mediated alkylation from carboxylic acid-access to 4-alkyl-amino-4H-chromene	29
1.7.2	Visible-light induced metal-free selenylation of Tryptamines/3-methylindoles	29
1.7.3	Visible light driven an unprecedented site-selective trifluoromethylation/ perfluoroalkylation <i>via</i> C-H activation of benzocore of aryl/alkylidene malononitrile and Coumarins	29
1.7.4	Photoinduced stereoselective C - C bond formation	30
1.8	References	32
Chapter 2. Visible light mediated alkylation from carboxylic acid-access to 4-alkyl-amino-4H-chromene		
2.1.	Introduction	36
2.2.	Result and discussions	40
2.3.	Conclusion	44
2.4.	General information	45
2.5.	Preparation of starting material	45
2.5.1.	Preparation of 2-iminochromenes (102a – 102l)	45
2.5.2.	Preparation of aliphatic carboxylic acid	46
2.6.	Mechanistic Investigation	47
2.6.1.	Fluorescence titration of photocatalyst	47
2.6.2.	UV- Vis studies	48
2.6.3.	Cyclic voltammetry (CV) experiments	49
2.7.	General procedure of the alkylation of 2-iminochromenes	50
2.8.	Representative ¹ H NMR and ¹³ C NMR spectra	57
2.9.	Crystallographic data	69
2.10.	References	71
Chapter 3. Visible-light-induced metal free selenation of Tryptamines/3-substituted indoles		
3.1.	Introduction	74
3.2.	Result and discussion	76
3.3.	General information	82
3.4.	Preparation of substrate	
3.4.1.	Preparation of substituted tryptamine derivatives	83
3.4.2.	General procedure for the Cbz protection of tryptamines	83

3.4.3.	General procedure of synthesis of 3-substituted indole (119h – 119g)	84
3.4.4.	General procedure of synthesis of 3-substituted indole (119k – 119l)	85
3.4.5.	General procedure of synthesis of aryl diselenide (120a – 121e)	87
3.4.6.	General procedure of synthesis of alkyl diselenide (120f)	88
3.5.	Visible-light induced metal-free selenation of Tryptamines: general procedure	88
3.6.	Mechanistic investigation	
3.6.1.	UV-Visible studies	95
3.6.2.	Fluorescence quenching study	96
3.7.	Plausible mechanism	97
3.8.	Crystallography data	98
3.9.	Representative ¹ H NMR, ¹³ C and ⁷⁷ Se NMR Spectra	100
3.10	References	111
Chapter 4a. Site selective trifluoromethylation and perfluoroalkylation of aromatic ring of alkylidene malononitrile/heteroarenes		
4.1.	Introduction	114
4.2.	Result and discussions	118
4.3.	Mechanistic studies	124
4.4.	Conclusion	129
4.5.	General information	129
4.6.	Experimental studies	129
4.6.1.	Preparation of substrates	129
4.6.1.1	Preparation of aryl/alkylidene malononitriles	129
4.6.1.2.	With respect to perfluoroalkanesulfinates	137
4.6.2.	General experimental procedures and analytical data for 133 .	138
4.6.2.1.	General procedures for the synthesis of 133 .	138
4.6.2.2.	Analytical data for products	138
4.6.3.	General experimental procedures for the preparation of 134 .	158
4.6.3.1.	Analytical data for products	159
4.6.4.	General procedure for preparation of thiophene core	165
4.6.5.	General procedure for alkylidene reduction (133-b)	166
4.6.6.	Synthesis of 4-trifluoromethyl propiophenone	166
4.6.7.	General procedure of vinylogous annulation cascade reaction	167
4.7.	4.7.1. Radical trapping experiments	168
	4.7.2. Kinetic isotope effect experiment	170
	4.7.3 Fluorescence titration of photocatalyst	173
	4.7.4. UV- Visible studies	175
	4.7.5. <i>In-situ</i> IR studies	176
	4.7.6. Cyclic voltammetry (CV) experiments	177
	4.7.7. Cross over/competitive experiment	178

