Chapter

Visible-Light Photocatalysis of Aldehyde and Carbonyl Functionalities, an Innovative Domain

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Abstract

The chemistry of aldehydes and resembling chromophores portraits a natural tendency to undergo chemical reactions through nucleophilic reagents, owing to the polarization arising from the electronegativity of oxygen atom, and they also can enolize as a result of the acidic nature of the α-hydrogen of the carbonyl functional group; thereby the C—C bond forming reactions can be attained either intra- or intermolecularly. Carbonyl addition reactions, enolate chemistry coupled with their capability to undergo [2+2] cycloaddition reactions, and the chemistry of carbonyl compounds are being mind-numbingly exploited in the design and process development of industrially, commercially, pharmacologically, and biologically value-added compounds. Ultimately abundant name reactions were registered, and many novel reactions endlessly appear; of late, prodigious development has been reported under the heading of visible-light photocatalysis (VLPC). Fascinatingly, VLPC has opened a new domain in the synthetic organic chemistry, and this domain paves the way to access broad spectrum of organic compounds with the ease of operations. In this chapter the chemistry of carbonyls by VPLC is briefly presented, which is comprising of not only functional group transformations but also asymmetric syntheses of complex organic compounds.

Keywords: aldehydes, VLPC, photosensitizers, asymmetric alkylation, enamines

1. Introduction

The periodic table comes to the mind when thinking of elements in chemistry, while organic chemistry brings to mind substances such as alcohol, aldehydes, ketones, aromatics, and other compounds based on the functional groups. Aldehydes, ketones, and carbonyl moieties are the most popular and routinely exploited functional groups in synthetic organic chemistry and in the design of organic synthesis since they render the desired synthetic manipulation and spring an easy access to complex molecular architecture. Not only in modern times but also from the times of alchemy, formaldehyde is very well utilized for embalming and preserving dead animal species by biologists; consequently, aldehyde class of compounds ranks to be the parent compounds for many other classes of compounds. Acetyl coenzyme derived from aldehyde functional group or acetaldehyde moiety is

responsible for the wide variety of natural products through biosynthesis, while toward the syntheses and manufacture of chemicals on the laboratory and in industries, also the aldehyde functional group is very well synthetically manipulated. They were not only converted into structurally complex compounds through enzymes, catalysts, and thermal process, but also photons convert aldehydes into other molecular architectures by means of eminent photochemical-chemical reactions such as Norrish-type photolysis, cyclobutanol formation through Yang reaction, and [2+2] cycloaddition with alkene (Paternó-Büchi reaction). Apart from conventional catalytic way, traditional synthesis uses name reactions and photochemistry; of late, visible light is being used [1]. Apparently, solar energy is a benign, benevolent, and renewable source of energy. Visible light emerging from the source of sun promotes chemical transformations through single-electron mechanism. Basically using visible light as energy source and in the presence of catalytic amount of metal photosensitizers or organocatalysts, the chemical reactions are carried out, and this process is termed as visible-light photocatalysis and abbreviated as VLPC [2, 3]. This opens a new chapter in the textbook of organic synthesis [4]. Photosensitizers are special molecules which support these light-induced molecular transformations by electron or energy transfer using its abundant light absorbance and redox property [5]. Aldehydes are subjected to VLPC conditions either protected as acetals or directly during the course of a reaction [6]. Further transformations such as oxidation to COOH are also essential reaction of aldehydes [7]. Aldol condensations and enamines are further variations in their reactions as building blocks in organic synthesis [4]. Thus, the application of aldehydes as building blocks is now elaborated with their VLPC reactions adding to its reaction repertoire. In this chapter we will discuss on the recent developments on VLPC of aldehydes.

VLPC is advantageous over the conventional catalysis since it employs the clean, renewable, and readily available visible light from our sun and this state-of-the-art protocol is convenient in its operation. Bench chemists are fascinated by VLPC due to the ease of recycling the heterogeneous catalytic material by simple filtration and because reactions are carried at ambient temperature and the work-up procedure is quite simple. Eventually, this field and phenomenon of synthetic organic chemistry have emerged as an innovative subdiscipline over the last decade; the scientists have made a step forward by carrying out the asymmetric induction [8]; with the advancement in modern analytical tools and the hard work of enthusiastic chemists, VLPC of aldehydes is emerging exponentially.

In the visible-light photocatalysis, the catalytic species is activated by the action of light, and the photocatalytic material is mostly a semiconducting material which in turn is capable of activating even the small molecules [5]. When the catalytic material is irradiated with light, it undergoes the absorption of photon, and the electron (e^-) is excited from the valence bond to the conduction band; consequently, a positive electron hole is generated in the semiconducting material (h^+), and this process is termed as *photoexcitation*. The excited electron then comes to the ground state through the mechanisms such as recombination and dissipates by means of non-radiative mechanism; in a sense, following the photoexcitation process, the catalytic material excited transfers the energy to the molecules in its close proximity through an orthodox redox mechanism in a pure chemistry sense, and the single-electron transfer (SET) occurs. For brevity, the mechanism is provided succinctly; in a nutshell, light source excites the catalytic material and transfers the energy to other molecules close by, and the chemical reaction occurs by means of electron transfer mechanism. This new discipline opened a new science of photophysics and photochemistry of transition metal coordination compounds. In this chapter a discussion of visible-light photocatalysis of aldehyde compounds is

presented; the discussion revolves around the recent developments on the chemistry of aldehydes in the domain of VLPC (**Figures 1** and **2**).

The polypyridyl complexes of Ru and Ir afford unique chemical reactivities due to their long-lived excited states when excited by visible light [5]. They are chemically robust and possess redox properties that are further fine-tunable by modifying the polypyridyl ancillary ligands. The $Ru(bpy)_3Cl_2$ is a widely known and commonly used photoredox molecule. The absorption of visible light leads to excited states that can function both as oxidants and reductants, which allows the generation of radical cations or radical anions under mild conditions. The amphoteric redox reactivity of the excited triplet state of $Ru^{II}(bpy)_3{}^{2+}$, $(^{*}Ru^{II}(bpy)_3)^{2+}$, enables two distinct catalytic cycles, namely, the reductive quenching (RQC) and the oxidative quenching cycles (OQC). In RQC, $(^{*}Ru^{II}(bpy)_3)^{2+}$ first oxidizes a reductant into a radical cation and reduces into $Ru^{I}(bpy)_3{}^{+}$ which subsequently reduces an oxidant into a radical anion species and converts itself into the ground-state catalyst. OQC starts with the oxidation of the complex $(^{*}Ru^{II}(bpy)_3)^{2+}$ to $Ru^{III}(bpy)_3{}^{3+}$ followed by its reduction into $Ru^{II}(bpy)_3{}^{2+}$.

Based on these viewpoints, cyclometallated Ir complexes have been rapidly developed due to their superior photophysical and photochemical properties. These photocatalysts are chemically robust and possess long-lived excited states. Their favorable redox properties allow redox-neutral reactions to be carried out as both reductants and oxidants that can be transiently generated during different stages in the catalytic process. This reactivity pattern thus is beneficial allowing exploration of

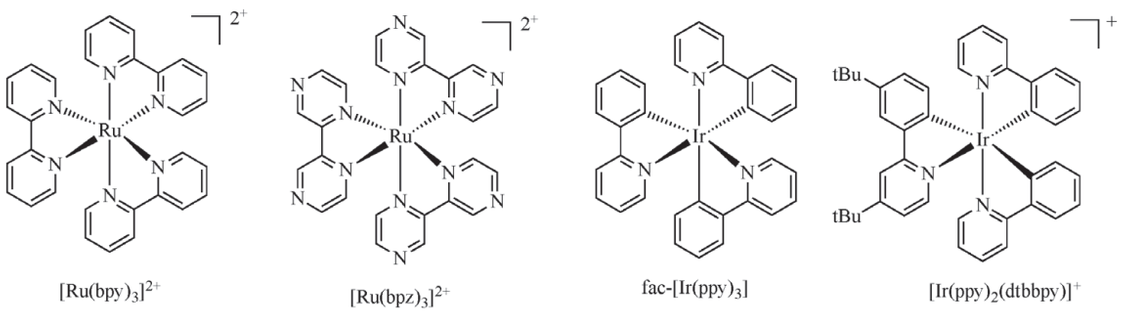

Figure 1.
Photosensitizers: $[Ru(bpy)_3]^{2+}$, $[Ru(bpz)_3]^{2+}$, fac-$[Ir(ppy)_3]$, $[Ir(ppy)_2(dtbbpy)]^{+}$. Properties of $[Ru(bpy)_3]^{2+}$ photocatalyst—[MLCT – λ = 452 nm].

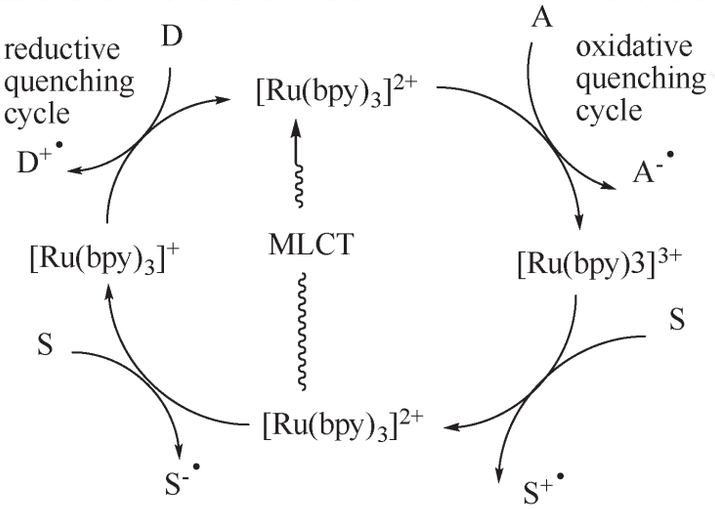

Figure 2.
Ru redox cycle: A—sacrificial electron acceptor; D—sacrificial electron donor; S—substrate; bpy—2,2′-bipyridine; MLCT (metal to ligand charge transfer) – λ = 452 nm.

alternate reaction pathways under benign reaction conditions. They have thus been used as photoredox catalysts and serve as photosensitizers in organic synthesis [5].

