Photo-Induced Oxidative Coupling *via* C-H/S-H Functionalization

Thesis submitted in the partial fulfillment for the

Award of Degree

DOCTOR OF PHILOSOPHY

By

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It is certified that the work contained in the thesis titled ***"Photo-Induced Oxidative Coupling via C-H/S-H Functionalization"*** by ***"Ambuj Kumar Kushwaha"*** has been carried out under my supervision, and this work has not been submitted elsewhere for a degree.

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Dedicated to my loving family…

DECLARATION BY THE CANDIDATE

I, ***"Ambuj Kumar Kushwaha"*** certify that the work embodied in this thesis is my own bonafide work and was carried out by me under the supervision of ***"Dr. (Mrs.) Sundaram Singh"*** from ***"July 2019"*** to ***"2024"*** at the ***"Department of Chemistry,"*** Indian Institute of Technology, Banaras Hindu University, Varanasi. The matter embodied in this thesis has not been submitted for any other degree/diploma award. I declare that I have faithfully acknowledged and given credits to the research workers wherever their works have been cited in my work in this thesis. I further declare that I have not willfully copied any other's work, paragraphs, text, data, results, etc., reported in journals, books, magazines, reports, dissertations, theses, etc., or available at websites and have not included them in this thesis and have not cited as my own work.

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It is certified that the above statement made by the student is correct to the best of my knowledge.

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Ambuj Kumar.

Date: 17-05-2024

Ambuj Kumar Kushwaha

Research Scholar

List of Notations, Symbols and Abbreviations

Notations	**Abbreviations**
%	Percentage
<	Less than
>	More than
°	Degree
Å	Angstrom
Ac	Acetyl
Ac_2O	Acetic anhydride
AcOH	Acetic acid
Bas	Barbituric acids
BHT	Butylatedhydroxytoluene
Bn	Benzyl
Bz	Benzoyl group
brs	Broad singlet
Obser.	Observed
Calc.	Calculated
Conc.	Concentration
©	Copyright
$CHCl_3$	Chloroform
CH_3COOH	Acetic acid
CD_3OD	Methanol-d_4
$CDCl_3$	Deuterated chloroform
cm	Centimeter
J	Coupling constant
DMF	Dimethylformamide
DMSO-d_6	Deuterated dimethyl sulfoxide
D_2O	Deuterated water
ºC	Degree Celsius
d	Doublet
DCE	Dichloroethane
DCM	Dichloromethane

dd	Doublet of doublet
ddd	Doublet of doublet of doublet
ddt	Doublet of doublet of triplet
DMSO	Dimethyl sulfoxide
dq	Doublet of quartet
dt	Doublet of triplet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DABCO	1,4-Diazabicyclo[2.2.2]octane
DPA	Diphenylamine
E^0	Standard electrode potential
equiv.	Equivalent
EtOH	Ethanol
EtOAc	Ethyl acetate
EDG	Electron donating group
EWG	Electron withdrawing group
EY	Eosin Y
EY*	Excited eosin Y
$EY^{\cdot -}$	Eosin Y radical anion
$EY^{\cdot +}$	Eosin Y radical cation
g	Gram; Gravitational force
h	Hour
H_2DEBA	Diethylbarbituric acid
H_2O_2	Hydrogen peroxide
HAT	Hydrogen atom transfer
HRMS	High-resolution mass spectroscopy
Hz	Hertz
IR	Infra-Red
J	Coupling constant
$KMnO_4$	Potassium permanganate
KOH	Potassium hydroxide
LED	Light emitting diode
LDA	Lithium diisopropylamide
m	Multiplet
M	Molar

MB	Methylene blue
MeCN	Acetonitrile
MeOH	Methanol
mg	Milligram
MHz	Megahertz
min	Minute
mL	Milliliter
mm	Millimeter
mmol	Millimole
µm	Micrometer
mol%	Mole percentage
m.p.	Melting point
m/z	Mass by charge ratio
nm	Nanometer
NMR	Nuclear Magnetic Resonance
n-BuLi	*n*-Butyllithium
PC	Photocatalyst
pH	Potential of hydrogen
ppm	Parts per million
RHAT	Reverse hydrogen atom transfer
rt	Room temperature
S	Singlet
SET	Single electron transfer
SCE	Standard calomel electrode
t-Bu	Tertiary butyl
TBHP	*tert*–Butylhydroperoxide
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxidanyl
THF	Tetrahydrofuran
TLC	Thin-Layer Chromatography
TMS	Tetramethylsilane
UV	Ultraviolet
W	Watt
XRD	X-ray Diffraction