4.8.	Computational details	180
4.8.1.	Calculation of single electron transfer steps by Marcus-Hush theory	180
4.8.2.	Schemes of computed reaction pathways	181
4.8.3.	Computed energies of all stationary points	182
4.9.	Sunlight-driven experiment	183
4.10.	Crystallographic data	184
4.11.	Representative ^1H NMR, ^{13}C and ^{19}F NMR Spectra	188
4.12.	References	200
Chapter 4b. Polar-effect-directed control in site-selectivity of radical substitution enables C-H perfluoroalkylation of coumarins		
4b.1.	Introduction	204
4b.2.	Result and discussion	207
4b.3.	General information	213
4b.4.	Preparation of starting materials	214
4b.4.1.	Preparation of coumarins	214
4b.4.2.	Preparation of 3, 4-disubstituted cyanocoumarins	214
4b.4.3.	Preparation of 3-cyanocoumarins	214
4b.4.4.	Analytical data of products	217
4b.4.5.	Preparation of perfluoroalkanesulfonates	220
4b.5.	General experimental procedures for the preparation of 142	221
4b.5.1.	Analytical data	221
4b.6.	General procedures for the synthesis of 144	240
4b.7.	Sunlight-driven experiment	243
4b.8.	Mechanistic investigation	244
4b.8.1.	Fluorescence titration of photocatalyst	244
4b.8.2.	Electron paramagnetic resonance (EPR) analysis	245
4b.8.3.	In-situ IR studies	247
4b.9.	Crystallographic data	247
4b.10.	Representative ^1H NMR, ^{13}C and ^{19}F NMR Spectra	253
4b.11.	References	272
Chapter 5a. Visible light mediated diastereoselective decarboxylative alkylation of Coumarins		
5a.1.	Introduction	275
5a.2.	Result and discussion	281
5a.3.	Conclusion	285
5a.4.	General information	286
5a.5.	Preparation of starting materials	286
5a.5.1.	Preparation of coumarins	286
5a.5.1.1.	Preparation of 172b	287
5a.5.2.	Preparation of <i>N</i> -(Acyloxy)phthalimides- 145	287
5a.6.	General methods for diastereoselective decarboxylative alkylation of coumarins.	288

5a.7.	Fluorescence titration of photocatalyst	292
5a.8	Representative ^1H NMR and ^{13}C NMR spectra	296
5a.9.	References	304
Chapter 5b. Visible light mediated enantioselective alkylation using deaminative approach-access to unnatural amino acids		
5b.1.	Introduction	307
5b.2.	Result and discussion	314
5b.3.	Conclusion	318
5b.4.	General information	318
5b.5.	Preparation of starting material	319
5b.5.1.	Preparation of 8-qminoquinoline derivatives (190)	319
5b.5.2.	Preparation of Katritzky salts (174)	319
5b.6.	General methods for enantioselective deaminative reaction	320
5b.6.1.	Analytical data	320
5b.7.	Mechanistic studies	349
5b.8.	Representative ^1H NMR and ^{13}C NMR Spectra	351
5b.9.	References	360
	Biodata	362