2. Photoacetalization

Aldehydes are prone to oxidation and amenable to attack by nucleophiles and can enolize, and as a result the —CHO functional group needs to be protected while carrying out the complex molecular architecture. Protection, de-protection, and reversing the reactivity or polarity through umpolung are the rudimentary strategies in the realm of organic synthesis. For these important tactics, recently VLPC has contributed a protection methodology, and the authors have protected the —CHO group as acetal [6]. The advantage of this protocol is that it does not employ the strong mineral, Lewis, and other acidic conditions; consequently the VLPC strategy presented by the chemists ranks as green technology. The protection was carried out using an organic dye, Eosin Y, with the use of [light-emitting diode (LED)] irradiation to promote the reaction under a milder condition. Several aldehydes were catalyzed in very high yields under household irradiation to the corresponding acetals (**Figure 3**).

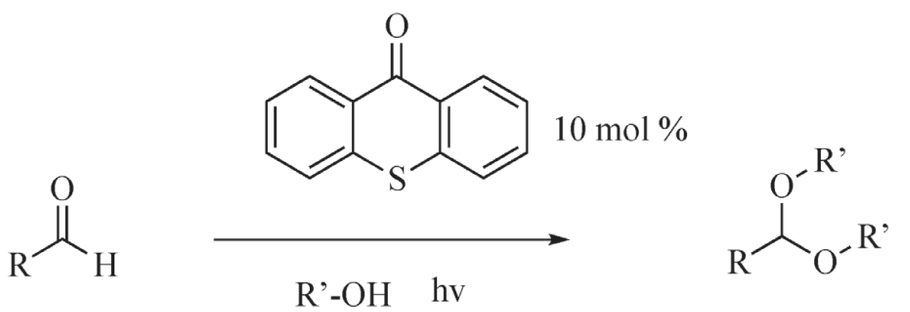

Figure 3.
Photocatalytic synthesis of acetals from aldehydes.

3. Photo-oxidation of aldehydes

The oxidation of organic compounds is being continuously explored since it is an important functional group modification, and the bench chemists are looking for environmental compatible and cost-effective methodologies for the same. By means of commercially affordable catalytic materials, several aldehydes were conveniently converted into their respective carboxylic acids where the $^1[O_2]$ is used as oxidant catalyzed by Ru and Ir catalytic materials. The reaction is notably chemoselective and does not distress other oxidizable functional groups assembled within the molecule. Among the photosensitizers studied, $Ir(dFppy)_3$ was the most efficient giving 99% yield of product from p-anisaldehyde. A wide range of aldehydes was studied with this catalyst and efficaciously oxidized under visible light [7] (**Figure 4**).

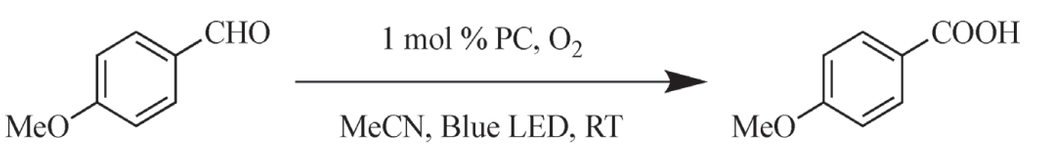

Figure 4.
Photocatalytic oxidation of aldehydes [7].

4. Direct C—H arylation and alkylation of aldehydes

Direct and catalytic C—H activation or functionalization comprising of arylation, alkenylation, alkylation, allylation, and annulation reaction is an important field in the synthetic organic chemistry in the manufacture and the process development of pharmacologically and biologically active ingredients. Knowing the importance of C—H activation, direct arylation of aldehydes has been achieved in a synergistic manner, where nickel catalyst was employed in combination with VLPC system. In this outstanding redox system, a hydrogen atom transfer (HAT) was achieved on the reactions in between commercially available aldehydes and aryl and alkyl bromides under milder conditions; it is interesting to note that the yields are excellent [9] (**Figure 5**).

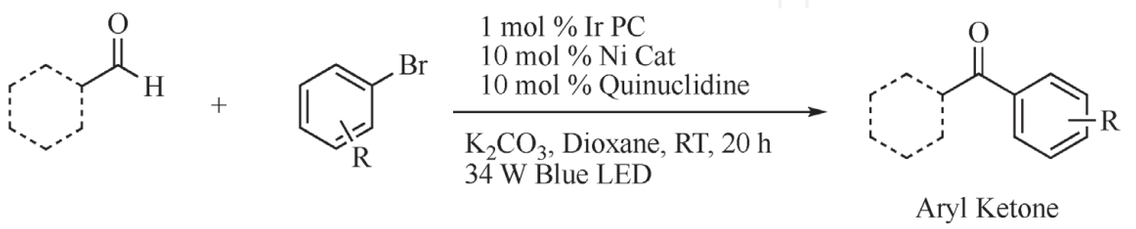

Figure 5.
Direct C—H arylation and alkylation of aldehydes [9].

The mechanism is based on the photoexcitation of the Ir photocatalyst which gives rise to the highly oxidizing species Ir* Ir[dF(CF3)ppy]2(dtbbpy) which oxidizes quinuclidine to form a cation radical. This radical cation then engages in a HAT event with any aldehyde to generate the acyl radical. Simultaneously oxidative addition of aryl bromide to LnNi (0) generates the aryl-Ni (II) species which is intercepted by the acyl radical to form the acyl-Ni complex. Both the Ni and the Ir photoredox catalysts then turn over in a critical reductive elimination step to the desired ketone product while regenerating the Ir and Ni catalysts. It is interesting to note that using this protocol, a pharmacologically active ingredient, namely, haloperidol, a typical antipsychotic drug, was synthesized [9] (**Figure 6**).

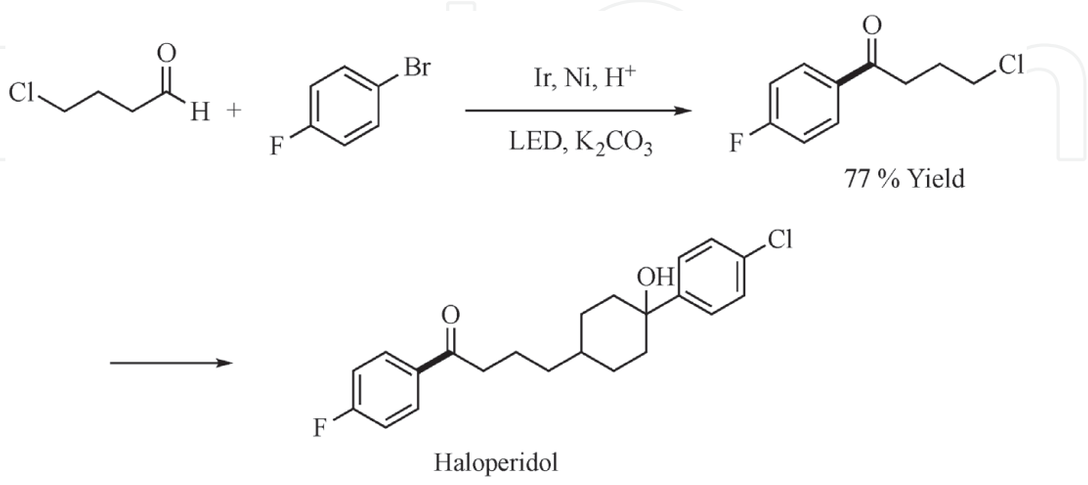

Figure 6.
Synthesis of haloperidol.

A two-step synthesis of haloperidol was achieved by this photoredox methodology. 1,4-Chlorobutanal was merged with 1-bromo-4-fluorobenzene using the

photoredox protocol to yield the ketone in high yield. Further exposure of this to the piperidine nucleophile thus gave haloperidol in short steps.

5. C—C bond formation enhanced by VPLC and alkylation of aldehydes through alkenes as alkylating agents

The α-alkylation of carbonyl compounds is a routine affair for synthetic chemists both for making substituents and also to synthesize pharmaceutically active ingredients (**Figures 7** and **8**). In the case of α-alkylation of aldehydes, the acidic methylenic (CH_2) hydrogen atoms are acidic in nature, and they can be removed; as a result an enol form is produced which directs the alkylating agents attached to the α-alkylation. A skillful execution of three catalytic materials together in a synergistic fashion enables an enantiomeric α-alkylation of aldehydes; mechanistically, the triple catalytic process is sequenced to deliver a hydrogen atom transfer, electron

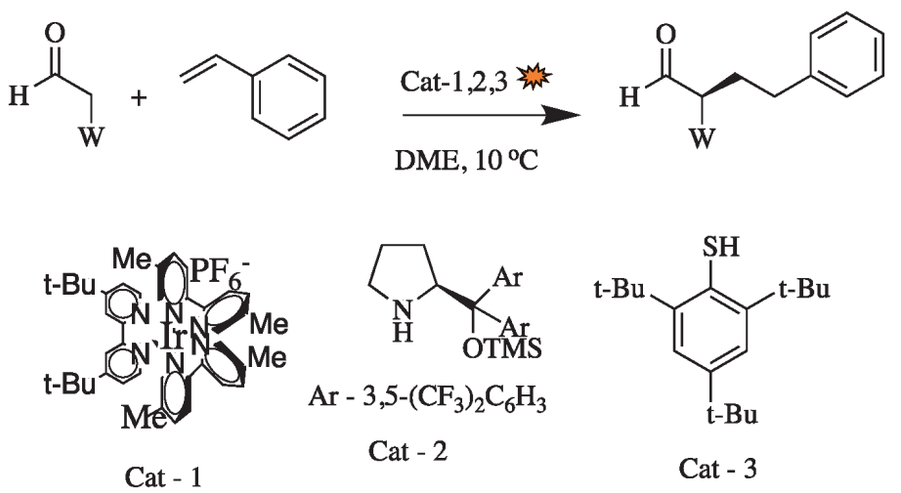

Figure 7.
Intermolecular alkylation with alkenes.

