1
Introduction

1.1 Visible Light in Organic Synthesis

Light, which behaves as electromagnetic waves, is generated by the interaction of electric and magnetic fields traveling through space. Electromagnetic radiation's frequency determines the specific energy quantities carried by photons, which are discrete packets of energy.[1] The energies of a photon can be expressed using a mathematical formula:

$$E = h\nu \quad \text{---------- (1)}$$

E = Energy, h = Planck's constant, and ν = frequency of the light.

Being more specific and focusing on a photon energy correlation, this equation shows the dependence of the energy of a photon with frequency and with a certain wavelength. For electronic transitions, electrons normally in their ground state level can be raised to a higher energy level, more commonly called the excited state, when molecules absorb photons.[2] This process is crucial in photochemistry and occurs when the photon's absorbed energy precisely matches the energy gap between a molecule's ground and excited states.[3] The equality of these energy levels is also a condition for the transition, ensuring that the molecule effectively absorbs and uses the energy of photon carries to reach its excited state. Many photochemical reactions depend on this concept, so without it, there would not be a clear way to understand how chemical processes can be brought about by light.

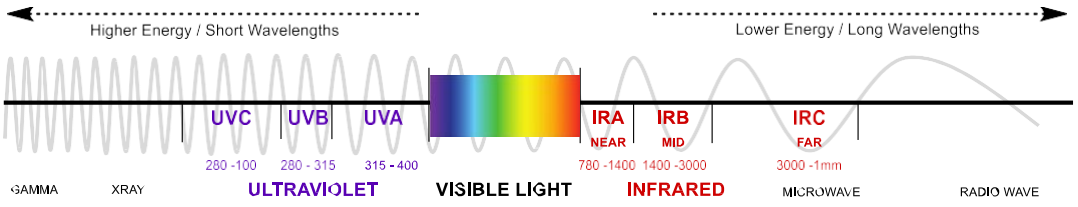


Figure 1.1 Spectrum of Electromagnetic Waves.

A relatively low-energy photon in light is responsible for a small portion of the electromagnetic spectrum.[1] However, the most significant region, which covers the necessary 400-700 nm wavelength, is of utmost importance in photochemistry, as it drives several light-induced chemical processes (Figure 1.1). These include fundamental processes such as photosynthesis,[4] Which is most important for driving life on Earth and uses visible light. Equally important is the isomerization of retinol in the visual cycle,[5] and the conversion of vitamin D from cholesterol in the skin,[6] Which is also induced by the visible or near ultraviolet region. Somehow, nature tends to use that energy carried by uniquely precise wavelengths.

Given the ubiquity of visible light, it can be viewed as a rich energy source for driving chemical transformations. Due to its widespread availability, visible light has become a subject of particular interest in contemporary photochemical studies. To understand catalysis, let's first explore the photophysical properties of any light-mediated reactions. The way photocatalysts mimic energy conversion strategies from nature has provided a platform for designing many

new reactions, including C–H functionalization, cross-coupling, cyclization, and radical-based transformations.[7] Light-mediated processes change modern organic synthesis by providing environmentally friendly alternatives to traditional chemical methods. Excited-state energy structure and kinetic factors driving the photochemical processes establish the photochemical behavior of organic compounds. Simplified energy diagrams provide a conceptual basis for explaining the trends and reactivity that involve photoredox catalysts, as shown in (Figure 1.2), helping to rationalize these reactions.[8]

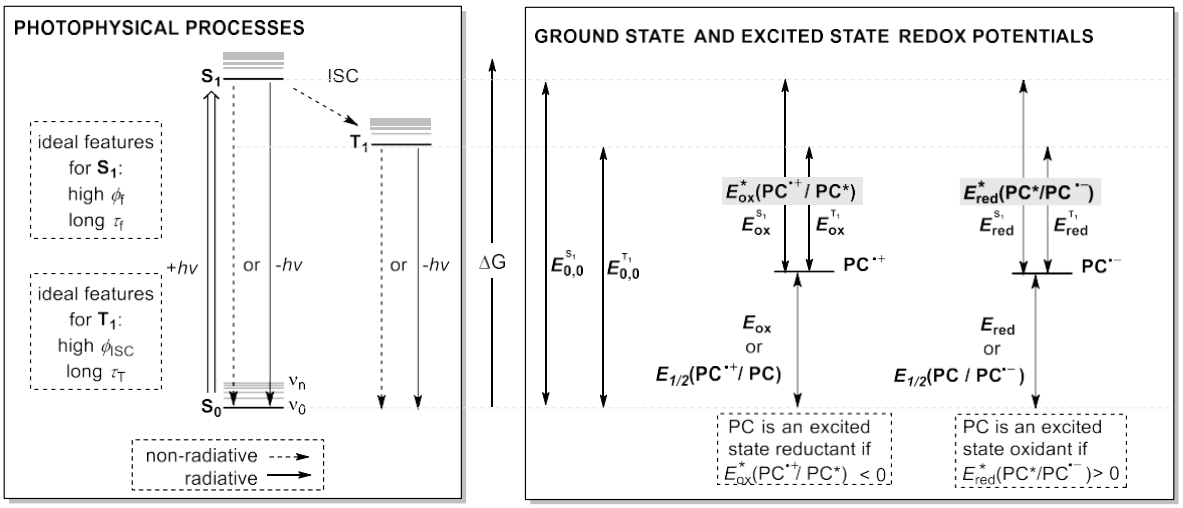


Figure 1.2 Photophysical Process of Photoredox Catalysts.

The absorption of light (indicated by +hυ) by a photocatalyst (**PC**) triggers its transition to an electronically excited state. Typically, this occurrence involves the transfer of an electron from its ground-state singlet (S_0) to an elevated singlet energy level. The wavelength of the absorbed light influences which of the various singlet excited states the **PC*** may inhabit, with these states exhibiting distinct vibrational energy characteristics. These excited states have pulses of high energy that relax within picoseconds to the lowest energy, vibrationally stabilized singlet excited state, S_1. After S_1, several photophysical pathways may occur (radiative and nonradiative). Radiative transitions emit light (−hυ) when the **PC*** returns to a lower energy state, while nonradiative transitions release part of its energy as heat. S_1 returns to S_0 via fluorescence (a radiative event) or internal conversion (IC, a nonradiative process). An alternative pathway for S_1 involves a spin-forbidden mechanism known as intersystem crossing (ISC). This process leads to the formation of an excited triplet state (T_1). The shift from T_1 to S_0 states is also spin-forbidden, typically causing T_1 states to have prolonged durations. These states decay through radiative mechanisms (phosphorescence) and nonradiative processes, generally the predominant mode under ordinary circumstances.[9]

1.2 Photochemistry as an Essential Tool in the Synthesis

The profusion of visible light makes it an essential energy input for driving chemical changes, placing it at the heart of modern photochemistry. Mastering the efficient use of this energy has become very important for improving synthetic methods. Within this specialized area of photochemistry, photocatalysis considers light-driven reactions as typical processes catalyzed by the ultimate energy source required for starting chemical conversions. This approach takes advantage of the copious supply of visible light and attempts to convert photons into chemical energy to catalyze reactions very efficiently. Efforts in this field are therefore directed toward unveiling new synthetic methodologies to broaden the horizon of modern chemistry. The following sections discuss these aspects in detail. Here, we looked at three sustainable photochemical ways to use visible light for chemical reactions (Figure 1.3).

(1) Organic Photoredox Catalysis. (2) Electron Donor-Acceptor Complex. (3) Direct Photolysis.

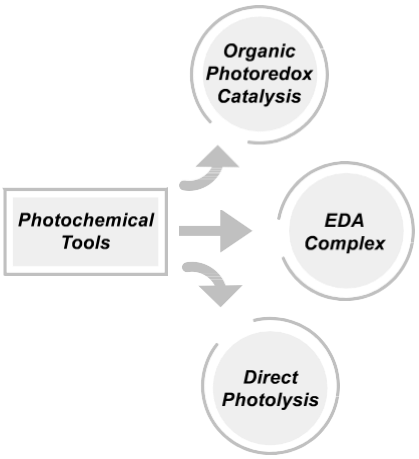


Figure 1.3 Sustainable Photochemical Tools.

1.2.1 Organic Photoredox Catalysis

Over the years, polypyridyl complexes derived from ruthenium and iridium have been used as benchmark catalysts in photoredox catalysis for synthetic organic chemistry applications.[10] These relevance complexes have been an indispensable pillar in driving the field's growth since then; they are finding utility over various reactions. However, despite their widespread use and robustness, their broader application is constrained by two main factors: relatively moderate excited state redox potentials and the high cost associated with these precious metals.

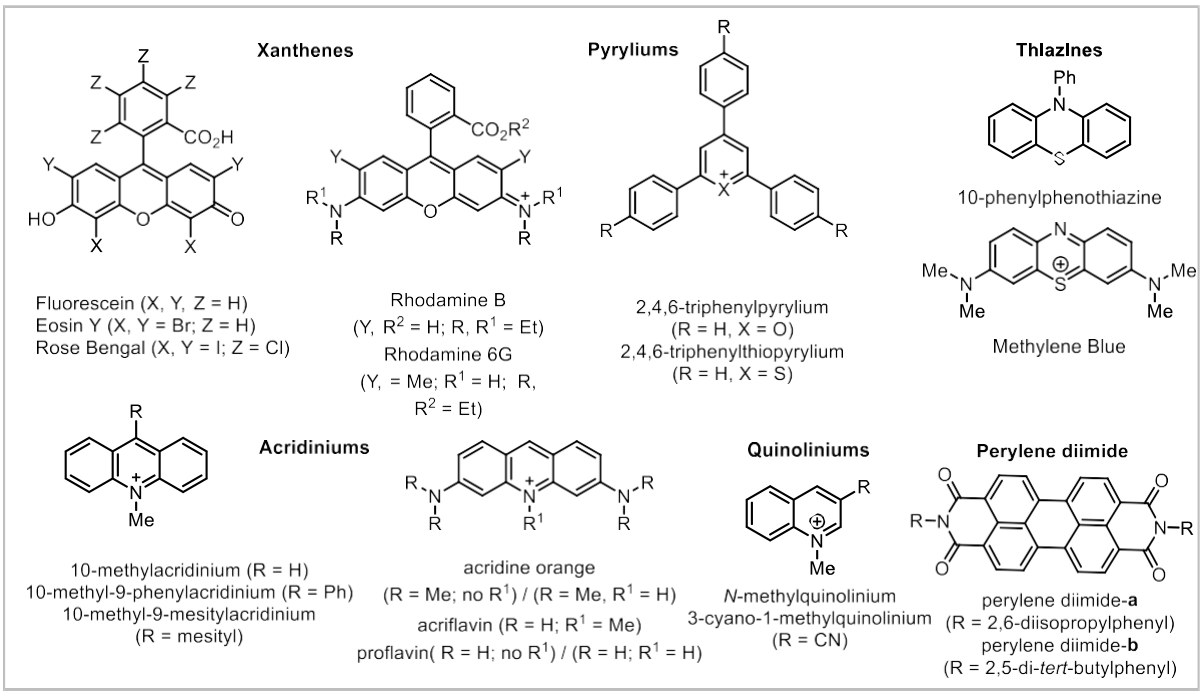


Figure 1.4 Widely Utilized Organic Photoredox Catalysts.

Researchers have focused on organic chromophores as greener and more economical alternatives. Although photoinduced electron transfer (PET) in these compounds was recognized early, using such compounds as catalysts has not been widely studied as metal-based complexes. Recent studies have demonstrated that organic dyes can act as efficient photoredox catalysts.[11-14] Xanthenes, pyryliums, thiazines, acridiniums, quinoliniums, and

perylene diimides are representative examples that have been shown to facilitate competitive redox capabilities necessitated by a wide array of photoredox processes, often providing comparable outcomes to select transition-metal catalysts (Figure 1.4). These organic dyes present significant cost and sustainability benefits and represent a suitable replacement for photoredox systems, greatly broadening the scope of light-mediated synthetic strategies.

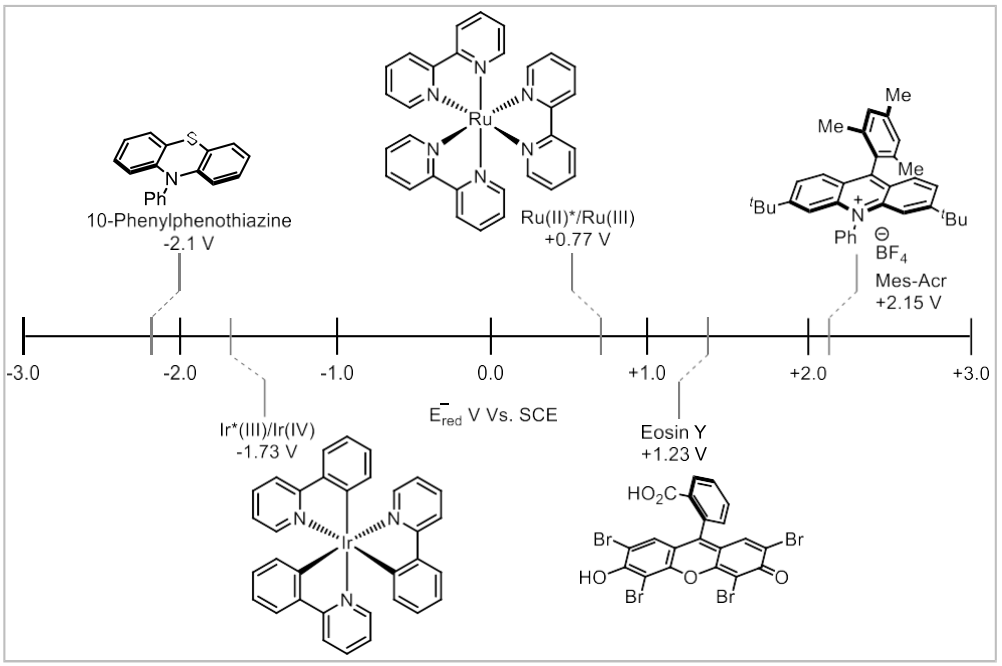


Figure 1.5 Excited State Redox Potentials: A Comparative Analysis.