List of Figures

Figure No.	Figure Caption	Page No.
1.1	Electromagnetic spectrum- wavelength of visible light spectrum	3
1.2	Papers published per year in the field of photocatalysis and photoredox as well (Bar graph), Branches of science working in the field of photocatalysis (Pie Chart).	4
1.3	Energy levels of a typical organic molecule/transition metal complexes and the photophysical processes- Jablonski Diagram	4
1.4	Mechanistic schemes for photoredox catalysis	7
1.5	Representative mechanism of EDA complex	9
1.6	Reductive quenching cycle. [cat] – photocatalyst, [cat]* – photocatalyst in excited state, [sub] – substrate, [red] – reductant, [ox] – oxidant	10
1.7	Oxidative quenching cycle. [cat] – photocatalyst, [cat]* – photocatalyst in excited state, [sub] – substrate, [red] – reductant, [ox] – oxidant.	11
1.8	Molecular orbital diagram: Jablonski diagrams for $[\text{Ru}(\text{bpy})_3]^{2+}$	12
1.9	Mechanistic pathway of Cu(I) complex	13
1.10	Mechanistic pathway of Cu(II) complex	13
1.11	Cooperative dual photoredox catalysis	14
1.12	Non- superimposable image of human hand (Concept of chirality)	15
1.13	Representative chiral auxiliaries for asymmetric induction	16
1.14	Representative chiral ligands for asymmetric induction	17
1.15	Representation of mode of catalysis	18
1.16	Mechanistic pathway of chiral Cu-ligand complex	19
1.17	Representative examples of cyanoarenes based photocatalysts	20
1.18	Representative examples of Acridinium dyes	23
1.19	Representative cyanobenzene photocatalysts	25
1.20	Representative examples of xanthine dyes	27
1.21	Photophysical mechanistic pathways of Eosin-Y dye	28
2.1	Representative natural products with 4H-chromene	39
2.2	Fluorescence response of $[\text{Mes-Acr-Me}^+]\text{BF}_4^-$ upon successive addition of 109e and 102a (1 mM in MeCN)	48
2.3	Stern Volmer plot for 109e and 102a	48
2.4	UV-Visible studies spectrum	49
2.5	Cyclic voltametric spectrum	49
2.6	ORTEP structure of compound 110f	69
2.7	Single crystal X-ray structure of compound 110f	70
3.1	Biologically relevant organoselenium scaffolds	74

3.2	Fluorescence response of NH-Cbz tryptamine upon successive addition of diphenyl diselenide	80
3.3	Cyclic voltammetry experiment for 119i .	81
3.4	Absorption spectra of NHCbz-tryptamine 119a , diphenyl diselenide 120a and their complexes with diphenyl phosphate in light in MeOH.	95
3.5	Absorption spectra of NHCbz-tryptamine 1a (119a) -diphenyl phosphate at different interval of time of irradiation with blue light.	95
3.6	Absorption spectra of 1a(119a) , diphenyl diselenide 2a(120a) and diphenyl phosphate at different interval of time of irradiation with blue light.	96
3.7	Absorption spectra of diphenyl diselenide 2a(120a) and diphenyl phosphate at different interval of time of irradiation with blue light	96
3.8	Fluorescence response of NHCbz tryptamine upon successive addition of diphenyl phosphate.	97
3.9	ORTEP structure of compound 121d	98
3.10	Single Crystal X-ray structure of compound 121d	99
4.1	Biological relevant trifluoromethylated scaffolds	114
4.2	Computational studies on the reaction mechanism (in kcal mol ⁻¹).	126
4.3	Design plan for site selective trifluoromethylation. Hypothesis of the mechanism for photoinduced site selective alkylation	128
4.4	GC-MS Spectra for diphenylethene	169
4.5	GC-MS Spectra for BHT	169
4.6	GC-MS Spectra for radical clock	169
4.7	¹ H NMR of [D5]- 130b	171
4.8	EPR spectra at immediately and after 7 min at 77 K	173
4.9	EPR spectra after trapping with nitron at 7 and 20 minutes at 77 K	173
4.10	Fluorescence quenching experiments with (NH ₄) ₂ S ₂ O ₈ and Stern-Volmer plots of (NH ₄) ₂ S ₂ O ₈	174
4.11	Fluorescence quenching experiments with CF ₃ SO ₂ Na and Stern-Volmer quenching of Eosin-Y with CF ₃ SO ₂ Na	174
4.12	Fluorescence quenching experiments with (130b = 1a) and Stern-Volmer quenching of Eosin-Y with 130b	174
4.13	UV Spectra	175
4.14	<i>In-situ</i> FTIR studies for the detection of SO ₂ and monitoring the reaction pathway.	176
4.15	(a) Reduction Range for 130b and (b) Oxidation Range for 130b	177
4.16	Calculated photocatalytic reaction pathway; energies in kcal/mol	181
4.17	Single crystal X-ray structure of compound 133c	186
4.18	Single crystal X-ray structure of compound 133zr	187
4b.1	Biological relevant C-7 substituted coumarins	204
4b.2	Time dependent EPR analysis of standard solution	246
4b.3	EPR analysis of nitron solution and time dependent EPR analysis of nitron solution	247