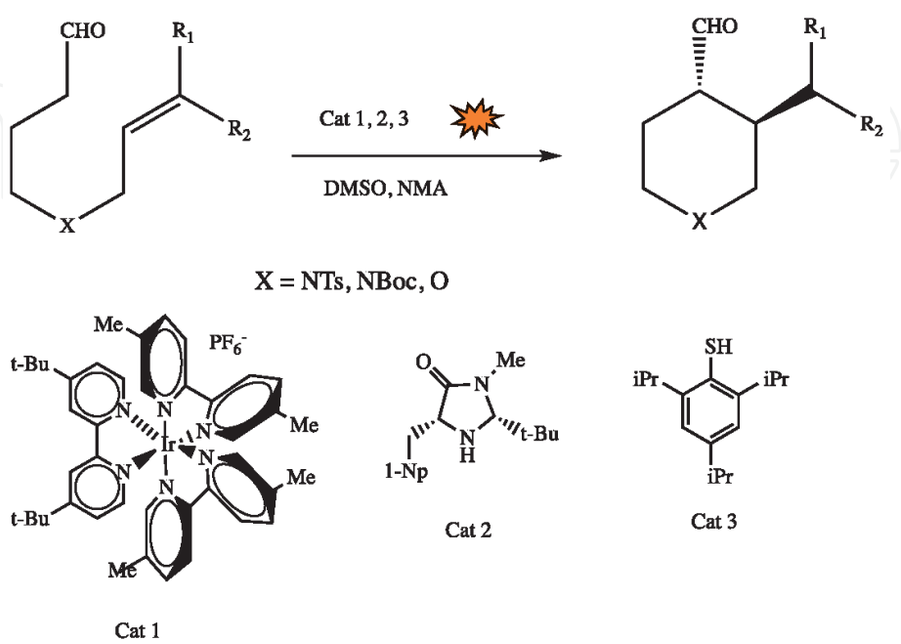

Figure 8.
Intramolecular alkylation.

borrowing tendency, and chirality induction through chiral imidazolidinones or prolinols with a thiophenol where the iridium catalyst transfers the activation of molecules by means of light energy (λ). The α-alkylation is carried out both by inter- and intramolecularly where the alkenes are alkylated at the α-position to the aldehyde functional group to furnish cyclic and acyclic products. The process is atom economical with a stereoselective process, allowing the production of value-added molecules from feedstock chemicals in a single step while consuming only one photon [10].

The mechanistic pathway is based on the excitation of Ir complex, and simultaneously the chiral reagent adds to the aldehyde compound through elimination of water and forms an enamine. The excited iridium complex oxidizes the enamine present in the reaction medium through a single-electron transfer mechanism; thus formed enaminyl radical adds to the alkene substrate producing a carbon radical which is finally trapped by the hydrogen atom transfer catalyst. During the work-up procedure, the iminium ion is hydrolyzed to get the enantiomerically enriched product, and the organocatalyst is regenerated. Finally the reduction of the thiyl radical by the Ir(I) species regenerates the thiol catalyst as well as the Ir(III) catalyst to complete the redox cycle.

With the success in the α-alkylation protocol, its intramolecular version also achieved where an intramolecular cyclization with tethered alkenes was first attempted to determine the feasibility of enantioselective ring formation reaction. Interestingly, carbocycles and heterocycles were synthesized with high yield and enantiocontrol. Tosamide- or carbamate-protected N-tethered aldehydic alkenes gave rise to the corresponding piperidines, ether-linked systems provided trans-substituted tetrahydropyrans, and carbocycles were also attained. Pyrrolidines were also formed as well as seven-membered rings such as azepanes or cycloheptanes. High stereocontrol was obtained with trisubstituted alkenes, and where multiple alkenes were available, only proximal alkenes reacted to provide the corresponding cyclic molecule.

Following this successful reaction, intermolecular reactions with styrene was attempted. A variety of substituted aldehydes provided the alkylated products in high yields and selectivity. Terminal alkenes were suitable substrates though 1,1-disubstituted alkenes reacted with moderate efficiency.

6. Enantioselective α-trifluoromethylation and α-perfluoroalkylation of aldehydes

The fluorinated hydrocarbons possess unique physical properties and are so useful in dyes, polymers, agrochemicals, and drugs. In pharmaceuticals the perfluoroalkylated compounds which impart valuable physiological properties that enhance binding properties elevate lipophilicity and/or improved metabolic stability. The enantioselective incorporation of the CF_3 and perfluoroalkyl groups has thus been a challenging task for the synthetic chemists, and the enantioselective α-alkyl trifluoromethylation of ketones and aldehydes has been elusive. First the enantioselective and organocatalytic α-trifluoromethylation and α-perfluoroalkylation of aldehydes have been successfully achieved using a commercially available iridium photocatalyst and imidazolidinone catalyst. MacMillan et al. describe the enantioselective trifluoromethylation of aldehydes via the successful merger of enamine and photoredox catalysis [11]. Their reaction is based on the property of electrophilic radicals to combine with facially biased enamine intermediates (derived from aldehydes and chiral amines). The radicals are derived from the reduction of alkyl halides by a photoredox catalyst (Ir(ppy)2(dtbbpy)). A broad

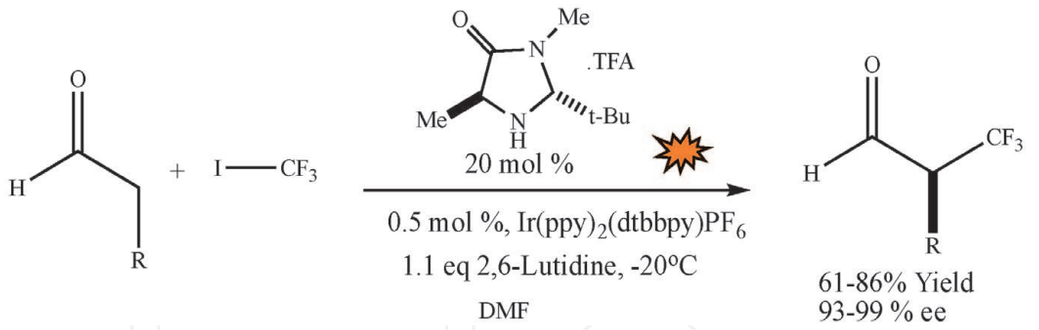

Figure 9.
α-Trifluoromethylation of aldehydes [12].

range of perfluoroalkyl halides were found to participate in the enantioselective alkylation reaction. N-perfluoroalkyl substrates of varying chain length undergo successfully reductive radical formation and enamine addition with high yields and enantioselectivity (**Figure 9**).

The α-alkylation of carbonyl compounds is always an essential tool in the synthetic organic chemistry. It can be carried out both inter- and intramolecularly; the intramolecular version builds up the cyclic compounds with enhanced stereoselectivity. Among the α-alkylation reactions, of late, α-trifluoromethylation reactions are being much exploited since these compounds are of greater importance in agrochemical and pharmaceutical compounds. Iodotrifluoromethane is employed as a trifluoromethylating agent under a VLPC condition where the reaction and optical yields are highly appreciable. Mechanistically, the light excites the Ir complex, which oxidizes the enamine compound through a single-electron transfer mechanism; the enamine radical adds with the alkene substrate producing carbon-centered radical; thus series of reaction provides the desired compound, and the catalyst is regenerated [12].

7. Reaction of chiral enamine with α-bromocarbonyl compounds

Photoredox catalysis and organocatalysis are two powerful fields of molecule activation that have found widespread application in the areas of inorganic coordination and organic chemistry. The merger of these two fields is an important solution in asymmetric chemical synthesis. Specifically, the enantioselective intermolecular α-alkylation of aldehydes with α-bromocarbonyls has been accomplished using an activation pathway that combines both the photoredox catalyst Ru $(bpy)_3Cl_2$ (where bpy is 2,2′-bipyridine) and an imidazolidinone organocatalyst. This simple alkylation reaction, which was previously elusive, is now broadly applicable and highly enantioselective [11].

The initiation of the reaction requires quenching of the photocatalyst excited state $^*Ru(bpy)3^{2+}$ by a sacrificial amount of enamine to provide the strongly reducing $Ru(bpy)_3^+$. Electron transfer to the alkyl bromide induces fragmentation, affording bromide and the electron-deficient radical. Condensation of the aldehyde with the imidazolidinone organocatalyst furnishes chiral enamine. The C—C bond formation then occurs by the radical electrophile addition to the accessible *Si* face of the enamine and generates the α-amino radical. The two catalytic cycles then intersect with the single-electron oxidation of $^*Ru(bpy)_3^{2+}$ to yield $Ru(bpy)_3^+$ and the iminium ion. Hydrolysis of the iminium releases the α-alkylated product and regenerates the organocatalyst (**Figures 10** and **11**).