These organic catalysts often show a higher excited-state redox potential and can participate in SET with substrates inaccessible to iridium- or ruthenium-based photocatalysts (Figure 1.5).[8] The enhanced photophysical properties of organic photoredox catalysts have facilitated the development of novel and more efficient reaction pathways that were previously unfeasible. For example, the reduction potentials of $Ir(ppy)_3$ and 10-Phenylphenothiazine are -1.73 V and -2.1 V, respectively. Furthermore, the oxidation potentials for $Ru(bpy)_3$, Eosin Y, and the Mes-Acridinium catalyst are +0.77 V, +1.23 V, and +2.15 V, respectively, as shown in Figure 1.5. This shows organic photoredox catalysts can potentially reduce or oxidize substrate better than metal catalysts.

1.2.2 General Mechanisms Involved in Organic Photoredox Catalysis

The photoredox catalytic reactions are governed by one of the two mechanisms illustrated in Figure 1.6. Understanding the mechanisms associated with the oxidative and reductive quenching cycles in photoredox catalysis is crucial for understanding how light-activated catalysts promote chemical transformations.[15] An oxidative quenching cycle starts with the absorption of light of a certain wavelength by a photocatalyst (**PC**), which then transitions from its stable ground state to an excited state (**PC***). When energized, **PC*** behaves as an electron donor, donating an electron to an electron-accepting substrate (often written as sub or **[ox]**). This electron transfer generates an oxidized photocatalyst (**PC**$\bullet^+$) and a reduced substrate (**sub**$\bullet^-$ or **[ox]**$\bullet^-$). Because the catalyst loses an electron, this phase is called oxidative quenching (Figure 1.6A). Finally, for this cycle to be complete, **PC**$\bullet^+$ must obtain an electron to revert back into its ground state. This is typically achieved through interaction with a reductant, restoring the **PC**, and enabling the process to repeat. In contrast, **PC*** is an electron acceptor in the reductive quenching cycle. It receives an electron from a reductive substrate (sub or [red]), yielding a reduced catalyst (**PC**$\bullet^-$) and an oxidized donor (**sub**$\bullet^+$ or [**red**]$\bullet^+$). Obtaining an electron induces this process, called reductive quenching of the catalyst (Figure 1.6B). This

regenerated **PC•⁻** species then donates an electron to an electron-deficient substrate (e.g., an oxidant), reforming the original catalyst (**PC**), thus continuing the catalytic cycle. Based on these quenching cycles, photoredox catalysts can perform complex chemical transformations by shuttling between oxidation and reduction states and light energy for sustainable and efficient synthesis.

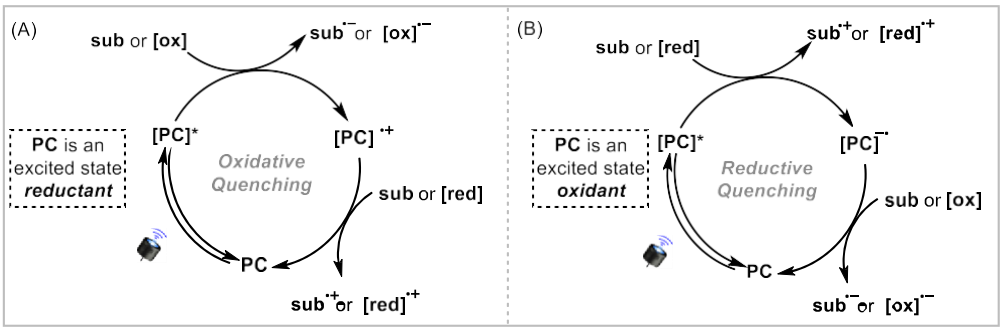
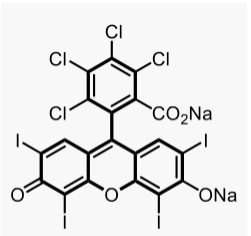


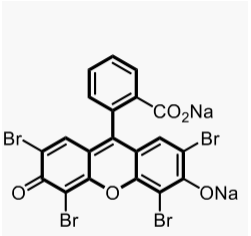
Figure 1.6 Types of Quenching Cycles.

Dyes like Eosin Y and Rose Bengal are cost-effective for visible light-promoted organic transformations. These are low-toxic homogenous photocatalysts in organic synthesis. These organo-photocatalysts usually promote reactions via two pathways: photoinduced energy transfer or single electron transfer. Rose Bengal and Eosin Y's versatile redox potential enables it to operate through oxidative and reductive quenching pathways (Figure 1.7).



Rose Bengal

	Ground state reduction potential (V *vs.* SCE)	Excited state reduction potential (V *vs.* SCE) S_1	Excited state reduction potential (V *vs.* SCE) T_1
$E^{red}_{1/2}$	-0.99	$E^{S_1}_{red}$ +1.18	$E^{T_1}_{red}$ +0.81
$E^{ox}_{1/2}$	+0.84	$E^{S_1}_{ox}$ -1.33	$E^{T_1}_{ox}$ -0.96

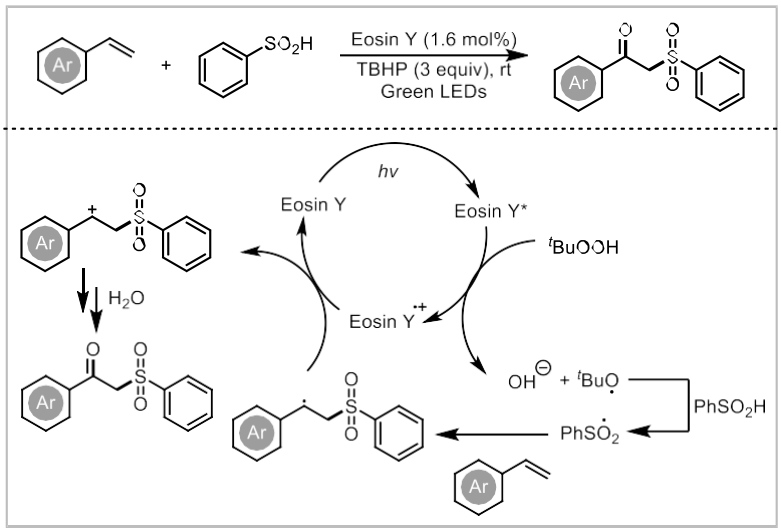


Eosin Y

	Ground state reduction potential (V *vs.* SCE)	Excited state reduction potential (V *vs.* SCE) S_1	Excited state reduction potential (V *vs.* SCE) T_1
$E^{red}_{1/2}$	-0.1.13	$E^{S_1}_{red}$ +1.23	$E^{T_1}_{red}$ +0.83
$E^{ox}_{1/2}$	+0.72	$E^{S_1}_{ox}$ -1.58	$E^{T_1}_{ox}$ -1.15

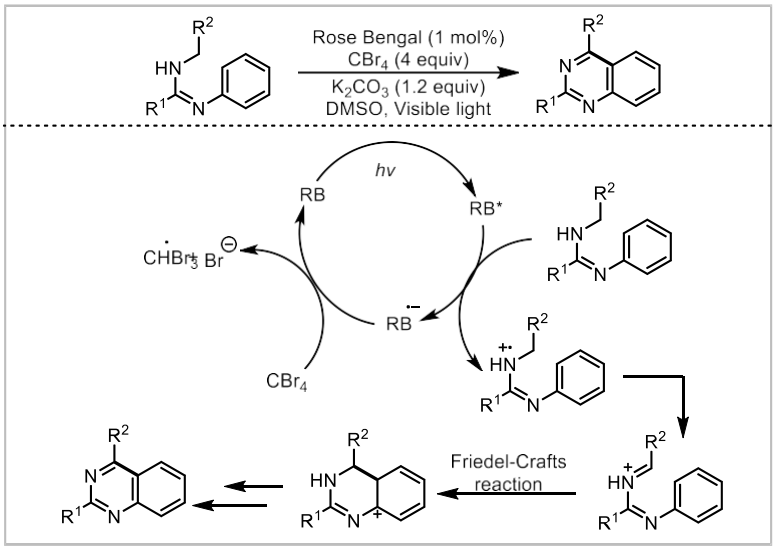
Figure 1.7 Redox Potentials at Different States of Rose Bengal and Eosin Y.

Wang *et al.* described a method for constructing *β*-ketosulfones from styrene and benzenesulfonic acid (Scheme 1.1). Under visible light at room temperature, Eosin Y was used as the photocatalyst, and TBHP was used as the sacrificial oxidant. Eosin Y was excited to Eosin Y*, which underwent a single-electron transfer reaction. TBHP captured the electron, generating a *tert*-butoxy radical and a hydroxyl anion. The *tert*-butoxy radical subsequently abstracted the hydrogen from benzenesulfonic acid, forming a sulfonyl radical. It also reacted with styrene, yielding a benzyl radical intermediate. This intermediate is then oxidized by the catalyst to produce the final product.



Scheme 1.1 The Synthesis of *beta*-ketosulfones from Styrene and Benzenesulfonic Acid.

In a recent study, Tang *et al.* reported the visible-light-excited oxidative cyclization of amidines, followed by the reaction with multi-substituted quinazoline derivatives. This reaction used Rose Bengal as a photocatalyst and proceeded through an oxidative mechanism (Scheme 1.2). CBr_4 was used as the oxidizing agent, and Cs_2CO_3 was used as a base. The substrate was oxidized during the photocatalytic cycle, and a CBr_3 radical extracted a hydrogen atom to generate a radical intermediate. The intermediate was then cyclized intramolecularly to obtain the final product.



Scheme 1.2 Reductive Quenching-Driven Cyclization of Amidines using Rose Bengal.

Apart from nonradiative decay, another possibility is that excited molecules dissipate energy through triplet-triplet energy transfer (TTET), a process that has garnered interest in both the fundamental and applied areas of science.[16] In the case of TTET, the excited donor (D) species directly transfers its energy to an acceptor molecule (A), which causes the donor to return to its ground state but puts the acceptor into an excited state (Figure 1.8). While TTET is useful, it can be rated competitive with electron transfer processes because many organic compounds have elevated triplet state energies, often greater than 60 kcal/mol (2.6 eV), leading to preferential electron transfer.[17] However, energy and electron transfer mechanisms can occur simultaneously under the same conditions. Understanding the fundamental aspects of energy transfer dynamics is paramount for designing successful photocatalytic cycles, such as those

used in selective C-H functionalization. In these processes, radicals are produced, and the radical pathways are modulated in a controlled fashion using photocatalysts.

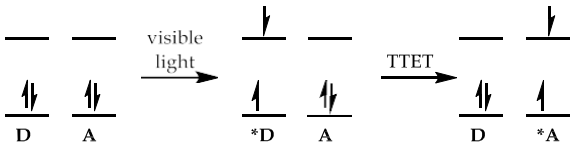


Figure 1.8 Overview of Light-Induced Energy Transfer.