4b.4	Single crystal X-ray structure of compound 142a	249
4b.5	Single crystal X-ray structure of compound 142zd	250
4b.6	Single crystal X-ray structure of compound 144a	252
5a.1	Some examples of biologically active coumarin derivatives	278
5a.2	(a) Fluorescence quenching with DIPEA (b) Stern-Volmer of DIPEA	284
5a.3	Plausible mechanism	285
5a.4	Fluorescence quenching experiments with DIPEA	293
5a.5	Stern-Volmer plot with DIPEA	293
5a.6	Fluorescence quenching experiments with 172b	294
5a.7	Stern-Volmer plot with 172b .	294
5a.8	Fluorescence quenching experiments with 145c	295
5a.9	Stern Volmer plot with 145c .	295
5b.1	Representative chiral biological relevant 8-aminoquinoline scaffolds.	311
5b.2.	UV-Visible spectra	348
5b.3.	Fluorescence quenching experiment with 174c	349
5b.4.	Stern Volmer plot with 174c	350

List of Tables

Table No.	Table Caption	Page No.
2..1	Selected optimization reaction condition results	40
2.2	Scope of decarboxylative C-4 alkylation of 2-iminochromene with various secondary and tertiary carboxylic acid	41
2.3.	Scope of decarboxylative C-4 alkylation of substituted 2-iminochromene with cyclohexane carboxylic acid	42
2.4	Starting material (2-iminochromenes Scope)	46
2.5	Starting material (Acid Scope)	47
2.6	Crystal data and structure refinement for 110f	70
3.1	Optimization of C-H selenation with NHCbz-Tryptamine (119a) with diphenyldiselenide (120a)	77
3.2	Substrate scope for C-H selenation	78
3.3	Crystal data and structure refinement for 121d	99
4.1	Optimization of reaction condition	118
4.2	Scope of alkyl substituents	119
4.3	Scope with electron deficient and electron rich arenes	120
4.4	Scope with electron deficient and electron rich chalcone derivatives	122
4.5	Scope of heteroarene trifluoromethylation/perfluoroalkylation	123
4.6	Calculated Energies of SET processes.	181
4.7	Calculated Energies of all Stationary Points for Reaction Pathways.	182
4.8	Crystal data and structure refinement for 133c	184
4.9	Crystal data and structure refinement for 133zr	186
4b.1	Optimization of reaction condition	207
4b.2	Scope of C-7 alkylation of C-4 substituted coumarins with Langlois reagent	208
4b.3	Scope of benzocore trifluoromethylation of 3-cyano-coumarins with Langlois reagent	210
4b.4	Preparation of solution	244
4b.5	Crystal data and structure refinement for 142a	248
4b.6	Crystal data and structure refinement for 142zd	249
4b.7	Crystal data and structure refinement for 144a	251
5a.1	Optimization table	282
5a.2	Scope of diastereoselective decarboxylative C-4 alkylation of chiral coumarin-3 carboxylate having chiral auxiliary with secondary and tertiary carboxylic acid derived NHPI esters	283
5b.1	Optimization of reaction condition	312
5b.2	Scope of enantioselective alkylation	313
5b.2	Scope of enantioselective alkylation	314