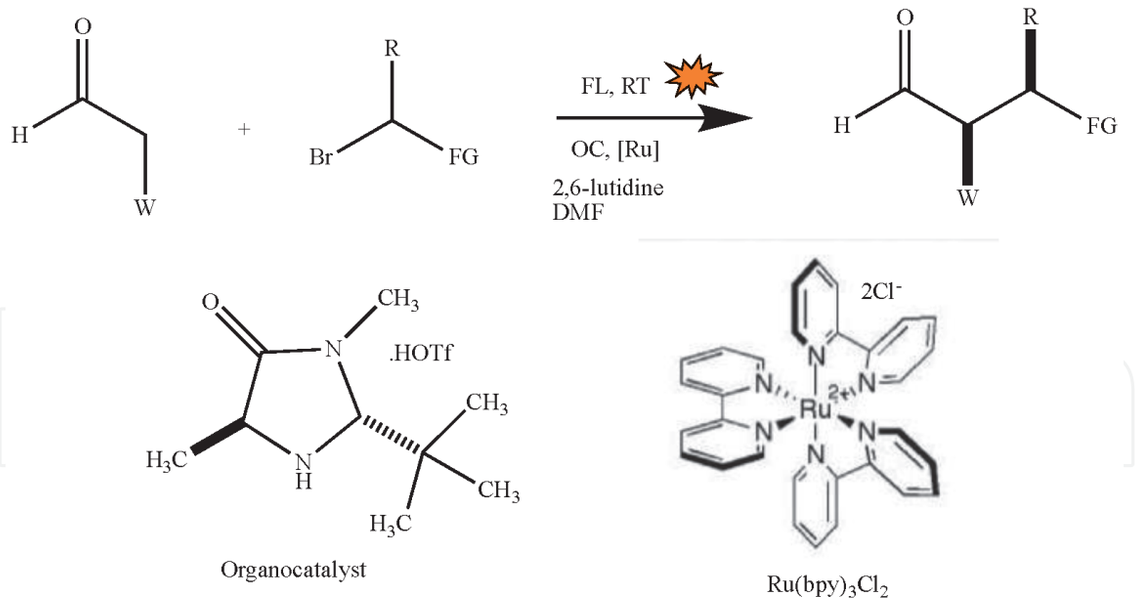

Figure 10.
The direct asymmetric alkylation of aldehydes.

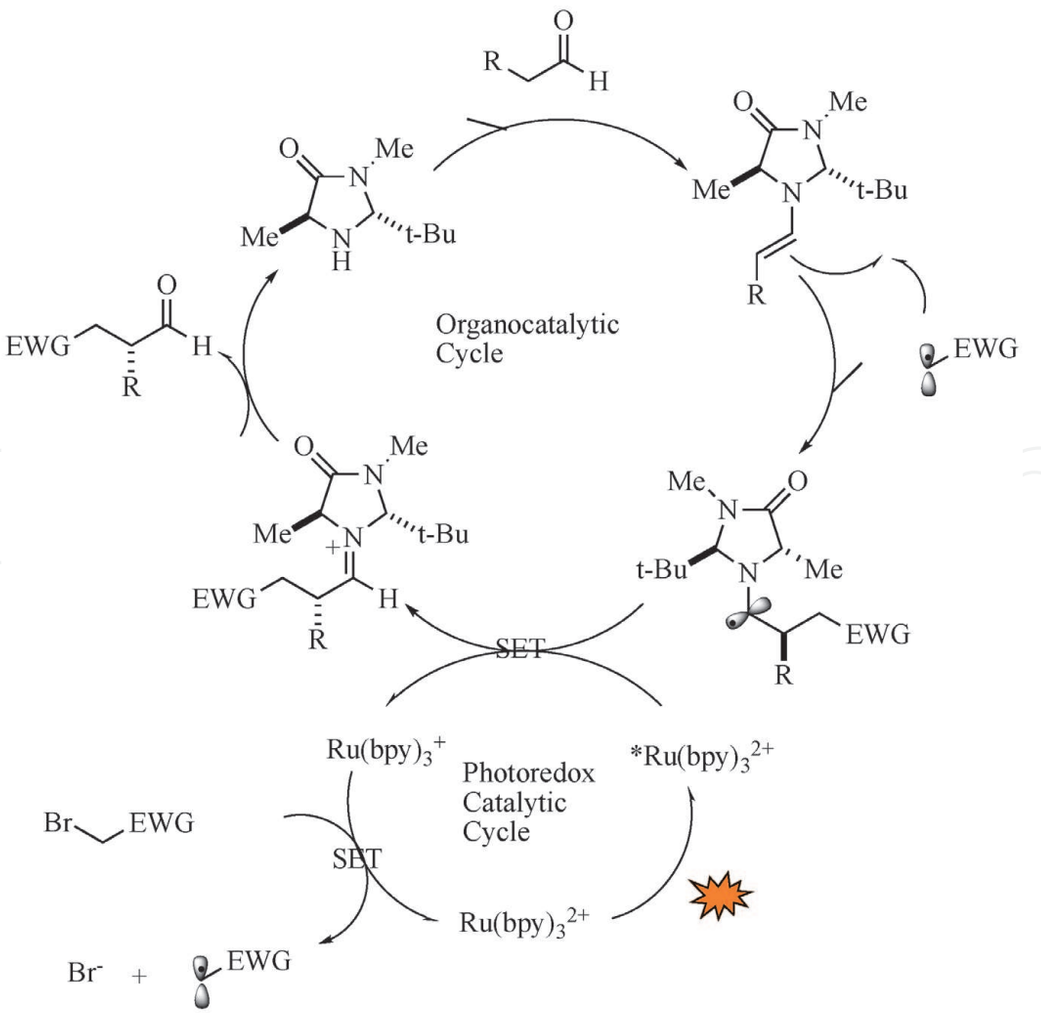

Figure 11.
Catalytic cycle—the direct asymmetric alkylation of aldehyde.

8. Asymmetric α-amination of aldehydes by means of photoredox and organocatalysis

The synthetic design and developing methodology on the creation of C—N bonds within the complex molecular architecture in a stereospecific manner is a challenging task which is routinely needed in the process development of drug molecules. Consequently, α-amino aldehydes are the valuable structural motifs in the process development of drug molecules. However, asymmetric α-amination of aldehydes poses a plethora of potential challenges since the reaction medium contains reagents and chemicals that can racemize product molecule. In this context, a VLPC methodology has been demonstrated for α-amination of aldehydes in an enantioselective fashion using nitrogen-centered radicals which enables the synthesis stable to racemization, a tactful synthetic methodology. N-centered radicals are easily generated using dinitrosulfonyloxy groups (ODNs) which are capable of producing the requisite heteroatom-centered radical upon exposure to household light and in the presence of designed catalyst. The nitrogen-centered radical thus is produced when treated with a transient π-rich enamine (derived from the coupling of an imidazolidinone catalyst with the aldehyde); upon photonic excitation, single-electron transfer reaction produces nitrogen-centered radical. Then the reaction proceeds to yield an iminium ion, which up on hydrolysis gives rise to enantiomerically enriched α-amino aldehyde [13] (**Figures 12** and **13**).

This is an organocatalytic and photoredox-based approach to the asymmetric α-amination of aldehyde, where a functionalized nitrogen is directly coupled with a formyl precursor. This protocol provides a ready access to N-substituted α-amino aldehyde architecture without any racemization with more than 85% enantiomeric excess.

9. Catalytic α- and γ-alkylation of aldehydes and enals, a direct photoexcitation approach

The α- and γ-alkylations of aldehydes and enals, respectively, are an important C—C bond forming reaction and very important in the building complex molecular architecture. These alkylations were reported as a photo-organocatalytic reaction where the product is enantioselective. The procedure is executed utilizing the commercially available aminocatalyst and carried out under the illumination of fluorescent light bulb in the absence of photoredox catalyst. The authors have demonstrated a strategy in which photochemical activation of substrates provides reactive radical species by the action of visible-light active photoredox catalyst. In this system the catalyst is chiral that acts as a dual catalytic system and provides an

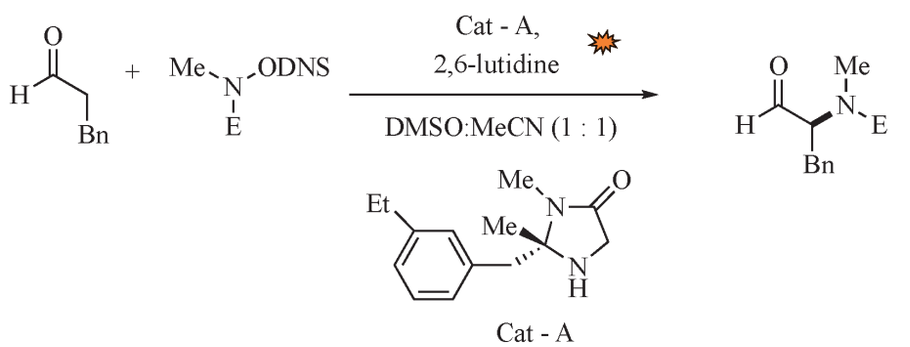

Figure 12.
α-Amination of aldehydes.