1.2.2 Photoinduced Electron Donor-Acceptor Complex

In the previous section, it was demonstrated that photocatalysts can efficiently drive chemical reactions. The following section will describe the concept of the electron donor-acceptor (EDA) complex in organic synthesis. While sunlight drives photosynthesis to energize specific molecules, other chemical reactions depend on the delicate interplay between electronic forces. Electron transfer in organic chemistry is fundamental to most reaction mechanisms since the electron exchange process does not spontaneously occur. The formation of an EDA complex occurs when there is an interaction between the donor molecule (HOMO) and the acceptor molecule (LUMO).[18] This interaction gives rise to a ground-state molecular orbital configuration, exhibiting a specific electronic structure that is noticeably different from the individual donor and acceptor molecules. This interaction gives rise to a new distinctive absorbance band, i.e., the charge transfer (CT) band, that exhibits a bathochromic shift (redshift) relative to the individual absorbance bands of the free donor or acceptor molecules (Figure 1.9). During the 1950s, Robert Mulliken introduced a quantum mechanical framework called Mulliken CT theory to elucidate the formation of this CT band.[19]

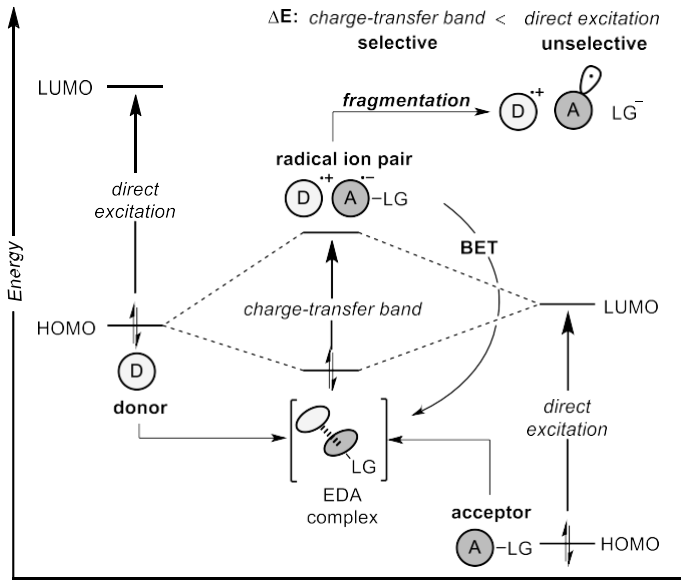


Figure 1.9 Comparative Analysis of Molecular Orbitals in Direct vs. EDA Complex Photoexcitation.

The charge transfer (CT) band represents an electronic shift from the electron donor-acceptor (EDA) complex's ground state to its excited state. This process simulates a light-induced single electron transfer (SET) within the complex, where electrons move from the donor to the acceptor, forming radical intermediate pairs, which can subsequently engage in various chemical reactions.[20] These reactions provided the foundation for valuable insight into photoinduced electron transfer processes and eventually paved the way for modern applications of EDA complexes in synthetic photochemistry.[21-22] Upon exposure to light, neutral molecules form a charge transfer (CT) complex, which subsequently generates a radical ion pair [electron donor-acceptor, EDA] (Figure 1.10A). In the case of oppositely charged ions, such as

anions and cations, preliminary equilibrium interactions lead to the formation of a contact ion pair (CIP). When exposed to light, these pairs undergo charge transfer (CT) reactions, behaving similarly to EDA complexes' ability to generate neutral radical species (Figure 1.10B). The energy required for this electronic transition, denoted ($h\upsilon_{CT}$), can be spectroscopically determined from the absorption maximum of the CT band (Figure 1.10C).

According to Mulliken theory, the charge transfer energy ($h\upsilon_{CT}$) can be determined using three components: the donor's ability to give electrons, i.e., the ionization potential (IP); acceptor's ability to accept electrons, i.e., electron affinity (EA), and the energy of interaction a coulombic term (ω).[19, 23]

$$h\nu_{CT} = IP - EA + \omega \quad \text{----------} \quad (2)$$

The connection illustrates how the CT energy diminishes and moves toward longer wavelengths as the capacity for electron donation (lower ionization potential) or electron acceptance (higher electron affinity) increases. The EDA complexes generate paired radicals upon irradiation, which may initiate chemical reactions. However, overcoming back electron transfer (BET) to utilize these radicals effectively is necessary, which can revert them to their initial state before dissociation or further reactions occur. BET proceeds rapidly, thereby limiting the reactivity of the intermediates. The radical ion pair must undergo an irreversible process for efficient chemical reactions. For this reaction to circumvent these constraints, it must proceed at a rate exceeding that of BET, thus facilitating reactions within or outside the cage. Synthesizing compounds usually achieve this by adding fragmentable groups to the donor or acceptor. This change encouraged the decomposition of the radical ion intermediates. This strategy circumvents the limitations of BET and allows all radicals generated from the initiation to participate in subsequent successful reactions (Figure 1.10D).[23-24]

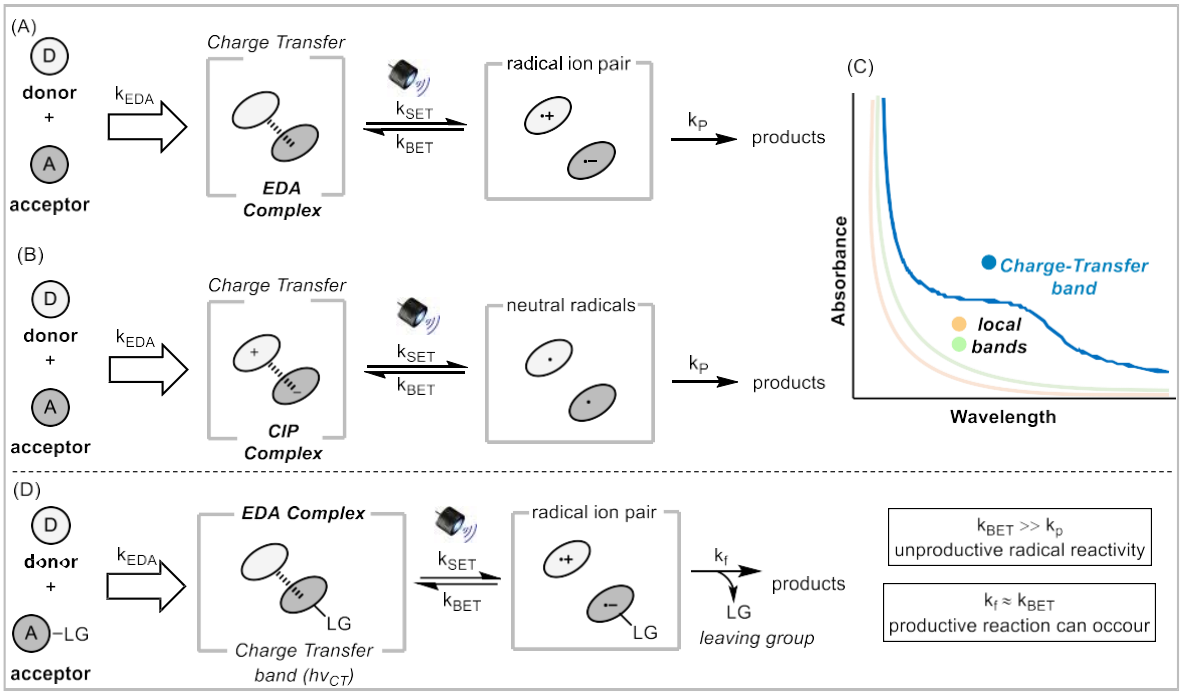


Figure 1.10 Principles of EDA Photochemistry.

In excited states, the transfer of electrons involves interactions between components that donate and accept electrons, reflecting the dynamics seen in donor-acceptor complexes in the ground state. However, the mechanisms and patterns of reactivity are quite different in excited-state transfer. Unlike ground-state transfers, excited-state electron transfer can occur from donor and acceptor molecules.[25] This is because the redox potentials of molecules in their excited states differ from those in their ground states. The changed redox potential enables new reactivity

features characteristic of excited-state dynamics and enhances the repertoire of possible chemical reactions.[26]

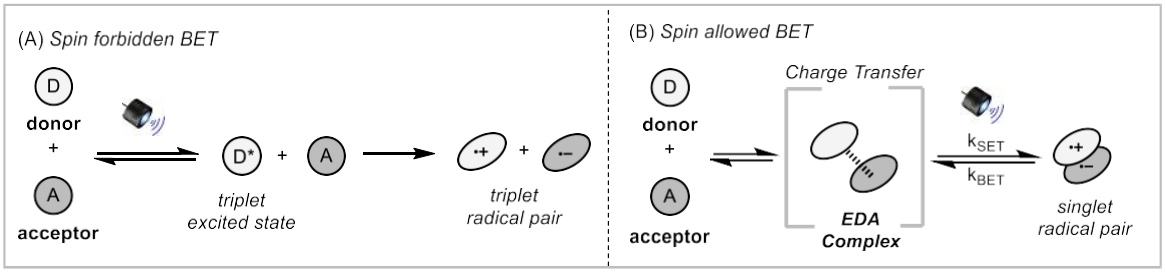


Figure 1.11 Contrasting Reactivities: Local vs. Charge-Transfer Band Activation.

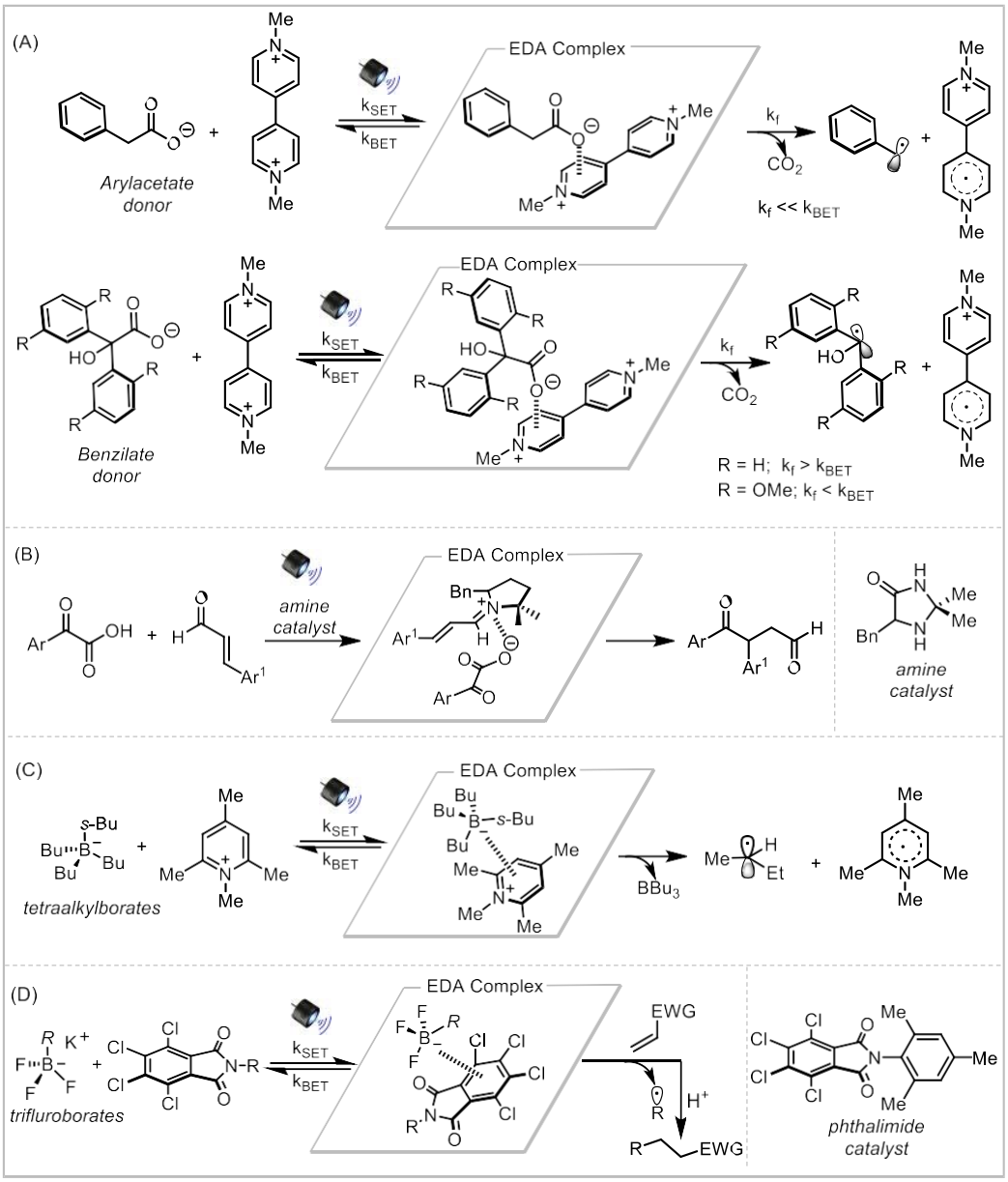
It should be noted that only when molecules are in a triplet state generally have a sufficient lifetime to diffuse and collide with other molecules for intermolecular reactions. It harnesses a photoinduced electron transfer process, whereby an excited molecular triplet transfers one of its electrons to a nearby ground-state molecule to form a triplet radical ion pair. In this triplet pair, the reverse reaction (back-electron transfer or BET) is prohibited by spin selection rules, resulting in an extremely slow process. The sluggish nature of this BET allows the radical species to persist for longer, thereby enhancing the likelihood of product formation (Figure 1.11A). In contrast, electron transfer in an EDA complex creates a (singlet) radical ion pair. This singlet state allows spin-allowed reverse electron transfer, resulting in fast BET competition with product formation. This competition limits the practical application of these radical intermediates (Figure 1.11B).[23] Thus, to achieve a more efficient synthesis, one must implement a leaving group in the structure of the donor or acceptor that is irreversible and instantaneously fragmented. This incorporation can suppress the BET and drive product formation.[27-30]

While numerous electron-rich compounds have demonstrated their capability as electron donors, the majority of bond cleavages employed in current synthetic applications are driven by the reduction of the acceptor species.[31-35] In 1997, Kochi *et al.* reported electron donor-acceptor (EDA) complexes based on carboxylates as efficient donor components. Benzilate and aryl acetate served as the two different classes of donors to form complexes with *N*-methylviologen-type acceptors (Scheme 1.3A).[36] The kinetics of decarboxylation were extremely fast compared to the benzilate donors' back electron transfer (BET) rate constants. In sharp contrast, arylacetates had two orders of magnitude lower than BET's. Attribution was made to the relatively stable radicals arising after decarboxylation, which would produce a large decrease in the decarboxylation rate for arylacetates compared to benzilates.