List of Schemes

Scheme No.	Scheme Caption	Page No.
1.1	General equation for redox potential for excited state	6
1.2	Rehm Weller equation	7
1.3	Commonly used HAT catalyst	8
1.4	Reaction mechanism involving a direct HAT approach in photo redox chemistry	8
1.5	HAT mediated photoinduced organic transformation	9
1.6	Enantioselective C– N bond formation <i>via</i> chiral copper complex.	19
1.7	Photoinduced cooperative iridium and copper mediated alkylation	20
1.8	Representative examples of DCA catalysed organic transformation	21
1.9	Photoinduced benzophenone catalysed 1,4 addition reaction	21
1.10	Plausible mechanism for hydrogen abstraction mediated by AQ	22
1.11	Photoinduced DDQ mediated hydroxylation of benzene and halobenzenes	23
1.12	Application of acridinium photocatalyst in organic synthesis	24
1.13	Synthesis of 4-CzIPN photocatalyst	24
1.14	Photoinduced hydroxylation using 4CzIPN	25
1.15	Photoinduced cyclodimerization <i>via</i> pyrylium photocatalyst	26
1.16	Photoinduced Diels Alder reaction mediated by TPT ⁺	26
1.17	Photoinduced Newman-Kwart rearrangement	26
1.18	Application of Eosin-Y in organic transformation	28
1.19	Visible light mediated C-4 alkylation of 2-iminochromene	29
1.20	Visible light mediated C-2 selenylation of tryptamines/3 alkyl indoles	29
1.21	Site selective trifluoro/perfluoroalkylation of benzocore of aryl/alkylidene malononitrile	30
1.22	Site selective trifluoro/perfluoroalkylation of benzocore of coumarins	30

1.23	Visible light mediated diastereoselective decarboxylative alkylation of coumarins	31
1.24	Visible light mediated enantioselective deaminative C(sp ³ -H) alkylation	31
2.1	Anti-Markovnikov hydroetherification of alkenols	36
2.2	Photocatalytic decarboxylative reduction of carboxylic acid	36
2.3	Intermolecular photocatalytic alkylation of imines	37
2.4	Radical addition of alkyl trifluoroborate to imines	37
2.5.	Decarboxylative benzylation of imines with aryl acetic acids	38
2.6	Photoinduced difluoromethylation of imines	38
2.7	Visible light induced HAT mediated alkylation of imines	38
2.8	Conjugate addition of nitroalkanes to 2-iminochromenes	39
2.9	Vinylogous addition of β,γ -unsaturated butenolide to 2-iminochromenes	39
2.10	Radical trapping experiments	43
2.11	Plausible mechanism	44
3.1	Photoinduced aerobic selenation of (hetero)arenes with diselenides	75
3.2	Visible light mediated Rose bengal catalysed selenylation	75
3.3	Electrochemical selenylation	75
3.4	Reaction of tryptophan derivative with phenylselenanyl bromide	76
3.5	Iodide-catalyzed oxidative 2-selenylation of tryptophan	76
3.6	C-2 selenylation of tryptamine in sunlight	79
3.7	Mechanistic investigation	80
3.8	Representative tryptamines derivatives/3-substituted indoles	83
3.9	Representative aryl/alkyl diselenides	87
3.10	Plausible mechanism for NH-Cbz Tryptamine/3 alkyl indoles.	97
4.1	Radical trifluoromethylation of arenes and heteroarenes <i>via</i> photoredox catalysis	114
4.2	Photochemical decarboxylation of trifluoroacetate	115
4.3	Electro-photo chemical trifluoromethylation of arenes	115
4.4	<i>para</i> -Selective trifluoromethylation of benzamide <i>via</i> iminium intermediate	115