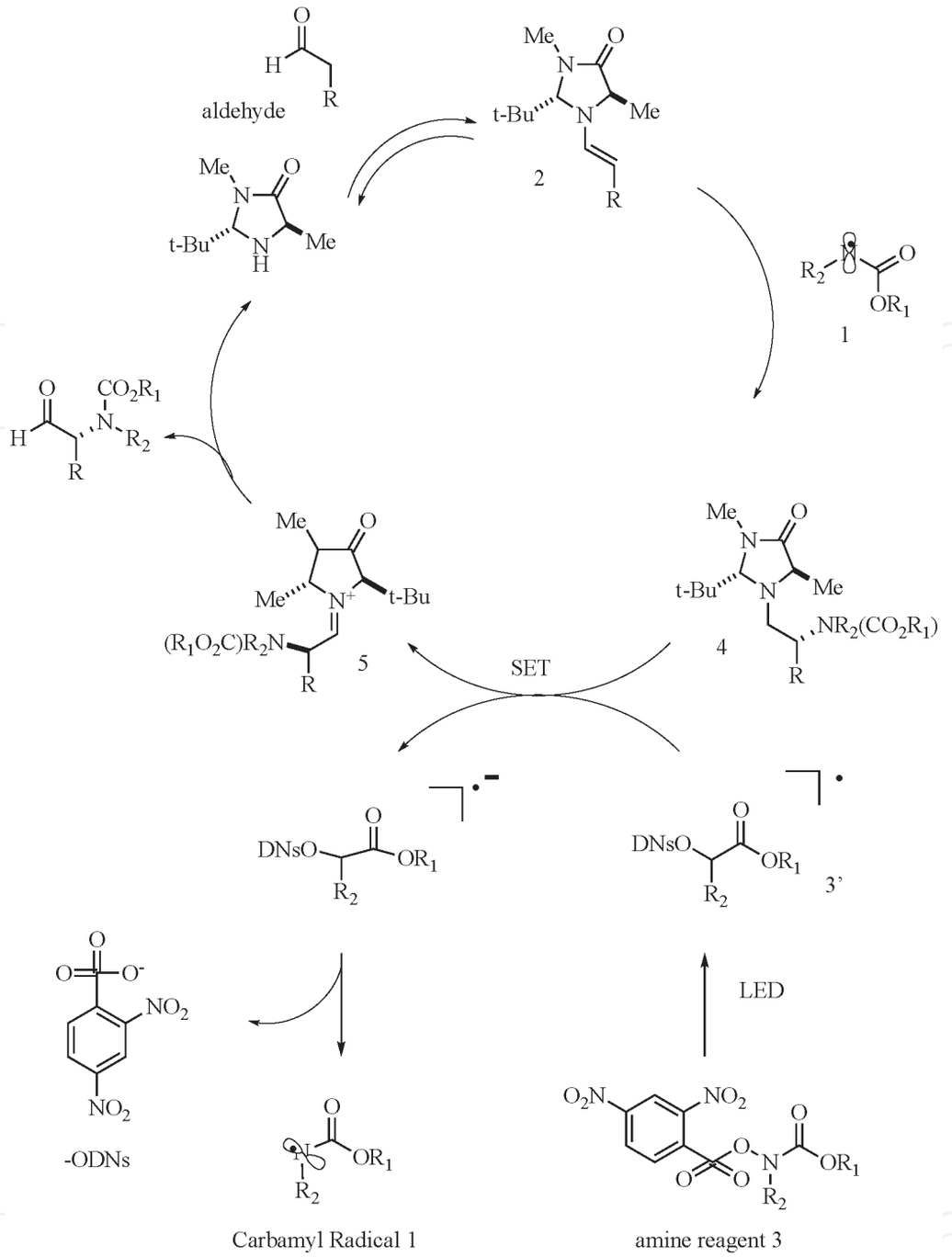

Figure 13.
Catalytic cycle of α-amination.

easy access to chiral molecules as products in an asymmetric fashion. In a sense, in the reaction medium, the transiently generated enamines undergo electronic excitation by the action of light form reactive radical species from organic halides, which, in turn, provide an effective stereochemical induction to yield enantioselective alkylated products [14] (**Figures 14** and **15**).

10. Photoredox cross-dehydrogenative coupling (CDC) of aldehydes with xanthenes (chiral enamines with diaryl compounds)

Aldehydes under the treatment with visible light underwent catalytic asymmetric cross-dehydrogenative coupling reactions with xanthenes and thioxanthenes, and it is interesting to note that xanthenes are important candidates in the dye stuff

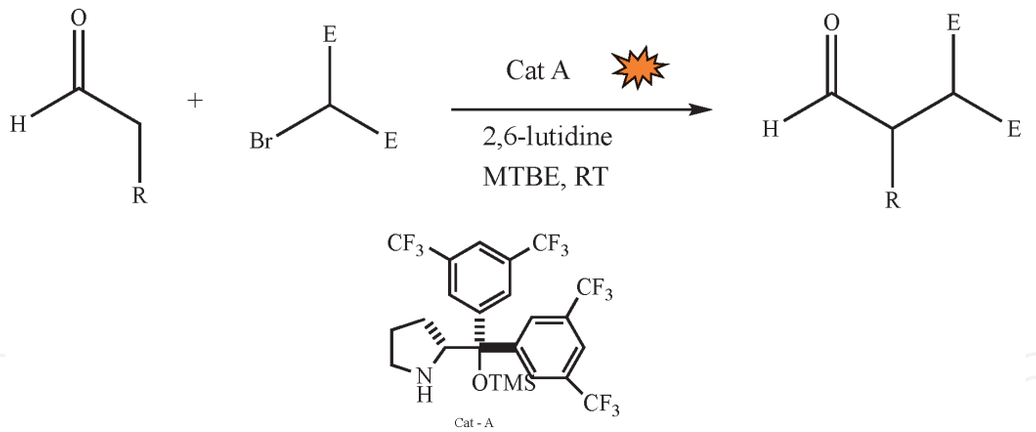

Figure 14.
α-Alkylation of aldehydes.

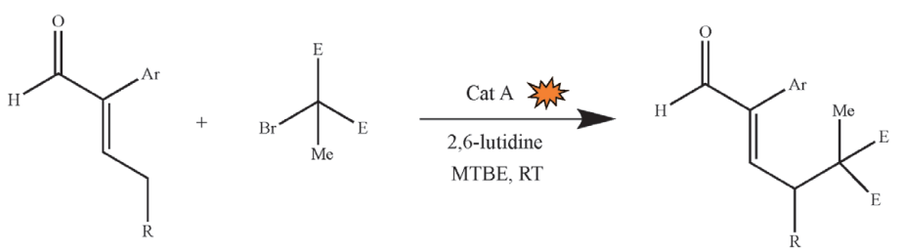

Figure 15.
γ-Alkylation of enals.

and drug industries. The coupling reactions are very highly enantioselective with good reaction and optical yields, and it was found to tolerate many functional groups under the reaction conditions that are described by the authors. They report that they were successful in their initial attempt itself on the symmetric cross-dehydrogenative coupling reaction between xanthene and pentanal employing Jørgensen's catalyst. With this protocol they developed the scope of enantioselective CDC of xanthenes with various aldehydes. Excellent product and optical yields were obtained with aliphatic aldehydes, while sterically hindered isobutyraldehyde gave poor yield but with excellent optical yield. Thioxanthenes too are tolerant under CDC reaction conditions [15] (**Figure 16**).

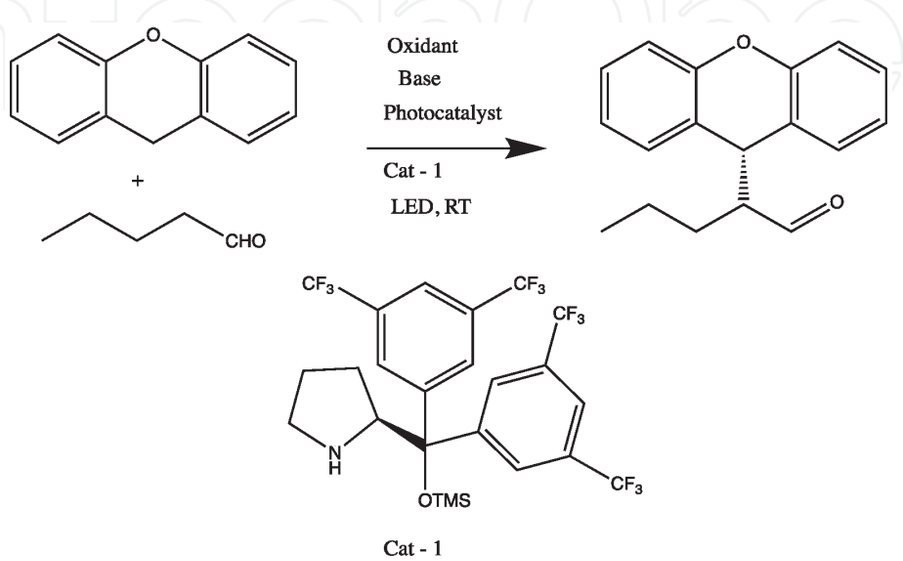

Figure 16.
Photoredox cross-dehydrogenative coupling of aldehydes with xanthenes.

11. Continuous flow α-arylation of N,N-dialkylhydrazones under visible-light photoredox catalysis

The α-arylation of aldehyde-derived N,N-dialkylhydrazones with electron-deficient aryl and heteroaryl cyanides gives rise to substituted products under visible-light conditions with the use of photoredox catalysts. These structural motifs hold interesting pharmacological activities, and by these novel technologies, α,α′-diaryl-N,N-cycloalkylhydrazones were obtained in moderate yields, and it is to be noted that conventional methods for the same are found to be non-cost-effective and time-consuming in nature. In this typical methodology, hydrazine and aryl or heteroaryl cyanides were subjected to 455 nm blue light-emitting diodes with 1 mol % of $Ir(ppy)_3$ as photocatalyst at 40°C with LiOAc (2 equiv) as base and DMSO as solvent to get the desired product [16] (**Figure 17**).