Recently, Gilmour *et al.* employed a decarboxylative electron donor-acceptor (EDA) interaction to induce a radical Stetter reaction. They proposed a process wherein an iminium ion is generated via the condensation of the amine catalyst with an α,β-unsaturated aldehyde, combined with the formation of an electron-donor-acceptor complex with the α-ketocarboxylates (Scheme 1.3B).[37] Under visible light irradiation, the EDA complex first promotes photoinduced charge transfer and then undergoes almost synchronous decarboxylation. The subsequent radical pair is geminate and collapses to replace the bond with a new carbon-carbon bond between the two with moderate to good yields.

Kochi *et al.* studied electron donor-acceptor (EDA) complexes, specifically focusing on borate compounds as electron donors, complementing earlier carboxylate research. In the late 1990s, their work showed that excited-state CIPs of an alkyl borate donor and an *N*-methylpyridinium acceptor could provide a route to produce carbon-centered radicals upon photoexcitation (Scheme 1.3C).[38] This process involves cleavage of a carbon-boron (C–B) bond

within the boranyl radical, produced by light-induced electron transfer. The weakest C–B bond is broken and easily forms a carbon-centered radical with the least reactivity, resulting in a more stable aromatic compound entering the most stable radical. This radical underwent solvent-caged radical recombination with the pyridinyl radical, illustrating a fundamental mechanism for producing carbon-centered radicals through EDA complex photochemistry.



Scheme 1.3 EDA-Driven Reactions Involving Different Donors.

In addition to other borate salts, alkyl trifluoroborates are popular precursors of alkyl radicals in photoredox catalysis because of their easy preparation and availability (Scheme 1.3D).[39] The mechanism includes photocatalyst-facilitated single-electron oxidation of trifluoroborate to produce a boryl radical that quickly fragments to give an alkyl radical and trifluoroborane. Such a decomposition mechanism involving trifluoroborates as donors has been further exploited in EDA photochemistry. Melchiorre *et al.* have recently employed various Giese additions with alkyl trifluoroborates to activate olefins.[40] In this work, EDA complexes formed between a tetrachlorophthalimide acceptor catalyst and trifluoroborate donors served as catalytic intermediates.

Although there are various types of donors described in the literature, this thesis has a specific interest in nitrogen donors. Several nitrogen-containing compounds can serve as efficient donors. Tri-aryl amines are reported to be excellent catalytic donors.[41] Some of the other examples are DBU, DABCO, MTBD, TMEDA, and triethylamine (Et_3N) have been identified as effective donor molecules (Figure 1.12).[42-46]

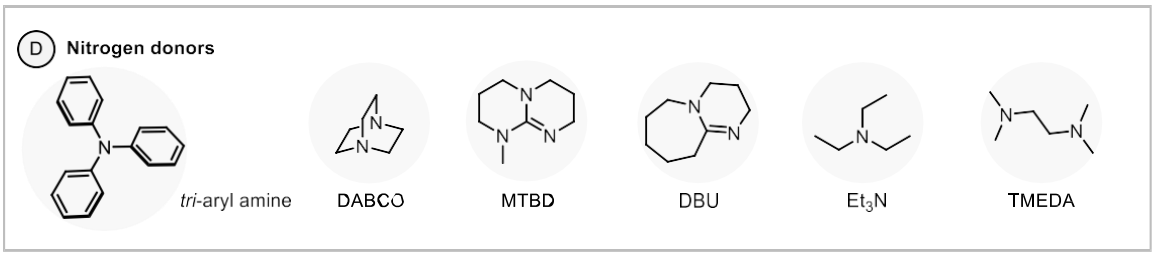


Figure 1.12 Nitrogen Donors in EDA Chemistry.

1.2.3 Direct Photolysis

The reactivity of organic synthesis using visible photons, which is environmentally friendly and has higher energy utilization efficiency, has received extensive attention.[47] Colored organic compounds are ideal activation targets for visible light, which drives various chemical transformations (Figure 1.13). If such a light-sensitive molecule that can be transformed directly by absorption of visible light is available, clearly no need for a photocatalyst. However, most organic compounds are colorless and absorb only ultraviolet radiation. To circumvent this limitation, researchers have established alternative strategies to generate chromophores *in situ* (or at least allow longer wavelengths to drive the process). Such success is manifested in numerous synthetic strategies developed with remarkable versatility, which have been adopted broadly from polyfunctionalized materials to late-stage functionalization of bioactive metabolites.[48]

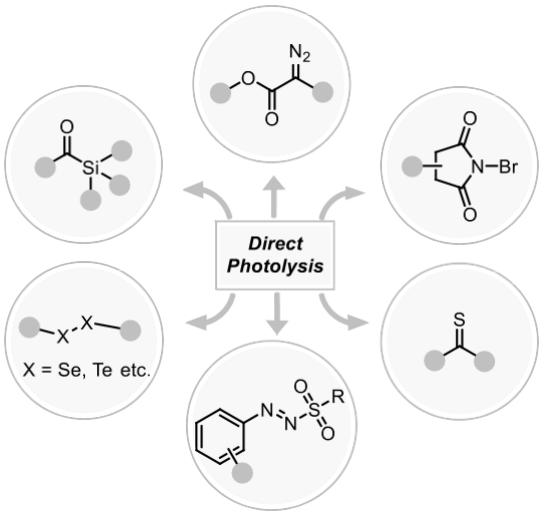


Figure 1.13 Direct Photolysis of Organic Compounds.

While photochemical reactions demonstrate significant theoretical potential, their actual applications within industrial chemical production or research and development activities continue to be limited, with the vast majority of processes constrained to established commodity chemicals developed many years ago.[49] Recent progress in photobiocatalysis has demonstrated that enzymatic catalysis and photoexcitation can be integrated into a potent new reaction

paradigm, where complementary reaction pathways open new opportunities in organic synthesis.[50] A brief overview is provided for substances containing light-sensitive color-producing molecules that absorb light in the visible spectrum.

The arylazo sulfone and arylazo sulfonate compounds showed maximum absorption in the 400–450 nm region due to an n-π* transition. Under blue-light irradiation, these N–S bonds cleave homolytically, producing aryldiazenyl, sulfonyl, and aryl radicals. This characteristic renders these materials exceptional candidates for catalyst-free C–C bond-forming reactions. Thioketones represent compounds that predominantly absorb light within the 500-600 nm wavelength range, a characteristic attributed to a dipole-forbidden n-π* electronic transition.[51] However, these compounds are rarely used in photochemistry as the ketones. Thioketones are primarily used as precursors in synthesizing thietanes via a thia-Paterno`-Bu¨chi reaction, though it is important to note that such reactions normally require ultraviolet (UV) irradiation.[52-53]

Some *N*-iodo and *N*-bromo amides and imides can absorb light at wavelengths longer than 400 nm to gain energy, leading to the cleavage of the *N*-halogen bonds and the release of halogen atoms.[54-55] Among hypervalent iodine(III) compounds, only benziodoxoles have been reported to undergo photoreactivity under visible-light irradiation, and they have been employed in alkynylations.[56] Diselenides and ditellurides demonstrate a pronounced absorption band in the visible spectrum, attributed to the n-σ* transition.[57-59] This transition facilitates the cleavage of the Se–Se and Te–Te bonds. Visible light is an essential source for dissociating functional groups in specific instances.[60]

Acylsilanes exhibit an absorption spectrum with a band of 350–420 nm, rendering them effective precursors for α-siloxy carbenes.[61] This was achieved through a 1,2-photo Brook rearrangement induced by visible light.[62] Similarly, the diazo groups in diazo esters and α-diazo ketones generate an absorption band in the 400-500 nm region owing to the N=N functional groups.[63-64] Collectively, this covers a range of areas in terms of organic synthesis and builds a foundation for new instances of light-induced reactivity to be deployed without the need for an external photocatalyst. This thesis includes our interest in the photolysis of aryl diazo esters due to their easy preparation, as they can be prepared from alcohols, which are more abundant than alkyl halides.[65]

1.3 Visible Light-Mediated Alkylation

The skeleton of many natural products, lead molecules at the pharmaceutical level, and agrochemicals consists of nitrogen-based heterocyclic compounds (Figure 1.14).[66-67] The direct functionalization of *N*-heteroarenes via alkylation enables late-stage structural modifications of clinical candidates and rapid expansion of chemical libraries containing drug-like compounds.[68-69] They provide rapid access to previously unexplored chemical space without relying on classical chemical synthesis methods. Most notably, the pharmaceutical research community has increasingly focused on late-stage functionalization tactics, as these methods facilitate the modulation of metabolic and pharmacokinetic properties of lead molecules.[68, 70] Thus, methods that avoid using strong oxidizing or reducing agents and high reaction temperatures are highly desirable from both academic and industrial perspectives. Open-shell alkyl radical intermediates were used to alkylate heteroarenes.[71-74] Studer and Curran conducted mechanistic studies suggesting that rearomatization proceeds via deprotonation, followed by sequential single-electron oxidation of the modified heteroarene after radical addition.[75] This reactive strategy towards heteroarene alkylation has been an integral foundation for modern drug discovery and development since the landmark work of Minisci.[76] In addition, generating radical intermediates from benign sources and via mild general methods has spurred extraordinary developments in heteroarene alkylation.[77-79]

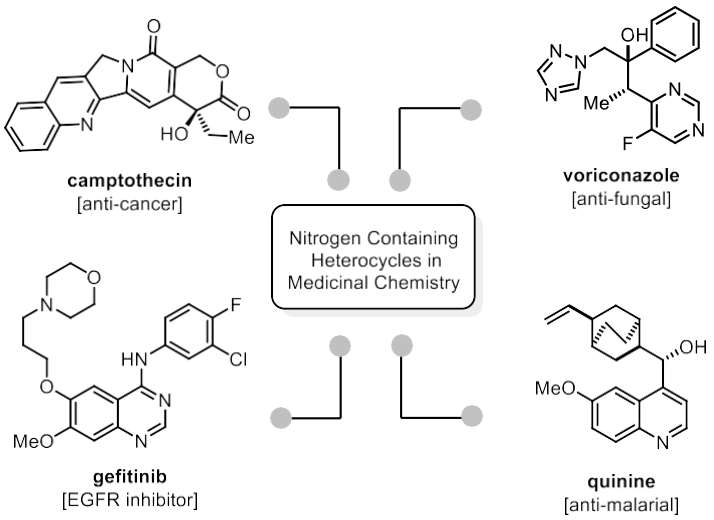


Figure 1.14 Nitrogen-Containing Heterocycles in Medicinal Chemistry.

Increasing the sp^3 character of molecules could improve many molecular properties, contributing to their clinical effectiveness. The expanded ability to tailor out-of-plane substituents and alter the molecular shape could increase the complementarity between receptors and ligands. This would allow for the formation of extra protein-ligand bonds that would not be achievable with planar aromatic groups, potentially enhancing the potency and selectivity of mitigating off-target properties. Although aromatic characteristics can promote π–π or π–cation matches, a greater saturation may improve the orientations of these moieties.[80-81] Furthermore, medicinal chemists widely believe that decreasing the aromatic character of a molecule can lead to improvements in its physical properties, such as solubility.[82-83] Recent studies have established the relevant signature of molecules to predict solubility, and the fraction of aromatic molecules is a key parameter (Figure 1.15).[84] This has been accomplished using certain sp^3 precursors to generate reactive intermediates in photochemical conditions and add to existing molecules.