4.5	Copper catalysed ortho-trifluoromethylation of arenes	116
4.6	Photochemical aromatic perfluoroalkylation of α -cyano arylacetates	116
4.7	Heterogenous catalyst mediated trifluoromethylation of aminoquinolines	116
4.8	Visible light mediates trifluoromethylation of arenes	117
4.9	Direct hydrogen atom transfer catalysis for olefinic alkylation	117
4.10	Metal free perfluoroalkyl BCP derivatization	118
4.11	Mechanistic investigation for the trifluoromethylation	125
4.12	Synthetic Application: A : Reduction of double bond. B : Converted to ketone. C . Synthesis of thiophene ring. D . Vinylogous annulation cascade for synthesis of highly functionalized indanone	127
4.13	Preparation of alkylidene malononitrile	130
4.14	Synthesis of (E)-2-(1,3-Diarylallylidene)malononitriles	130
4.15	Preparation of perfluoroalkanesulfinates	137
4.16	Preparation of trifluoromethylated alkylidene malononitrile	138
4.17	Preparation of trifluoromethylated/perfluoroalkylated heteroarenes	158
4.18	Crossover/competitive experiments with para-substituted alkylidene-malononitrile	178
4.19	Preparation of trifluoromethylated alkylidene malononitrile in sunlight	183
4b.1	Copper mediated trifluoromethylation using Togni reagent	204
4b.2	Trifluoromethylation using $\text{CF}_3\text{SO}_2\text{Cl}$ to generate 3-trifluoromethyl coumarins	205
4b.3	$\text{Ru}[(\text{DNM})_2\text{bpy}]_3^{2+}$ photocatalyzed trifluoromethylation of coumarin	205
4b.4	Trifluoromethylation of coumarins with Togni reagent	205
4b.5	Manganese (III)-mediated direct radical trifluoromethylation of coumarins	206
4b.6	Trifluoromethylation of coumarins in a continuous-flow reactor	206
4b.7	Electrochemical trifluoromethylation of coumarins	206
4b.8	Mechanistic investigation for the C-7 trifluoromethylation of coumarins	211
4b.9	Plausible mechanism	212

4b.10	Preparation of perfluoroalkanesulfonates	220
4b.11	Trifluoromethylation of 3 cyano-4 ethyl coumarin in sunlight	243
4b.12	General procedure for EPR study	245
4b.13	General procedure for EPR study with nitron	246
5a.1	Radical generation from <i>N</i> -(acyloxy)-phthalimide esters and acids	275
5a.2	Alkylation of styrene from <i>N</i> -(acyloxy)-phthalimide esters	276
5a.3	Oxyalkylation of styrene with <i>N</i> -(acyloxy)-phthalimide esters	276
5a.4	Visible light mediated decarboxylative alkylation of 2-pyridone derivatives	276
5a.5	Photoinduced C–H alkylation of azauracils with <i>N</i> -(acyloxy)phthalimides	277
5a.6	Photoinduced C–H alkylation of heterocyclic N-oxide with <i>N</i> -(acyloxy)phthalimides	277
5a.7	Heck coupling of coumarins with acrylates	278
5a.8	Dehydrogenative arylation of coumarins	279
5a.9	Cu(OAc) ₂ catalyzed benzylation of coumarins	279
5a.10	C-3 alkylation of coumarins with aliphatic acids	279
5a.11	Metal free C-4 alkylation of coumarins	280
5a.12	Di-functionalization of coumarins	280
5a.13	C-3 alkylation of coumarins	280
5a.14	Photoinduced C-4 alkylation of C-3 substituted coumarins	281
5a.15	Control experiment	285
5a.16	Synthesis of (1 <i>R</i> ,2 <i>S</i> ,5 <i>R</i>)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-oxo-2 <i>H</i> -chromene-3-carboxylate	287
5b.1	Deaminative alkyl-alkyl coupling	307
5b.2	Photoinduced deaminative C–H alkylation of isoquinoline	308
5b.3	Synthesis and reduction of alkylpyridinium salt through SET	308
5b.4	Catalytic photochemical enantioselective α -alkylation with pyridinium salts	309
5b.5	Visible light induced copper-catalyzed enantioselective deaminative arylation of amino acid derivatives assisted by phenol	309
5b.6	Dual photoredox and copper catalysis: enantioselective 1,2-amidocyanation of 1,3-dienes	310
5b.7	Enantioselective deaminative alkylation of aminoacids	310