The mechanism describes that single-electron transfer occurs from Ir(III) to cyanoarene, then the oxidized Ir(IV) undergoes a second electron transfer mechanism with hydrazine forming a radical cation, and the Ir is ready for the catalytic cycle. LiOAc deprotonates the proton from hydrazine system; then various steps of reactions yield the product. Ultimately, structurally complex α,α′-diaryl-N,N-cycloalkylhydrazones were obtained in moderate yields by the repetition of the direct arylation protocol. A continuous flow procedure for the preparation of α-aryl-N,N-dialkylhydrazones on a multigram scale has also been established.

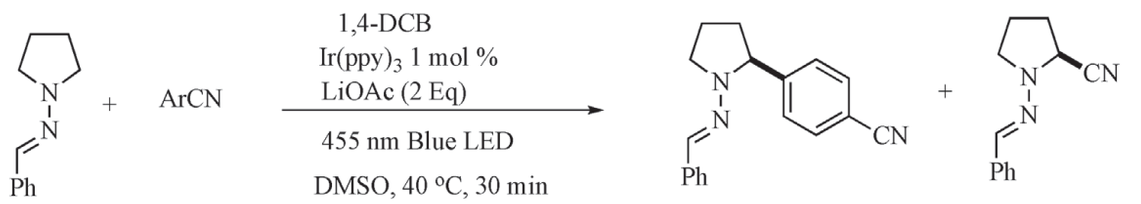

Figure 17.
α-Arylation of hydrazones.

12. Rapid access to pharmacophore fragments from β-cyanoaldehydes

Realizing the importance of asymmetric synthesis of the late chemists, they are making use of photoredox and organocatalysis together, among which C—C bond forming reactions are very important in the construction of biologically active compounds in a stereoselective fashion. One of the C—C bond forming reactions which enable the alkylation of aldehydes with a reserved cyanide functional group in the new bond is useful for synthetic manipulations. The research article presented describes the generation of C—C bond by making use of α-bromocyanoalkylated compounds as reagents, and this reaction generated β-cyano alkyls in a single synthetic operation with stereoselectivity. In a typical experimental procedure, an aldehydic compound α-bromoacetonitrile, $Ru(bpy)_3Cl_2$, asymmetric organocatalyst, and an imidazolidinone catalyst reaction mixture is irradiated by a 26 W CFL light source. The results are highly appreciable with preparative yield and with excellent enantioselectivity. More interestingly, this useful methodology has also demonstrated a total synthesis of a lignin natural product, namely, (−) bursehernin [17].

13. Photocatalytic synthesis of piperazines from aldehydes and ketones

Piperazines are important class of compounds with important pharmacological properties such as anthelmintic, antiallergic, antibacterial, antihistaminic,

antiemetic, and antimigrainic activities, and hence developing a working technology for the syntheses of piperazine analogues is very important to arrive at structural activity relationship. To arrive at an array of piperazines, recently a research article is reported that utilizes silicon-based reagents, and they denote this as silicon amine protocol (SLAP); in this process a variety of aromatic, heteroaromatic, and aliphatic aldehydes and ketones were employed to produce an array of piperazines using iridium-based photoredox catalyst ($Ir[(ppy)_2dtbbpy]PF_6$) and blue light radiation. The products obtained do not have any trace metal impurities since this protocol is tin-free alternative (SnAP—tin amine protocol). The reaction conditions enforced is mild and tolerates unprotected functional groups and steric hindrance and very importantly provides an access to wide array of piperazines without any trace metals for the SAR studies [18].

14. β-Arylation of aldehydes

The direct β-functionalization of carbonyl groups is very little known. MacMillan et al. first reported the combination of organocatalysis and photoredox catalysis for the direct β-C—H arylation of carbonyl compounds using benzonitrile as aryl donor (**Figure 18**). The proposed mechanistic rationale is shown in **Figure 19** and

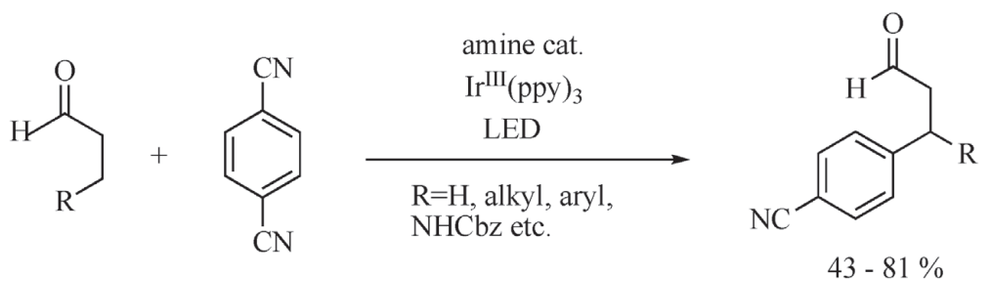

Figure 18.
β-Arylation of aldehydes.

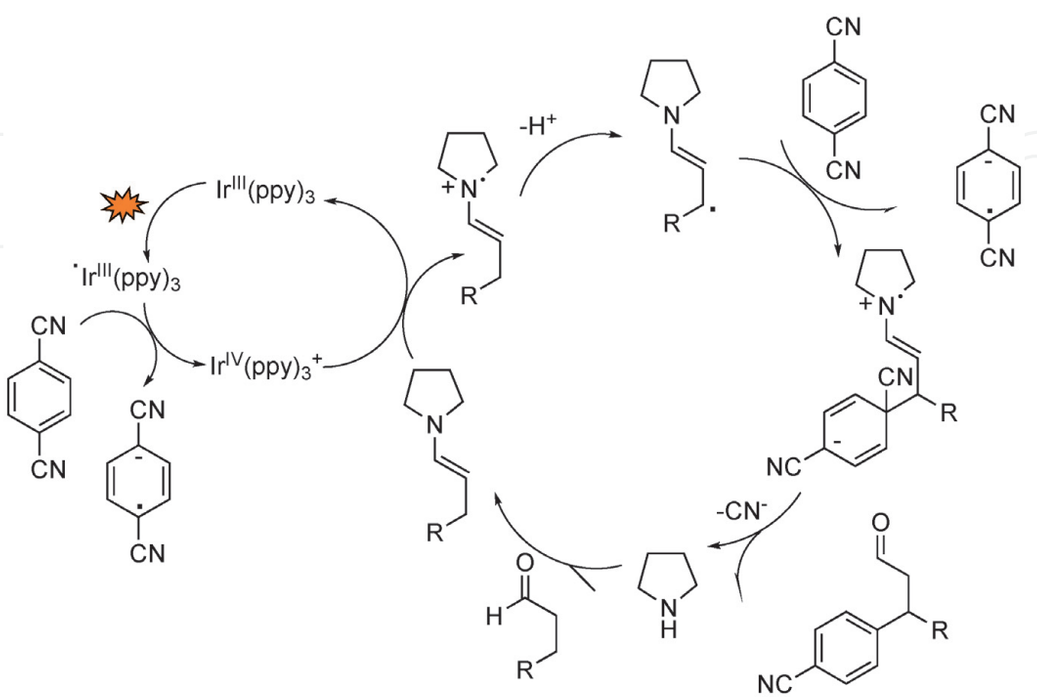

Figure 19.
β-Arylation of aldehydes—organocatalytic cycle.

follows an oxidative quenching cycle pathway, starting with the formation of a cyclohexadienyl radical anion [19].

15. Enamine, direct β-alkylation

Saturated aldehydes can be alkylated at the beta position directly by a synergistic combination of photoredox catalysis and organocatalysis [20]. Enamine oxidation by visible-light LED provides an activated β-enaminyl radical which readily combines with a wide range of Michael acceptors to produce β-alkyl aldehydes efficiently. Both inter- and intramolecular C—H functionalizations are possible in an atom economical redox-neutral process (**Figure 20**).

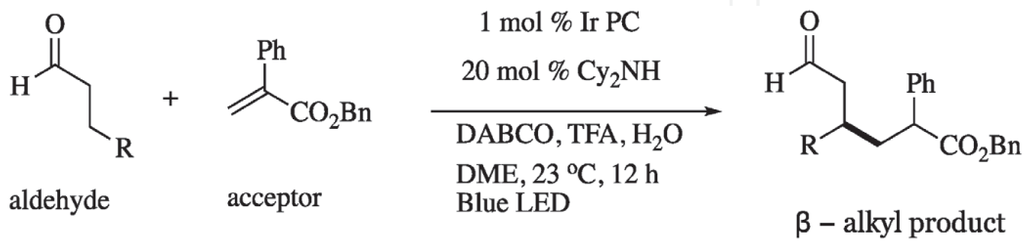

Figure 20.
Direct β-alkylation of enamines.

1,4-Diazabicyclo[2.2.2]octane (DABCO) as an organic base and DME as solvent were essential for the desired bond formation reaction. Thus a unique 5-πe-carbonyl activation utilizing the synergistic merger of organocatalysis and photoredox catalysis was used to accomplish the direct β-arylation of saturated ketones and aldehydes. A catalytically generated enaminyl radical formed via oxidation and β-deprotonation of an enamine and a radical anion generated by photocatalytic reduction of cyanoarene couple to form the β-carbonyl products. The generality of the activation platform was further demonstrated by a β-aldol reaction of ketones with transiently generated aryl ketyl radicals to form γ-hydroxy ketone adducts. The reaction was then further extended to intramolecular cyclization via formation of cyclic molecules through both 6-exo and 5-exo cyclizations with useful efficiencies and diastereocontrol. This proves further that the critical step does not involve radical-radical coupling (**Figure 21**).