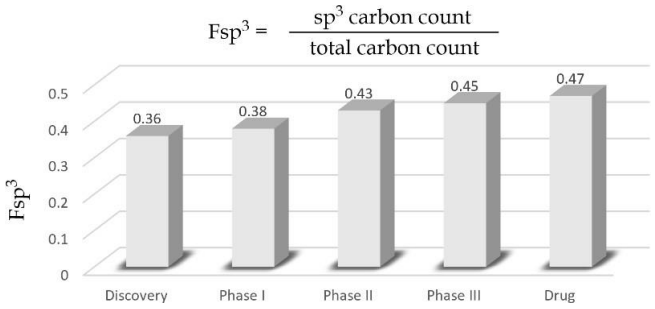
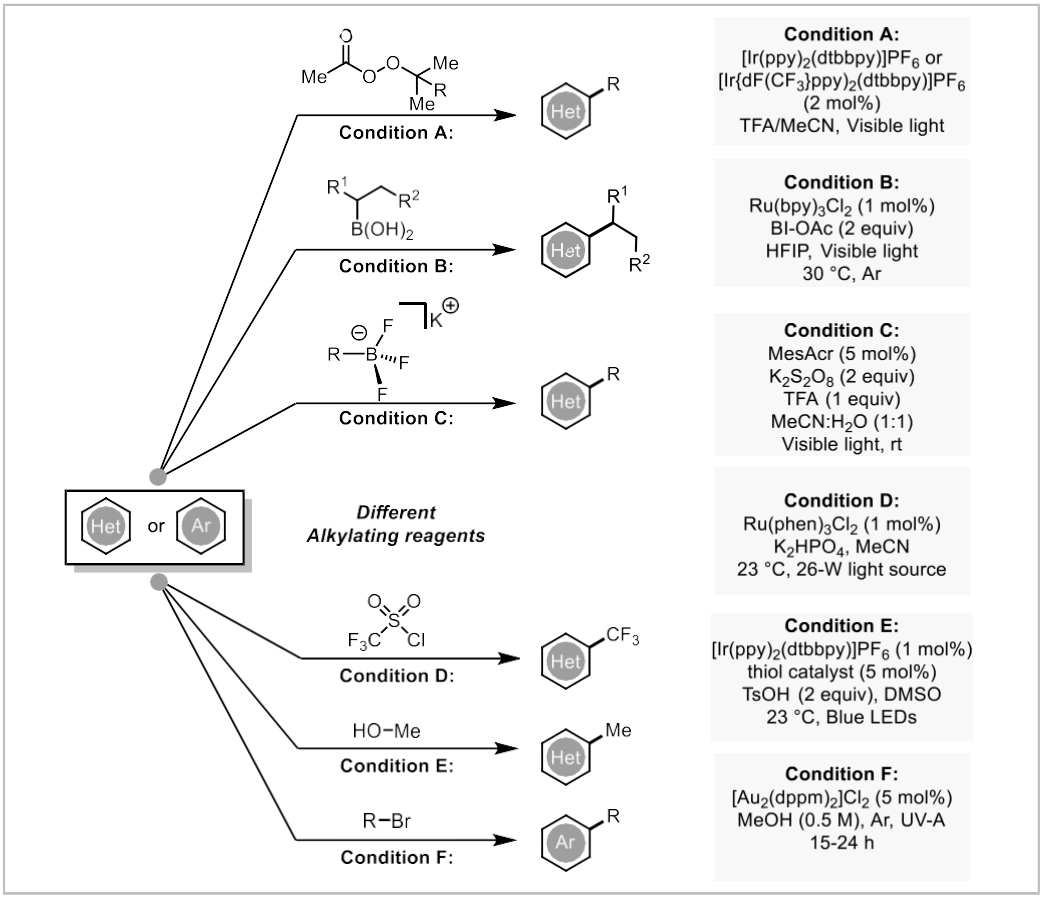


Figure 1.15 sp^3 Character in Drug Development.

Using stable organic peroxides as alkylating agents, DiRocco *et al.* developed a new platform for the late-stage functionalization of advanced pharmaceutical intermediates under photoredox conditions (Scheme 1.4A).[85] Researchers developed an alkylation methodology to enhance the structural diversification of advanced pharmaceutical precursors. Iridium(III) photocatalysts facilitated the generation of methyl, ethyl, and cyclopropyl radical species from readily available, stable alkyl peracetates. Furthermore, researchers have identified alkyl-boron species as radical sources for carbon-carbon bond-forming reactions via oxidative carbon-boron bond cleavage.[86-92] In 2016, Chen *et al.* reported a C–H alkylation approach for *N*-heteroarenes utilizing primary and secondary alkyl boronic acids (Scheme 1.4B).[93] This strategy uses $Ru(bpy)_3Cl_2$ as the photocatalyst and acetoxybenziodoxole as the oxidant.

Potassium organotrifluoroborates are preferable radical precursors relative to their boronic acid equivalents because of their increased stability and robustness under severe reaction conditions owing to the lack of an empty *p*-orbital.[94] In 2017, the Molander group built on their earlier manganese(III) acetate-mediated alkylation chemistry[95] and showed that commercially available alkyltrifluoroborates could mediate their method upon activation with a cheap and green organophotocatalyst (Scheme 1.4C).[96] Screening the reaction conditions, they determined that the optimal conditions for the C–H functionalization of heteroarenes involved a mesityl acridinium photocatalyst, potassium persulfate as the sacrificial oxidant, and trifluoroacetic acid as the proton source. The trifluoromethylation of heteroarenes is an important reaction in medicinal chemistry. Following dehalogenative alkylation, heteroarenes can also be trifluoromethylated. as the sacrificial oxidant and trifluoroacetic acid as the proton source (Scheme 1.4D).[97] A ruthenium photocatalyst was used to reduce trifluoromethanesulfonyl chloride, which liberated sulfur dioxide and generated a reactive trifluoromethyl radical. Different heteroarenes can then conveniently trap this intermediate radical, ultimately leading to C–H trifluoromethylation.



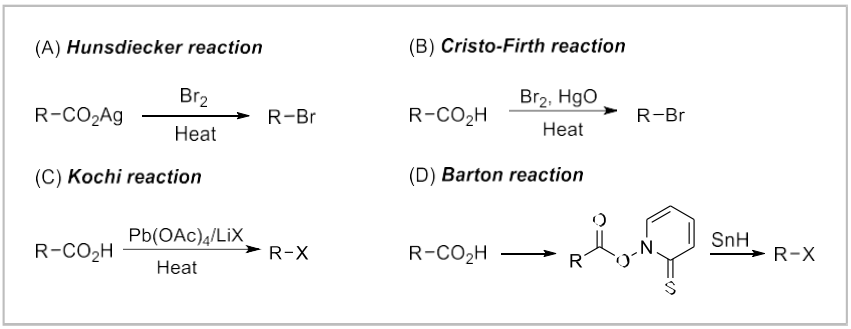
Scheme 1.4 Different Types of Alkyl Radical Precursors.

In 2015, the MacMillan group first employed alcohols in the visible-light-driven alkylation of heteroarenes (Scheme 1.4E).[98] The researchers proposed a mechanism for the methylation of heteroarenes involving the addition of a carbon-centered hydroxymethyl radical to the heteroarene substrate. Subsequently, the hydroxymethyl group was converted into the required methyl fragment through a spin-center shift and water loss. The resulting benzylic radical species were then expected to undergo reduction and protonation, yielding the final methylated product. In 2015, Barriault *et al.* reported gold photoredox catalysis for the alkylation of *N*-heteroarenes with unactivated alkyl bromides via intramolecular cyclization (Scheme 1.4 F).[99] The following year, they extended this methodology to intermolecular radical addition. In their 2016 work, the researchers presented a mechanistic proposal involving the formation of

an excited-state exciplex, which then underwent an inner-sphere electron transfer process to generate an alkyl radical intermediate.

1.4 *N*-(acyloxy)phthalimides as a Versatile Alkylating Reagent

Carboxylic acids are a stable and readily available class of precursors. Introducing alkyl groups into these organic frameworks is a promising platform for preparing complex molecular architectures and deriving diverse functional groups in organic chemistry.[100-102] Under light or oxidative conditions, carboxylic acids adopt a single-electron transfer reaction pathway that generates new carbon-carbon or carbon-heteroatom bonds.[103-106] In 1930, a classical method for alkyl bromide preparation via the reaction of the silver salt of alkyl carboxylate with bromine was reported. Upon heating, these salts decarboxylate via a radical to generate an alkyl bromide that is one carbon atom less than the parent compound. This reaction is known as the Hunsdiecker-Borodin reaction (Scheme 1.5A).[107-108] The most difficult aspect is isolating aliphatic carboxylic acid's dried silver salt (I).[109] Later, Cristol and Firth made some changes by replacing the silver salt with an amalgam of HgO, halogen, and acid derivatives (Scheme 1.5B).[110] However, HgO is also highly toxic. The Kochi modification used aliphatic carboxylic acids on $Pb(OAc)_4$ with lithium halides (Scheme 1.5C).[111-112] A derivative of the Barton modification reaction is the decarboxylation of the thio-hydroxamate ester, which generates an alkyl radical in the presence of highly toxic tin hydride as a reductant (Scheme 1.5D).[113-114] Furthermore, researchers have explored various alternative activated aliphatic carboxylic acid derivatives in radical decarboxylative reactions, including alkyl diacyl peroxides, alkyl peresters, and aryl iodine dicarboxylates. Nonetheless, these methods are limited in their application because of three main factors: high reaction temperatures, explosive properties that can present safety hazards, and restricted substrate scope.[115]



Scheme 1.5 Background of Decarboxylation.

Over the past decade, *N*-(acyloxy)phthalimides have emerged as a focus of attention, as they are redox-active esters that can be readily decarboxylated under thermal, photolytic, and electrochemical conditions, making them a potential alternative to radical-mediated decarboxylative cross-couplings.[116] Additionally, NHPI esters serve as inexpensive, stable, and commercially available alternatives to Barton esters, functioning as efficient radical precursor sources. These NHPI esters are known to be synthesized efficiently through carbodiimide-mediated coupling of carboxylic acids and *N*-hydroxyphthalimides.[117] Alkyl radicals derived from *N*-(acyloxy)phthalimide derivatives can be powerful tools for functionalizing molecules to add sp^3-character.[116, 118-119] Under single-electron transfer (SET) conditions and light, *N*-(acyloxy)phthalimide undergoes homolytic cleavage to give an alkyl radical. This radical is positioned at different types of reactive sites on a substrate, enabling unique alkylation and alkylative cascade annulation in a highly selective fashion (Figure 1.16). Incorporating these alkyl radicals creates sp^3-hybridized carbons in the molecule, contributing to three-dimensional characteristics and providing greater conformational flexibility and better pharmacokinetic properties.[120]

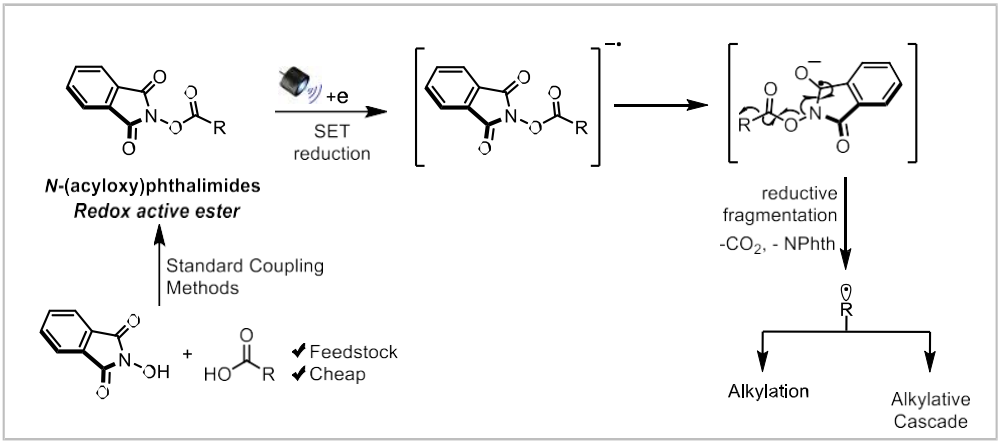
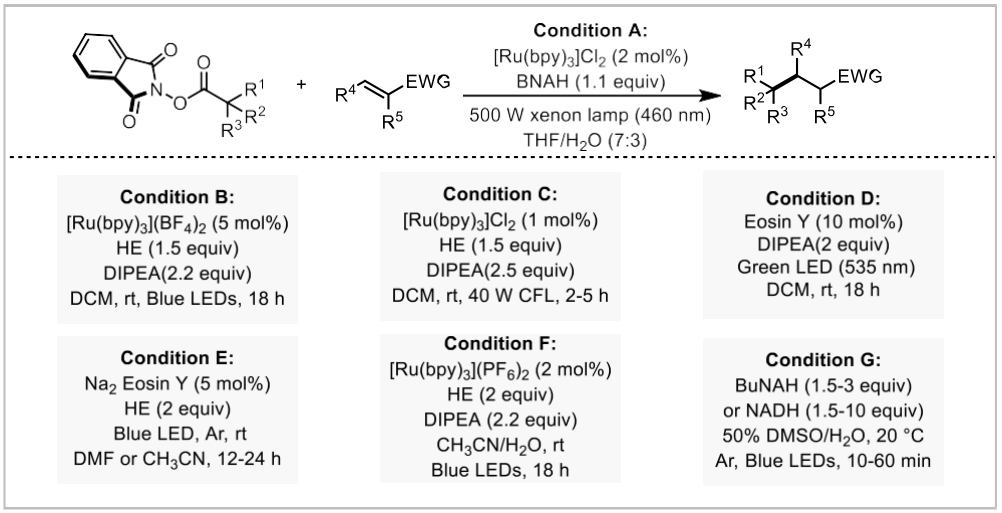


Figure 1.16 Redox Activity of Redox-Active Ester.