5b.8	Photoinduced enantioselective deaminative alkylation	311
5b.9	(A–F) Mechanistic investigation for the enantioselective deaminative alkylation	316
5b.10	Plausible mechanism	317

List of Abbreviations

Abbreviation	Full form
Ar	Aryl
Ag	Silver
ACN	Acetonitrile
Bn	Benzyl
Boc	<i>tert</i> -butyloxycarbonyl
^t Bu	<i>tert</i> -Butyl
BHT	Butylated hydroxytoluene
BuLi	n-Butyllithium
BCP	Bicyclo[1.1.1]pentanes
Cbz	Benzyloxycarbonyl
CDCl ₃	Deuterated chloroform
cm ⁻¹	Wavenumbers
°C	Degrees Celsius
Cu(OAc) ₂	Copper acetate
CuCl	Copper chloride
Cs ₂ CO ₃	Cesium carbonate
CH ₃ ONa	Sodium methoxide
CsF	Cesium fluoride
CF ₃ SO ₂ Na	Langlois reagent
CV	Cyclic Voltammetric
DCM	Dichloromethane
DFT	Density functional theory
DIPEA	<i>N,N</i> -diisopropylethylamine
DMA	Dimethylacetamide
DMAP	<i>N,N</i> -Dimethylpyridin-4-amine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene

d	Doublet
dr	Diastereomeric ratio
dd	Doublet of doublets
DPP	Diphenylphosphate
d ₆ -DMSO	Deuterated dimethyl sulfoxide
δ	Chemical shift
<i>ee</i>	Enantiomeric excess
EDA	Electron-donor acceptor
ESI-TOF	Electrospray ionization - Time-of-flight
EtOAc	Ethyl acetate
EtOH	Ethanol
FTIR	Fourier transform infrared
GS-MS	Gas Chromatography-Mass Spectrometry
H ₂ O	Water
HFIP	Hexafluoroisopropanol
HRMS	High resolution mass spectrometry
h	Hour
<i>J</i>	Coupling constant
λ	Wavelength
K ₂ CO ₃	Potassium carbonate
KF	Potassium fluoride
KOH	Potassium hydroxide
K ₃ PO ₄	Potassium phosphate
KO ^t Bu	Potassium <i>tert</i> -butoxide
KOAc	Potassium acetate
LDA	Lithium diisopropylamide
LED	Light-emitting diode
LiCl	Lithium chloride
LiHMDS	Lithium bis(trimethylsilyl)amide
Mes-Acr-Me ⁺	9-Mesityl-10-methylacridinium tetrafluoroborate
min	Minute
MTBE	Methyl <i>tert</i> -butyl ether
m	Multiplet

MBH	Morita-Baylis-Hillman
MHz	Megahertz
mL	Millilitre
μL	Microlitre
NH_4OAc	Ammonium acetate
NaHCO_3	Sodium hydrogen carbonate
PC	Photocatalyst
s	Singlet
SET	Single electron transfer
Na_2CO_3	Sodium carbonate
rt	Room temperature
NaO^tBu	Sodium <i>tert</i> -butoxide
NaH	Sodium hydride
TBHP	<i>tert</i> -butyl hydroperoxide
TBAF	Tetra- <i>N</i> -butylammonium fluoride
TFA	Trifluoroacetic acid
TFSP	Trifluoromethylsulfonyl pyridinium
TFFA	Trifluoroacetic anhydride
$^t\text{BuOH}$	<i>tert</i> -Butyl alcohol
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
UV	Ultraviolet