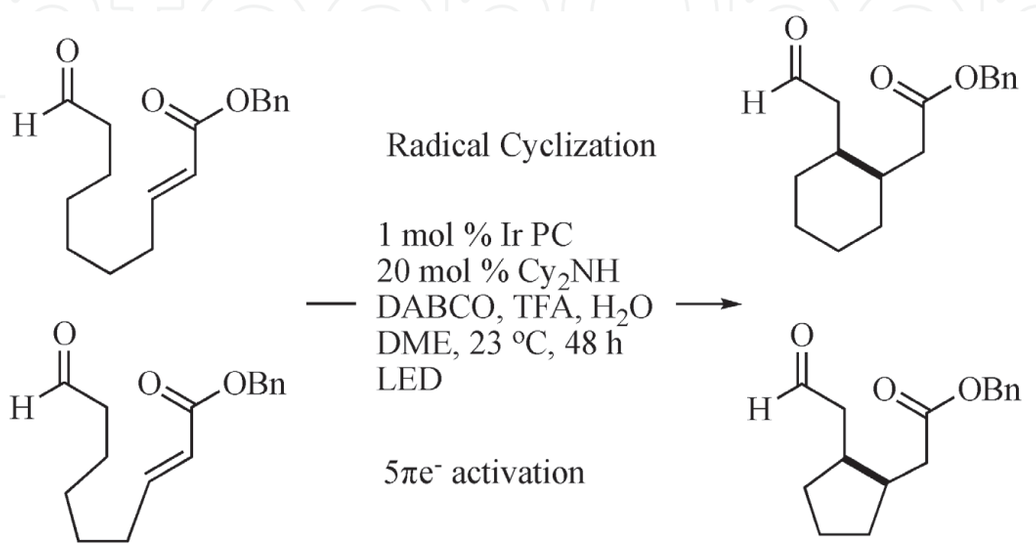

Figure 21.
5πe⁻ activation, 6-exo to 5-exo.

16. Iminium and enamine catalysis in enantioselective photochemical reactions

Chiral iminium ion photochemistry is an emerging synthetic field; with the creativity of synthetic chemistry, they utilized [2+2] photocycloaddition to arrive at complex molecular architecture. In order to execute the [2+2] photocycloaddition, they have first synthesized an alkene tethered to a chiral iminium perchlorate salt, to procure the chiral product; the iminium salt is produced using a C2-symmetric chiral auxiliary. The bench chemists observed that (i) substituents at positions C2 and C5 of the pyrrolidine were crucial, (ii) the reaction process proceeds through single-electron transfer, (iii) the reaction takes place at the singlet hypersurface, (iv) this notable [2+2] cycloaddition reaction takes place via a concerted pathway resulting from the strong π to π* absorption, and (v) the iminium salt absorbs light at 280 nm. The reward from this developed protocol was 82% ee and 40% chemical yield [21] (**Figure 22**).

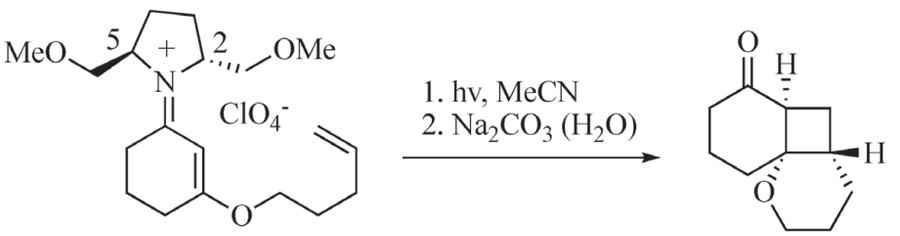

Figure 22.
Iminium catalysis: [2+2] photocycloaddition reaction of iminium salts.

17. Iminium catalysis: β-benzylation of enals and enones

The chemistry of ortho-quinodimethanes is very well exploited for the generation of six-membered carbocyclic frameworks by reacting with a diene and through an inter- or intramolecular [4+2] cycloaddition. Under VLPC condition, reports indicate that the photoexcitation of ortho-alkyl-substituted benzaldehydes and benzophenones generates the ortho-quinodimethanes, a diene intermediate, whereas instead of undergoing the [4+2] cycloaddition to yield the carbocyclic product, it gave solely the β-benzylated products through a Michael-type addition reaction. The secondary amine employed in this reaction is solely responsible for the Michael-type product (**Figure 23**).

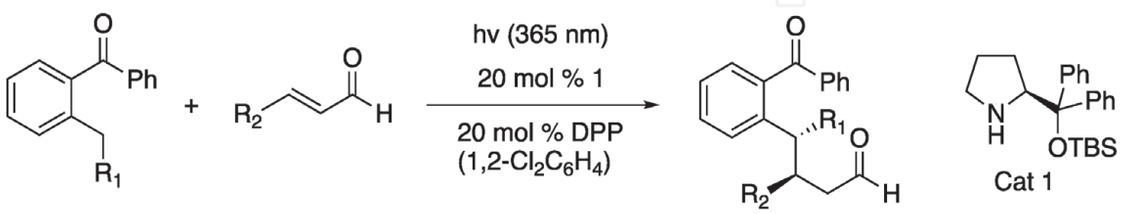

Figure 23.
β-Benzylation of enals and enones.

The reaction mechanism is very interesting for the academic enthusiastic personalities; the chiral secondary amines react with the α,β-unsaturated compound that is used in the reaction medium. When the reaction mixture was irradiated with λ = 365 nm, the photons enolize the ortho-alkyl-substituted benzaldehyde or

benzophenone to (E)-enol and then the iminium salts in close proximity with the other reactants to deliver the Michael-type addition products rather than [4+2] cycloadducts. A density functional theory (DFT) computational study was carried out by the authors to shed some light on this unusual reactivity, and the results indicated that this transformation proceeds through a water-assisted proton shuttle mechanism. The optical yields are excellent, and it is worth mentioning that no photocatalyst was needed in this reaction.

18. Iminium catalysis: β-alkylation of enals and enones

A major breakthrough in the field of asymmetric radical chemistry was represented by Melchiorre group; they achieved the first enantioselective radical conjugate addition (RCA) to β,β-disubstituted cyclic enones by a combination of photoredox catalysis and iminium-based organocatalysis. The organocatalyst and the primary amine moiety react with a α,β-unsaturated enone forming a chiral iminium ion as the reactive intermediate; the 1,3-benzodioxole present in the reaction medium upon irradiation by means of an UV light-emitting diode and in the presence of tetrabutylammonium decatungstate (TBADT) generates a carbon-centered radical. Thus generated carbon-centered radical being short-lived and active, it reacts with the chiral iminium ion producing an α-iminyl radical cation. Then through an intramolecular SET process, the α-iminyl radical cation was reduced to enamine. A tautomerism reaction, that is, enamine-imine tautomerization, regenerates photocatalyst TBADT, and finally the work procedure gives rise to the product with excellent enantio- and diastereoselectivities, and the chiral amine is recovered [22] (**Figure 24**).

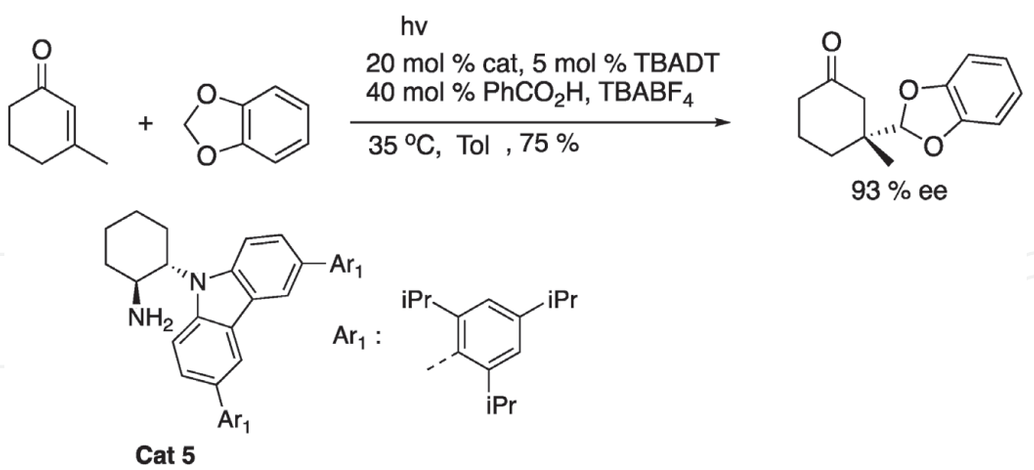

Figure 24.
Iminium catalysis: β-alkylation of enals and enones.