1.4.1 Alkylation Using *N*-(acyloxy)phthalimides

An important goal of synthetic organic chemistry is to develop new methods for alkylation, enabling the assembly and synthesis of complex, high-value molecular scaffolds.[121-122] Many groups have developed unique approaches for generating new C–C bonds with redox-active phthalimide esters. Approximately three decades ago, Okada *et al.* studied NHPI ester cleavage under visible light with a hydrogen donor (1-benzyl-1,4-dihydronicotinamide, BNAH) using $[Ru(bpy)_3]Cl_2$ as the photoredox catalyst (Scheme 1.6A).[123-125] This is accomplished through the reductive fragmentation of the redox-active ester (NHPI) to produce an alkyl radical that undergoes radical conjugate addition with acceptor, producing products in excellent yield. Interestingly, the potential application of NHPI esters was unknown until 2015, when Overman reported their use in a $[Ru(bpy)_3]Cl_2$ catalyzed photoredox reaction. This methodology facilitates the cross-coupling of sterically congested tertiary carbon radical species and enones, thus enabling the construction of intricate molecular frameworks. This procedure employed Hantzsch ester and DIPEA as the reductive quencher (Scheme 1.6B).[126]



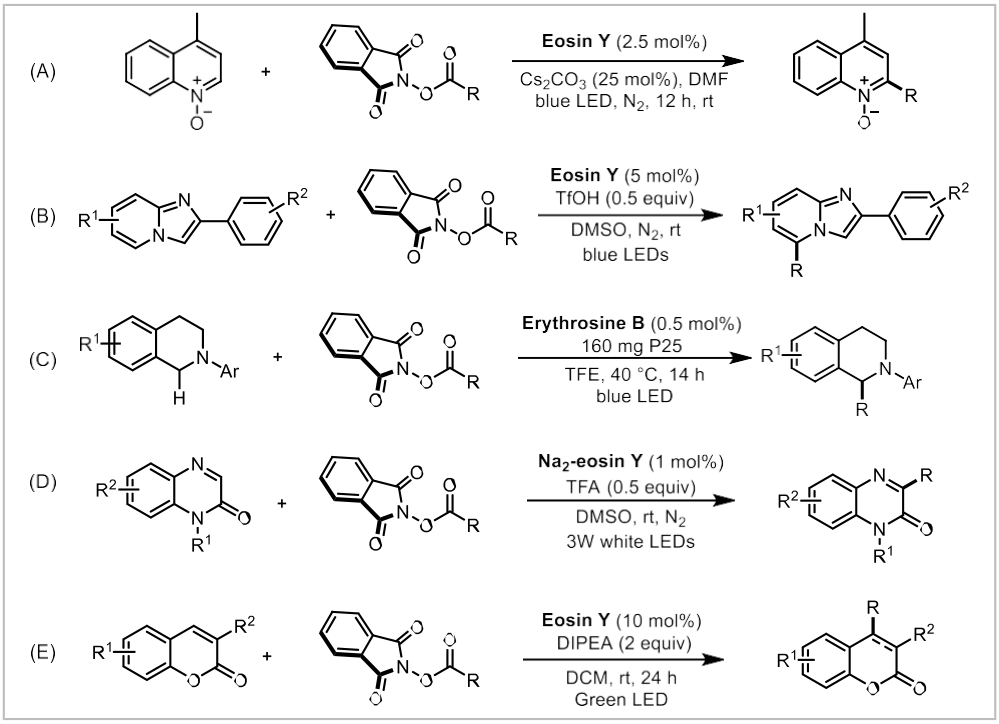
Scheme 1.6 Photoredox-Catalyzed Conjugate Additions of NHPI Esters to Alkenes.

Different research groups have devised new methodologies for the conjugate addition of stylable alkyl radicals derived from NHPI esters to various electron-poor alkenes. Fu *et al.* reported a new protocol for synthesizing unnatural chiral α-amino acids in 2016. Using radical coupling, they incorporated easily available genetically encoded proteinogenic amino acids, such as *L*-aspartic acid and glutamic acid-derived NHPI esters, as alkyl radical precursors, along with electron-deficient alkenes as radical acceptors (Scheme 1.6C).[127] At the same time, König *et al.* described the first report of a metal-free, visible-light-promoted decarboxylative radical

conjugation addition. The researchers employed NHPI esters derived from biomass-derived acids in combination with electron-deficient alkenes, utilizing Eosin Y as the organic photocatalyst and stoichiometric DIPEA as the reductant (Scheme 1.6D).[128]

In a more recent report, Liao characterized the cross-coupling reaction of vinyl sulfonyl fluorides and, for the relatively first time, non-fluorinated vinyl boronic esters with NHPI esters derived from primary, secondary, and tertiary acids. This procedure yielded the respective alkyl sulfonyl fluorides and the corresponding alkyl boronic esters in excellent yields (Scheme 1.6E).[129-130] Here, reductive quenching of the Na_2-Eosin Y photocatalyst involves adding HE as an electron donor. At the same time, Mancheño *et al.* reported a new method for the functionalization of dehydro-amino acids and peptides using alkyl radicals. The radicals were produced by the reductive C–C bond cleavage of NHPI esters using a [Ru]-based photocatalyst (Scheme 1.6F).[131] More recently, Mendoza *et al.* demonstrated the decarboxylative alkyl coupling ability of RAEs with electron-poor vinylogous equivalents. Their method employed specially designed NADH derivatives as photoreductants, affording various coupling products in a short reaction time (Scheme 1.6G).[132]

Subsequently, Qin *et al.* reported a novel visible-light-induced method for alkylating pyridine and quinoline *N*-oxides using Eosin Y as a photocatalyst. This methodology employed NHPI esters derived from 1°, 2°, and 3° alkyl carboxylic acids to enable the C-2 alkylation of heterocyclic *N*-oxides, delivering moderate to good yields (Scheme 1.7A).[133] Notably, the protocol displayed wide applicability for the alkylation of bioactive natural molecules, such as dehydroabietic acid or glycosyl-derived NHPI esters, affording the target products moderate to good yields. The mild reaction conditions also facilitated the late-stage functionalization of complex molecules, a natural product, and the antimalarial drug quinine, demonstrating the generality and utility of this strategy.



Scheme 1.7 Direct Alkylation of NHPI Esters to Heterocycles.

Jin *et al.* reported a visible-light-mediated method for the direct C–H alkylation of imidazopyridines, utilizing Eosin Y as the photocatalyst. This approach employs NHPI esters derived from various 1°, 2°, and 3° carboxylic acids to enable the selective synthesis of C-5 alkylated imidazopyridine derivatives in moderate to good yields (Scheme 1.7B).[134] This method

illustrates the effectiveness and generality of the synthesis of alkylated heterocyclic scaffolds under mild metal-free conditions.

In 2018, the group of Cong reported a visible-light-mediated method for direct Csp^3–H alkylation of *N*-aryl tetrahydroisoquinolines using a dual catalytic system based on erythrosine B and TiO_2 (Scheme 1.7C).[135] The approach facilitated the generation of diverse primary, secondary, and tertiary alkyl radicals from NHPI esters, which were rapidly coupled with tetrahydroisoquinolines to give the alkylated derivatives moderate to good yields. This strategy exemplifies the broad potential of NHPI esters to act as alkyl radical precursors under mild photocatalytic conditions.

Jin and co-workers developed a Na_2-eosin Y photocatalyzed strategy for the alkylation of quinoxalinones via decarboxylation of NHPI esters as alkyl radical precursors (Scheme 1.7D).[136] On the other hand, under very mild reaction conditions with excellent substrate tolerance for primary, secondary, and tertiary carboxylic acids, producing a range of alkyl-NHPI esters. The reaction always afforded the desired alkylated products in moderate-to-good yields. Notably, the efficiency of the Na_2-eosin system was superior to that of Li's previously developed Ir-photoredox-catalyzed method, thus rendering it favorable for the sustainable development of alkylation reactions.

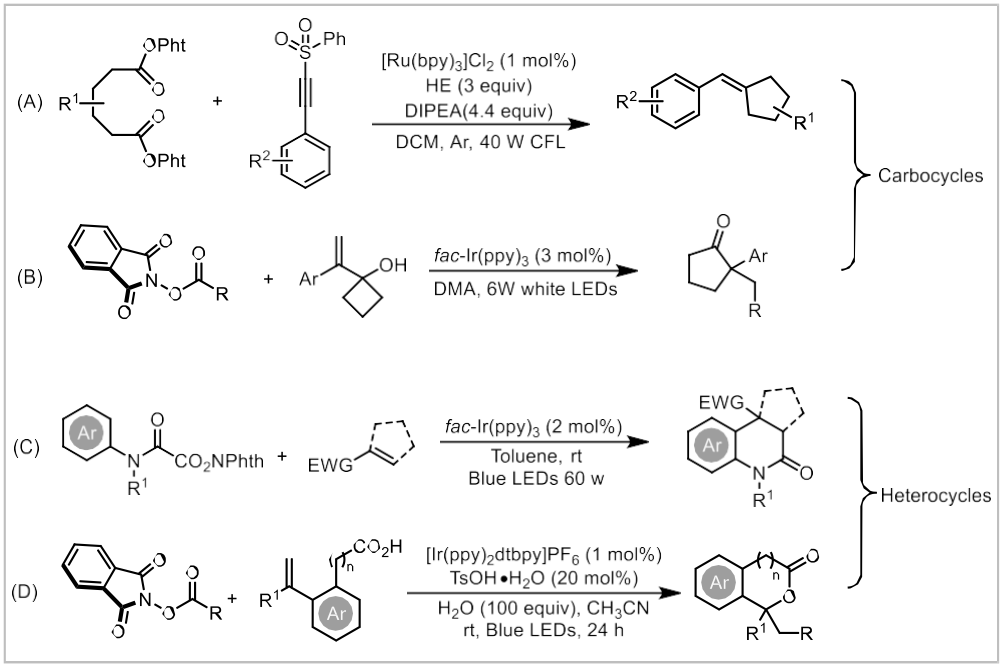
Recently, Singh and co-workers published a visible-light-driven organophotoredox methodology for the alkylation of coumarins at the C-4 position, utilizing NHPI ester as a source of radical species (Scheme 1.7E).[137] The reaction showed a unique reactivity profile; 4-alkylated-3-substituted coumarins were formed from primary carboxylic acid-derived NHPI esters, in contrast to secondary and tertiary alkyl-NHPI esters, which proved to be preferentially as chromanone derivatives. Its broad potential for modifying bioactive molecules was highlighted by the successful alkylation of coumarins by NHPI esters from natural products and drug-related carboxylic acids.

1.4.2 Alkylative Cascade Using *N*-(acyloxy)phthalimides

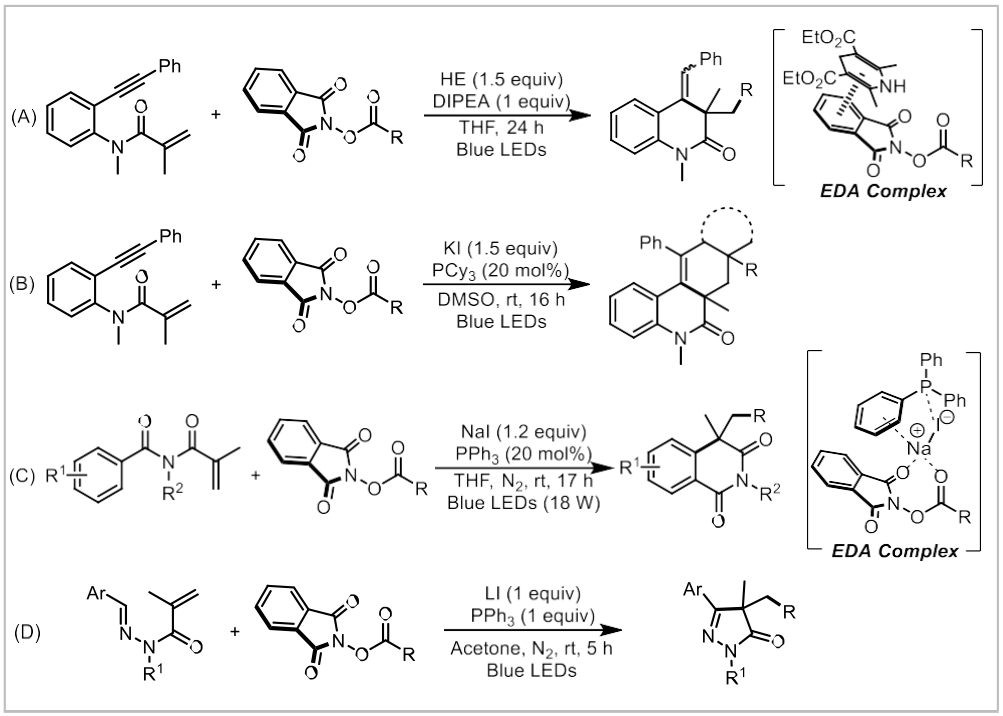
Cascade annulations are multiple bond-forming events that occur in a single reaction sequence, allowing the rapid assembly of complex structures from relatively simple precursors. When triggered using visible-light photons, these reactions can provide an effective yet sustainable means of increasing molecular complexity with a minimal environmental impact.[138-139] In 2016, the Fu research group published a new consecutive ruthenium-based photoredox-catalyzed cascade annulation methodology. This transformation benchmarks forming two C–C bonds via the reaction between NHPI esters prepared from adipic acid and 1-(2-rylethynylsulfonyl)benzenes using HE and DIPEA. The obtained carbocycles were formed in moderate-to-good yields (Scheme 1.8A).[140] Subsequently, Shi *et al.* discovered a cascade reaction catalyzed by an iridium-based photoredox system. Their approach was based on a sequential sequence of alkyl radical addition and pinacol rearrangement involving aliphatic NHPI esters and styrene derivatives with cyclobutanol substitution. This cascade reaction produces functionalized cyclic ketones in excellent yields under mild conditions (Scheme 1.8B).[141]

Using Ir-catalyzed visible photoredox catalysis, Taylor and Donald's group established a novel method for producing carbamoyl radicals from NHPI oxamide derivatives. The carbamoyl radicals underwent a cascade annulation process with electron-poor alkenes involving addition and cyclization. This methodology enabled the synthesis of a diverse array of valuable 3,4-dihydroquinolin-2-one products (Scheme 1.8C).[142-143] Subsequently, Han *et al.* established a highly efficient visible-Ir photoredox-catalyzed alkylation/lactonization cascade annulation. Using this technique with unsaturated carboxylic acids and alkyl-NHPI esters, it was possible to synthesize moderate to highly substituted lactones in moderate to good yields (Scheme 1.8D).[144] This methodology exhibited tolerance towards alkenoic acids and *N*-

(acyloxy)phthalimide esters derived from carboxylic acids of varying degrees of alkyl substitution, including primary, secondary, and tertiary alkyl groups.