α	Alpha
β	Beta
γ	Gamma
δ	Chemical shift
ϕ	Quantum yield
[ox]	Oxidation
R_f	Refractive Index
i.e.	that is
o	Ortho
m	Meta
p	Para
et. al.	et alia, Latin for “and others”
i.e.	that is
e.g.	Example
equiv.	Equivalents

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General Experimental Considerations

All the chemicals were procured from Aldrich, USA, TCI Chemicals, Japan, and E. Merck, Germany, and were employed without undergoing any additional purification. The solvents were purchased from Merck, India, and Ranbaxy, India, and were purified before their use. The preparation and particulars of the substrates employed for the work undertaken are given in their respective chapters.

Melting points were measured using Stuart Melting point apparatus SPM10 in open capillary tubes and are uncorrected. **UV-visible spectroscopy** of the reaction solution was recorded on a SHIMADZU UV-3600 UV-visible spectrophotometer.

The **^{1}H** (500 MHz), **^{13}C** (126 MHz), and **^{19}F** (471 MHz) **NMR** spectra were run on a Bruker Advance 500 MHz FT-NMR at 500 MHz spectrometers. Chemical shifts are given in δ ppm, using tetramethylsilane (TMS) as an internal standard in DMSO-d_6 and $CDCl_3$.

HRMS (m/z) were recorded in an electron ionization or electrospray ionization (ESI) mode on Waters-Q-TOF Premier-HAB213 and Sciex X500R QTOF instruments. The names of all products were generated using the PerkinElmer ChemBioDraw Ultra v.16.0.1.4 software package.

Thin-layer Chromatography (TLC) was performed on glass plates (7.5 × 2.5 and 7.5 × 5.0 cm) coated with Merck silica gel GF 254 using various combinations of ethyl acetate and n-hexane as an eluent. Visualization of spots was accomplished either in an iodine chamber or by exposure to UV light. Merck silica gel (100-200 mesh) was used for column chromatography (approximately 15-20 g per 1 g of the crude product).

The **Single Crystal XRD** of the products was determined by X-ray crystallography (Rigaku XtaLAB Synergy-I). The **Quantum yield** was recorded on a PerkinElmer LS 55 Fluorescence spectrometer.

Experimental setup

The light source used for photochemical synthesis in all the protocols was a blue LED strip (Aldrich® Micro Photochemical Reactor,) with 60 LEDs that is 280 cm long. The blue light's anticipated wavelength ranges from 390 to 490 nm. A fan was employed to cool the reactor (the reaction temperature within the reaction vessel was measured to be between 25-30˚C). The reaction tubes were positioned 5–6 cm from the blue LED strip.

Preface

The main goal of this thesis is to design new synthetic methods for oxidative coupling utilizing visible light as a clean, eco-friendly, and renewable source of energy. Visible light photons are a traceless source of energy that carry out the reaction, along with enhanced atom economy and green catalysis. The field of photoredox catalysis for C-H/S-H bond functionalization is rapidly expanding and has emerged as one of the extensively investigated areas for the synthetic chemists. This thesis work focuses on developing novel photo-induced oxidative coupling methodologies for organic transformations via C-H/S-H functionalization in distinct ways.

The effective synthetic strategies for C-H/S-H functionalization are embodied in the thesis titled **" Photo-Induced Oxidative Coupling via C-H/S-H Functionalization ".**

Chapter 1 provides the significance of visible light in photochemical reactions, its mechanisms, and several oxidative coupling reactions facilitated by photo-induced C-H/S-H functionalization.

Chapter 2 will describe the visible-light-absorbing C–N cross-coupling for the synthesis of hydrazones involving $C(sp^2)$–H/$C(sp^3)$–H functionalization. **Chapter 3** will disclose visible-light-initiated oxidative coupling of indole and active methylene compounds using eosin Y as a photocatalyst. **Chapter 4** will highlight photoinduced, metal-free hydroacylation of aromatic alkynes for the synthesis of α,β-unsaturated ketones via $C(sp^3)$−H functionalization. **Chapter 5** will present a metal-free photoredox catalyzed sulfonylation of phenylhydrazines with thiols. **Chapter 6** will summarize and conclude the total thesis work.

LIST OF SCHEMES