Scheme 1.8 Formation of Carbocycles and Heterocycles with NHPI esters.



Scheme 1.9 Formation of Nitrogen-Containing Heterocycles with NHPI Esters via EDA Complex.

Li *et al.* reported a simple strategy for photoinduced decarboxylative cyclization of 1,7-enynes and alkyl *N*-(acyloxy)phthalimide (NHPI) esters.[145] This methodology enables the efficient synthesis of complex polycyclic molecular frameworks with moderate to good yields (Scheme 1.9A). This process comprises decarbonylation, radical addition, and cyclization to generate carbocycle-fused polycycles in a single operation. Similarly, Paixão *et al.* developed a new methodology based on a photo-induced cascade reaction between 1,7-enynes and NHPI esters (Scheme 1.9B).[146] Sequential single-electron transfer reactions lend themselves to this

approach, allowing for the direct generation of quaternary carbon-bearing functionalized dihydroquinolinones. The resulting compounds were isolated with variable efficiencies, moderate-to-good yields, and high selectivity.

Li *et al.*, in 2024, developed a visible-light-promoted strategy to construct isoquinolinediones, representative structures of natural products and pharmaceuticals. Unlike traditional reductive pathways that need undesirable reaction parameters like harsh conditions or costly catalysts, this green protocol induces smooth reduction by employing cheap reagents such as NaI and PPh_3 (Scheme 1.9C).[147] This reaction involves cascade cyclization that achieves decarboxylation and ring formation in one step, providing a very efficient and sustainable approach to these useful building blocks.

We have also recently developed *N'*-arylidene-*N*-acryloyltosylhydrazides as novel platforms for synthesizing biologically relevant alkylated pyrazolone compounds. Exposing these substrates to light initiates a cascade reaction that leverages *N*-(acyloxy)phthalimides as cost-effective sources of alkyl radical species (Scheme 1.9D).[148] This approach utilizes a photoexcited charge-transfer complex formed between alkyl *N*-(acyloxy)phthalimide ester substrates and a readily available electron-donor system, wherein lithium iodide and triphenylphosphine cooperate.

1.5 Aryl Diazoesters as Alkylating Reagents

Carbenes are exceedingly reactive species with only six valence electrons at the divalent carbon center and are prominent intermediates in organic synthesis. This carbon forms two sigma bonds with neighboring atoms, whereas the remaining electrons move into the same orbital (singlet carbene) or different orbitals (triplet carbene), which has a significant impact on their reactivity.[149] Carbenes are elusive entities that cannot be isolated in their stable forms but have been particularly well characterized by spectroscopic techniques and computational models. The reactivity of these compounds is shaped by the surrounding functional groups, enabling diverse chemical transformations, such as the construction of carbon-heteroatom bonds.[150] Traditionally, the field has been dominated by metallocarbene complexes (carbenoids), particularly for asymmetric synthesis.[151-155] However, identifying photochemical reactivity to generate carbenes from diazo species in 2018 has changed their use, significantly increasing their synthetic usefulness.[156] Carbenes generated from diazo alkanes have remained relatively unexplored until the last few years. From the mid-to-late 20th century, much work has been devoted to studying the decomposition of diazo compounds and the formation of carbene intermediates. Platz, McMahon, and Sander were the first to use experimental techniques to shed light on the structure and behavior of many of these elusive species using spectroscopy.[150] Subsequently, the emergence of quantum chemical techniques, such as density functional theory (DFT), has led to a greater understanding of carbene chemistry. This greatly broadens our knowledge about their reactivity and, as such, considerably adds to their synthetic utility.[64]

The photolysis of diazo alkanes has become a powerful approach to carbenes in recent years.[64, 157] Ultraviolet (UV)photolysis and thermolysis were used in the initial phase, but both methods generally led to highly reactive carbenes that gave uncontrolled side products, leading to low practical value for synthetic use. A significant breakthrough was achieved in the mid-20th century with the development of metal-catalyzed carbene transfer reactions, which offered a much better approach to controlling carbene reactivity. Since then, a wealth of carbene-mediated synthetic strategies have shaped the field of organic chemistry.[150] Unlike diazo species, aryl alkyl diazoesters have emerged as a powerful class of precursors capable of generating singlet carbenes via photolytic nitrogen extrusion.[150] These reagents are appreciated for their simple syntheses, stability on the bench, and wide substitution tolerability, allowing for the fine-tuning of carbene reactivity.

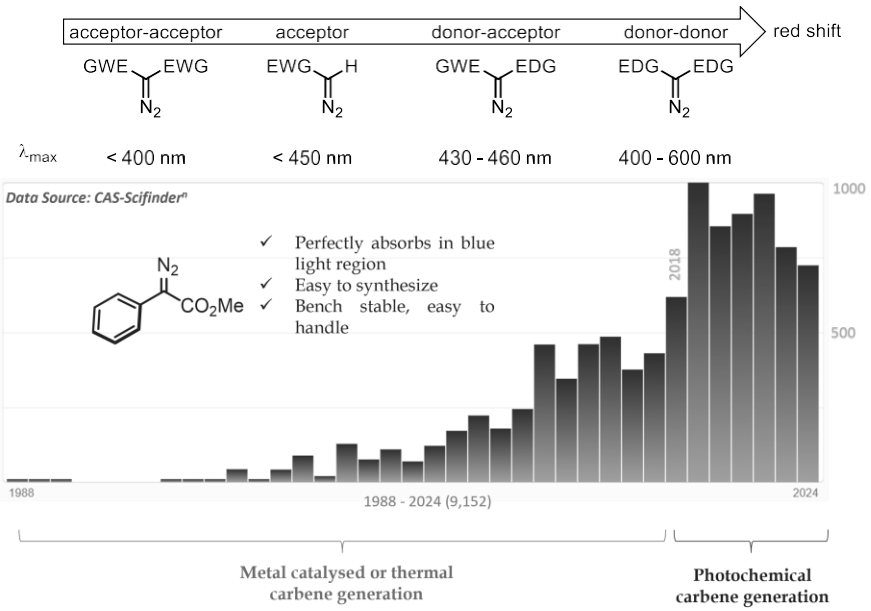


Figure 1.17 Carbene Precursors and Trend of Aryl Diazoesters Utilisation for Carbene Mediated Reactions.

Classical donor-acceptor diazoalkanes, especially aryl diazoacetates, have been commercially employed as carbene precursors in visible-light-mediated carbene transfer reactions. In most cases, diazo compounds are colored molecules (the absorption is strongly influenced by the substituents of the carbon bearing the diazo functional group). A donor moiety, typically an aryl ring in a symmetry-breaking twist configuration, is responsible for the absorption band's bathochromic displacement (Figure 1.17). As a result, the strong donation of π-electron density to the nitrogen atom lowers the LUMO energy without significantly affecting the HOMO level; thus, donor-acceptor diazo compounds (such as aryl diazoacetates) have intense absorptions in the visible wavelength range. Since Davies and Jurberg pioneered aryl diazoesters in 2018, their use has become a linchpin of sustainable synthetic method development.[156] These reagents are used frequently, with over 1,000 research publications per year detailing their use (Figure 1.17).

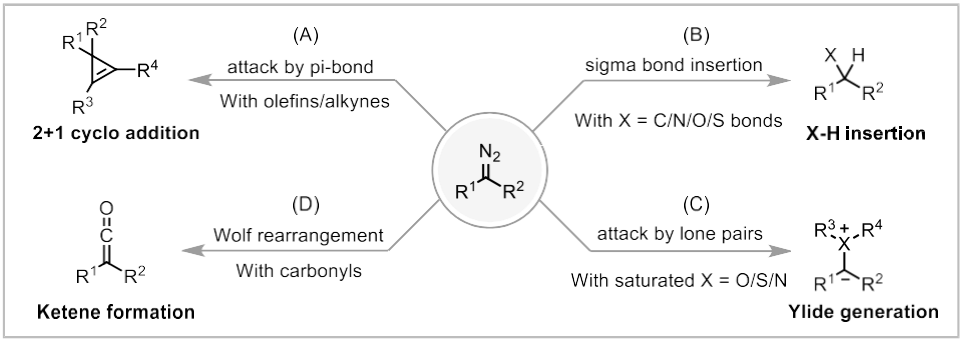
Carbene chemistry has served as a cornerstone for the progress of synthetic organic transformations, most notably by leveraging donor-acceptor (D-A) diazo compounds, including aryl diazoacetates.[151-152, 158-161] In these systems, the aryl group acts as the donor, and the ester group acts as an electron-withdrawing group, which leads to a highly reactive carbene center. The stereoelectronic properties of metal carbenoids arising from such compounds are crucial. X-ray crystallographic investigations of metal carbenoid substrates and related intermediates have provided detailed structural information that complements the mechanistic studies.[162] DFT calculations provide theoretical insights that complement experimental observations in the field, add a new dimension of activity, and provide robust support for evolution in practice.[163-164] Rhodium carbenoid complexes are among the most studied transition metals that produce unique reactivities for synthetic applications.[165-170] In this regard, the metal-free generation of D-A carbenes via blue LED light has recently provided exciting opportunities for sustainable synthetic methodologies. While D-A singlet carbenes show great promise, there is a major obstacle: they have been reported to decompose, making it impossible to obtain crystallographic data. This limitation requires integrating experimental data with computational modeling to bring their behavior to light. However, this was insufficient in some scenarios to capture the other reactivity characteristics.

The photolytic generation of singlet carbenes from alkyl aryl diazoesters affords a variety of electronic configurations, with the carbene carbon being sp^2 hybridized. Therefore, the

paired spins are placed in a non-bonded sp^2 orbital in this orientation, whereas the unhybridized *p*-orbital is empty.[171] These carbenes are generally considered electrophilic, similar to metal carbenoids, and their empty *p*-orbitals are a major component of their reactivities. However, in contrast to metal carbenoids, in which the lone pair from the carbene carbon atom is coordinated to a transition metal, singlet carbenes retain their lone pairs within the sp^2 orbital. This creates an interesting duality in reactivity. Although the empty *p*-orbital increases its electrophilic nature, a lone pair raises the potential for a nucleophilic nature, resulting in ambiphilicity. This double-electronic nature sets singlet carbenes apart from their metal carbenoids, often leading to disparate, even opposing, reactivities under analogous conditions.

Donor-acceptor (D-A) carbenes interact with nucleophiles, and their reactivity has been extensively studied, showing a wide range of reactivity patterns.[64] Nucleophiles (often derived from either oxygen or nitrogen species) engage the carbene through their lone pair, attacking the free p-orbital of the carbene carbon. This commonly results in O/N-H insertion products through a concerted reaction mechanism. Interestingly, other studies have also suggested different mechanisms of action. They often bind to singlet carbenes via hydrogen bonding to form a transient complex before progressing to the reaction, as shown for nucleophiles such as alcohols (R-OH).[172-173] In addition, reactions with cyclic ethers typically proceed through a different route, with the lone pair on the oxygen attacking the carbene carbon to generate an oxonium ylide as an intermediate.[174-175] A nucleophile can then attack the resulting intermediate, pushing the reaction towards additional transformations and further broadening the scope of carbene chemistry.

Different reactivities of singlet carbenes from aryl diazoesters have been reported based on the target substrate.[150] These species, with an empty *p*-orbital, are notable electrophiles, and the additional lone pair in their sp^2 orbital enables them to engage in other functional interactions, such as hydrogen bonding. Cycloaddition reactions with electron-rich olefins (e.g., styrene) or alkynes (e.g., phenylacetylene) generate singlet carbenes undergoing 2+1 cycloaddition via cyclopropanation or cyclopropenation (Scheme 1.10A).[157] Carbene insertion into an active X(=C/N/O/S)-H bond occurs through a concerted mechanism (Scheme 1.10B). During this reaction, the highest occupied molecular orbital (HOMO) of the X-H bond engages with the lowest unoccupied molecular orbital (LUMO) of the carbene, which is its vacant *p*-orbital. The interaction between the LUMO orbital of the X-H bond and the HOMO orbital of the carbene, represented by its filled sp^2 orbital, occurs simultaneously.[176] The electron-deficient carbene carbon withdraws electron density from the forming carbon-heteroatom bond, generating a partial negative charge and enabling proton transfer. This orchestrated route permits the highly efficient insertion of bonds.[176] Diazoesters have been extensively used for the photochemical generation of versatile singlet carbenes and metal carbenoids. Such intermediates have been used in transformations such as N-H, C-H, O-H, and S-H bond insertion into arenes, heteroarenes, and heterocycles, demonstrating their utility in modern synthetic chemistry.[150, 156-157]

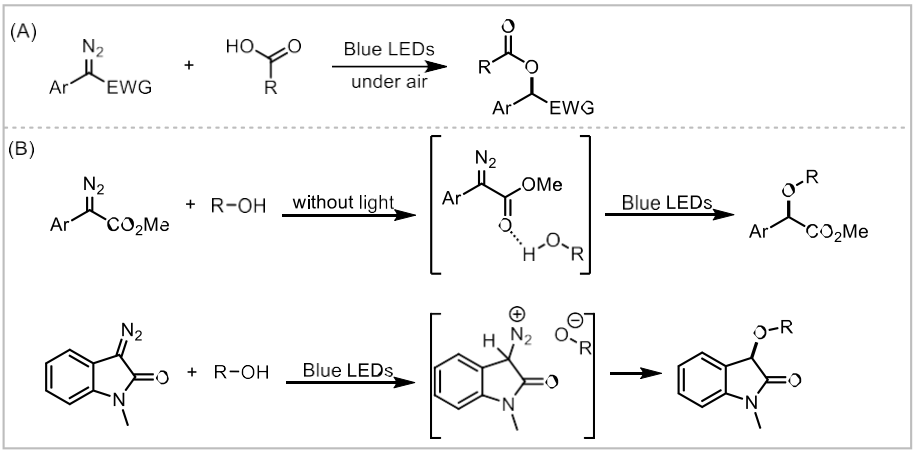


Scheme 1.10 Reactivity of Singlet Carbene in the Presence of Visible Light.

Carbene intermediates can generate ylides (e.g., nitrilium, pyridinium, oxonium, or sulfonium ylides) when the target substrate contains a saturated heteroatom, nitrogen, oxygen, or sulfur (Scheme 1.10C). These ylides are produced by the lone pairs of each heteroatom attacking the empty *p*-orbital of the carbene. The resulting ylides can then participate in dipolar cycloaddition reactions with the appropriate dipolarophiles, allowing for multicomponent reactions. This has become a focal point because dipolar cycloaddition is one of the most flexible strategies in organic synthesis.[177] α-keto diazo compounds are important carbene precursors. Carbene generation allows these intermediates to undergo Wolff rearrangement to produce reactive intermediates with broad synthetic applications in ketenes (Scheme 1.10D).[178-179] The combined reactivity of carbenes and ketenes also provides a powerful toolkit for developing efficient and unique transformations in organic synthesis.

1.5.1 *O*-alkylation Using Aryl Diazo Esters

The *O*-alkylation or O-H insertion reaction is a versatile method for assembling α-alkoxy or α-aryloxy Ketones, Esters, and oxygen-containing heterocycles.[180] This process often requires the formation of new C-O bonds, which can be achieved via the reaction of hydroxyl-containing molecules (e.g., water and alcohols, phenols, or carboxylic acids) with diazo compounds. The common mechanism involves a carbene intermediate, and interaction between a hydroxyl group and an electrophilic carbene, usually mediated by the catalytic system.[181] Subsequent proton transfer afforded the target *O*-alkylated product, demonstrating the power of this method to build complex oxygenated scaffolds under relatively mild conditions.

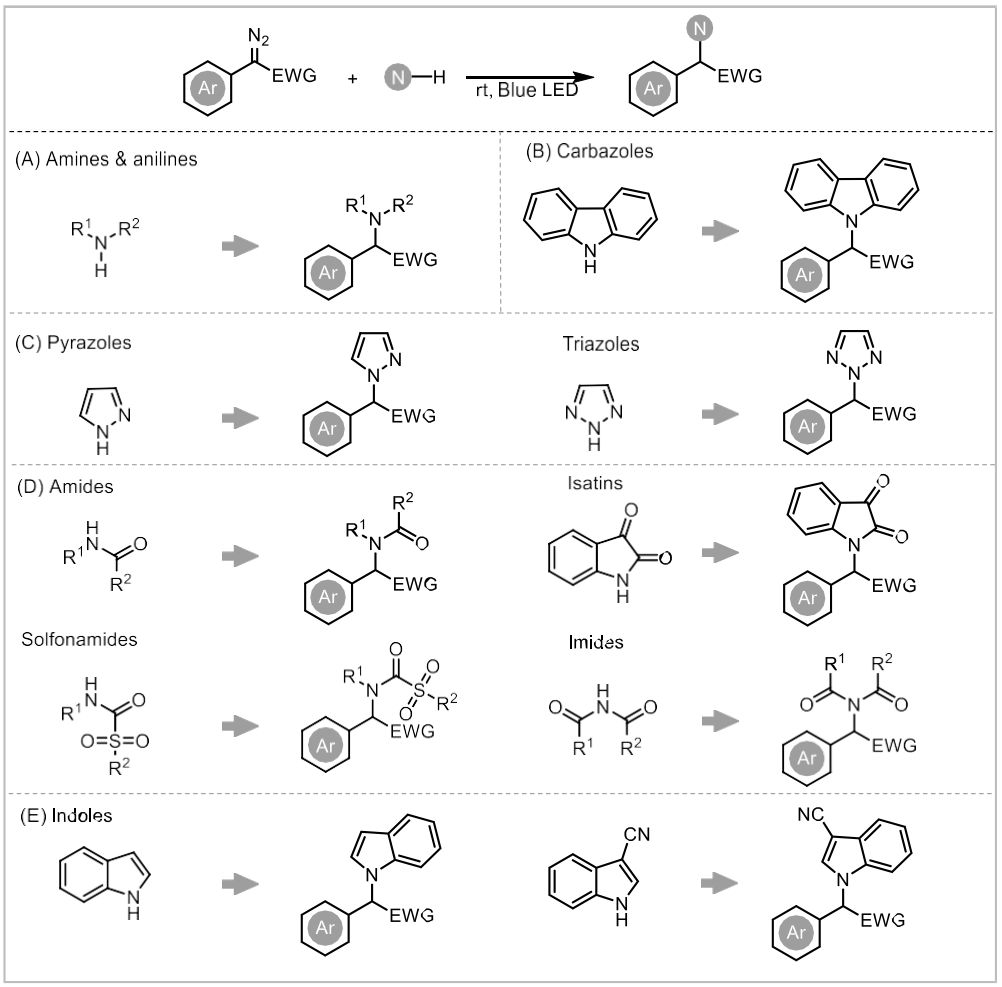


Scheme 1.11 Photoinduced O-alkylation of Diazo Compounds with Carboxylic Acids and Alcohols.

Recently, metal-free photochemical approaches have attracted great interest in enabling carbene-transfer reactions. One approach from the Davies group was the efficient O-alkylation of aryl diazoacetates with carboxylic acids under blue light irradiation, leading to ethers in good yields (Scheme 1.11A).[156] The Koenigs group subsequently developed a photoinduced approach to *O*-alkylation that differed from the previously mentioned reaction of aryl diazoacetates with less reactive alcohols and cyclic diazoamides, which proceeded by proton transfer (Scheme 1.11B).[173, 182-183] These studies illustrate the increasing applicability of light-driven metal-free methods in carbene chemistry.

1.5.2 *N*-alkylation Using Aryl Diazo Esters

Nitrogen-containing heterocyclic compounds are important owing to their high incidence in nature, like alkaloids and vitamins, and their role in pharmaceutical molecules and advanced materials. Moreover, due to their versatile nature, these compounds are also used in electroactive materials.[184-186] Forming new C–N bonds is crucial as a fundamental step because it allows the core heterocyclic frameworks to be constructed and existing molecules to be functionalized. However, developing efficient and eco-friendly protocols for introducing the amino group remains an attractive objective.



Scheme 1.12 *N*–alkylation of Diazo Compounds.

In a previous study, Jurberg and Davies demonstrated the insertion of N–H from aryl diazoacetates into amines and anilines under blue-light irradiation (Scheme 1.12A).[156] These steps produce a diverse array of *N*-alkylated products in high yields. Building on their experimental results, various research groups have enhanced the range and intricacy of this photochemical method for forming C–N bonds. This work demonstrates that aza-arenes are competent reactants for light-driven *N*–alkylation reactions with aryl diazoacetates. In 2019, *N*-alkylated products were synthesized using carbazoles as substrates by Patureau and Koenigs research groups (Scheme 1.12B).[187]

Later, Jurberg and co-workers described aryl diazoacetate *N*–alkylation into carbazoles, followed by pyrazoles and triazoles (Scheme 1.12C).[188] Notably, asymmetrical pyrazoles and 1,2,3-triazoles afforded distinct *N*-alkylated regioisomers. In addition to *N*-heterocycles, successful insertion reactions into the N–H bonds of compounds such as amides, isatins, sulfonamides, and imides have been performed, demonstrating a remarkable generality in the types of substrates that can be used in this type of reaction. Jurberg *et al.* reported that for less acidic N–H bond substrates (i.e. amides, isatins), only a catalytic amount of DBU was required to improve reaction yields (Scheme 1.12D).[189] In 2021, Sen *et al.* broadened *N*-heterocycles' scope to indoles under batch and flow conditions (Scheme 1.12E). [63]

1.6 Thesis Overview

The demand for chemical products is high owing to the increasing global population, which has stimulated industries to change their production strategies by adopting sustainable

and efficient production methods. Hence, the transition highlights the importance of processes that comply with environmental and safety regulations. The top of the pyramid is responsible for decreasing energy usage, eliminating harsh chemicals, and disposing of waste. With the increasing demand for sustainability in chemical production, the chemical industry must convert precursors to valuable products through improved methodologies and tractable and efficient methods to perform chemical transformations. However, balancing innovation and practical implementation is critical in responding to the world's growing demands. The exploration of novel photocatalytic approaches provides exciting pathways to tackle these challenges. Using the abundant and renewable energy sources that visible light constitutes, photocatalysis offers an energy-efficient pathway for reactions to proceed, typically at room temperature or moderately elevated temperatures. Furthermore, these light-driven transformations commonly circumvent toxic reagents, laying the foundation for eco-friendly and safe chemical transformations.

This thesis discusses developing novel visible-light-mediated strategies for the alkylation of nitrogen-containing heterocycles and the generation of heterocycles from an alkylative cascade process. These developments aspire to broaden the scope of classical synthetic methods and to discover new molecular reactivities. The aim was to increase the chemical diversity and complexity of mild and sustainable reaction conditions. Radicals and carbenes have traditionally been viewed as challenging and highly reactive species with limited-controlled synthetic utility; thus, their successful application reflects a unique step forward in modern chemistry.

Research Goal I.To develop a novel, more reliable, and photocatalyst-free methodology for constructing fused tetrahydroquinoline scaffolds. The approach utilizes visible-light-induced radical annulation between *N*-(acyloxy)phthalimides and *N*-substituted maleimides, with DIPEA as a crucial additive. This goal is addressed in **chapter 2**. The reaction proceeds through photoinduced charge-transfer (CT) complexes between the NHPI esters and DIPEA. So, here, we have constructed a nitrogen-containing heterocycle with a photocatalyst-free approach.

Research Goal II. To investigate the synthetic potential of alkyl radicals generated from NHPI esters and utilize these radicals in a synthetic context to contribute to the field of C(sp^3)-H functionalization and expand current options in molecular complexity. This goal is addressed in **chapter 3**. Herein, we describe a method utilizing organophotoredox catalysis for the C(sp^3)–H alkylation of 3,4-dihydroquinoxalin-2-ones. This method proved to be highly versatile, tolerating a variety of NHPI esters (both primary and secondary, as well as tertiary or sterically bulky substrates) while allowing for the successful alkylation of different 3,4-dihydroquinoxalin-2-ones. So, here we have functionalized nitrogen-containing heterocycle with photocatalyst and base as additive.

Research Goal III. To explore the direct photolysis methods, which use only photons to drive the chemical reaction. This goal is addressed in **chapter 4**. In this, we report green and sustainable visible-light-mediated *N*-alkylation of (aza)uracils with α-diazo esters, facilitating efficient and concurrent imide alkylation. Interestingly, combining (aza)uracils and α-diazo esters in cyclic ether solvents like THF and 1,4-dioxane undergoes an intriguing three-component coupling reaction. This versatile methodology facilitates the functionalization of natural products and pharmaceuticals, enabling the synthesis of potentially bioactive molecular frameworks. So, here we have functionalized nitrogen-containing heterocycle without any additive.