19. Enamine catalysis: β-alkylation of enals and enones

Following the footpaths of iminium catalysis, the twin brothers, namely, the photoredox catalysis and organocatalysis, fruitfully accomplished the enantioselective α-alkylation of aldehydes; the photoredox catalyst employed was 0.5 mol% of $Ru(bpy)_3Cl_2$ (bpy = 2,20-bipyridine), and the photocatalyst utilized was 20 mol% of a chiral imidazolidinone. Under the reaction condition, the

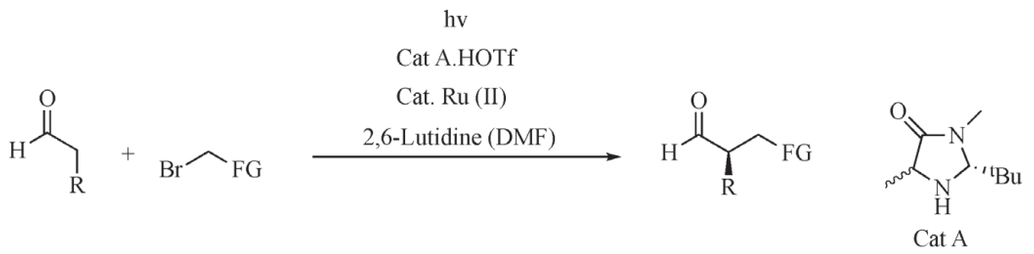

Figure 25.
Enamine catalysis.

substrate aldehydic compound reacts with a chiral enamine (organocatalyst) forming a chiral enamine intermediate; thereby the substrate is tuned to be nucleophilic in nature, and the nucleophilicity arises at the α-position to the aldehydic chromophore. Simultaneously, in the reaction medium, the photocatalyst is electronically excited by the visible light; once excited, it accepts a single electron from the chiral enamine, and the Ru [I] species then reduces the α-bromocarbonyl compound, and in this process the photocatalyst is regenerated. At the work-up the coupled product is released from the enamine with high stereoselectivity and in good yields (**Figure 25**).

20. Enamine catalysis: α-benzylation of aldehydes and ketones, α-hydroxylation, β-arylation

α-Benzylation and α-alkylation are thematically one and the same; however, much recent advances in α-benzylation of carbonyl compounds were reported with stereoselectivity (**Figure 26**).

A variety of electron-deficient aryl and heteroaryl methylene bromides were examined as the benzylating agents, and they were coupled with a range of aldehydes bearing different functional groups efficiently with excellent enantioselectivity. The benzylation reaction proceeds via an oxidative quenching cycle, in contrast to the reductive quenching cycle operation in the α-alkylation reaction. The hybrid organocatalytic cycle and photoredox catalytic cycle are similar to the reaction of aldehydes with alkyl halides described in **Figure 11**. The Ir photocatalyst fac-Ir(ppy)3 and imidazolidinone organocatalyst generate the benzyl radical from electron-deficient benzyl halides. This benzyl radical then couples with the chiral enamine providing α-amino radical which is oxidized by the intermediate Ir(IV) species. Hydrolysis of the iminium ion releases the α-benzyl aldehyde. A range of electron-deficient heteroaromatics such as pyridines, pyrazines, pyrimidines, quinolines, and benzimidazoles undergo facile reaction (**Figure 27**).

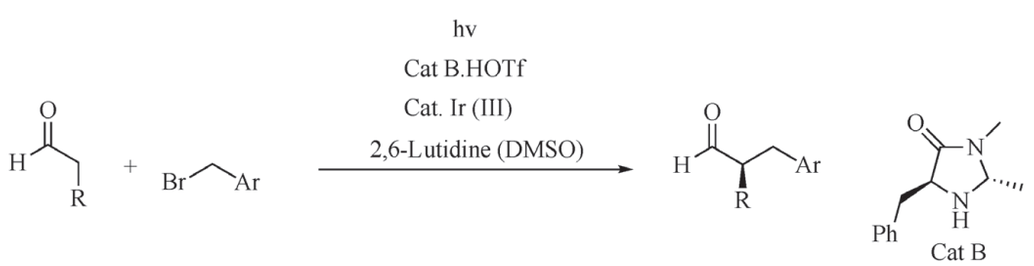

Figure 26.
Enamine benzylation.

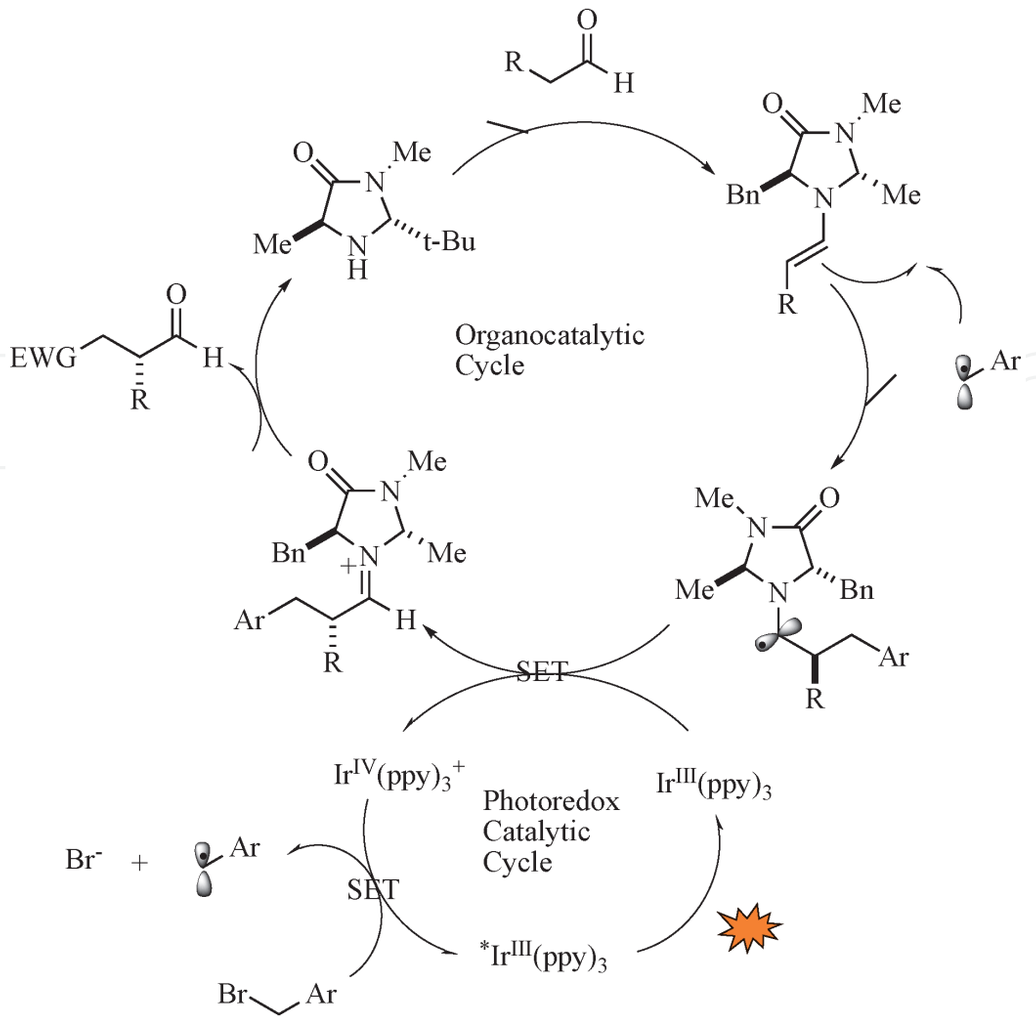

Figure 27.
A catalytic cycle—enantioselective benzylation of aldehydes.

21. Enamine catalysis: α-hydroxylation of aldehydes and ketones

The α-hydroxylation of carbonyl compounds is a very important class of reaction in the design of drug molecules; mostly the hydroxylation is appended in a stereoselective fashion. Conveniently it is achieved by enolizing the carbonyl, and the oxidation is done by oxidizing agents such as epoxides, OsO_4, and so on. Rarely the singlet oxygen is used for this functional group introduction. In this VLPC condition, the hardships related to the α-hydroxylation reactions are tackled with ease; an amine-catalyzed enantioselective α-hydroxylation of aldehydes under photochemical condition was achieved where (L)-α-Me proline-based organocatalyst was exploited and singlet oxygen is employed instead of explosive oxidizing agents. Mechanistically the amino acid-based organocatalyst activated the aldehyde, and

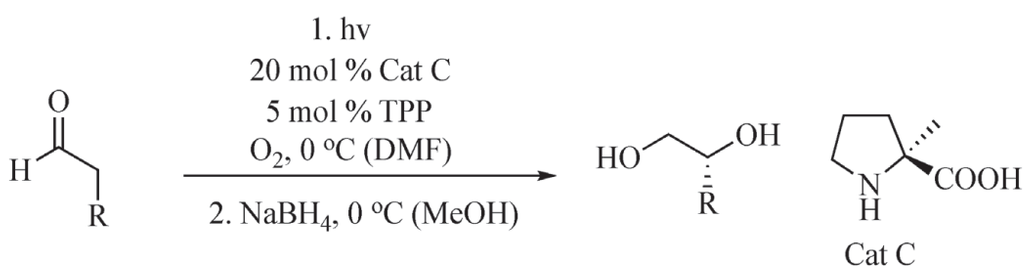

Figure 28.
Enamine hydroxylation.

the α-position is ready for reactivity. Photosensitizer tetraphenylporphyrin (TPP) sensitizes $^3O_2$ to $^1O_2$ by the action of visible light, which then reacts with the substrate enamine through an ene-type reaction, forming α-hydroperoxide which is then reduced using $NaBH_4$ to get 1,2-diols. Later this methodology was extended to cyclic ketones and yielded appreciable enantioselectivity (**Figure 28**).

22. Enamine catalysis: β-arylation of ketones

The α-functionalization of carbonyl compounds is easily carried out, whereas functionalizing at the β-position is not easy and requires multiple synthetic operations. With creativity and with clear understanding of radical chemistry using a VLPC protocol, these authors have enolized the cyclic ketones; thereby a double bond is formed, and the radical chemistry created an allyl radical at the β-position. In the reaction medium, the iridium-based catalyst generated arene radical cation from cyanoarenes, which reacts with the allyl radical and forms the β-substituted ketones with the elimination of the cyanide group from the arene (**Figure 29**).

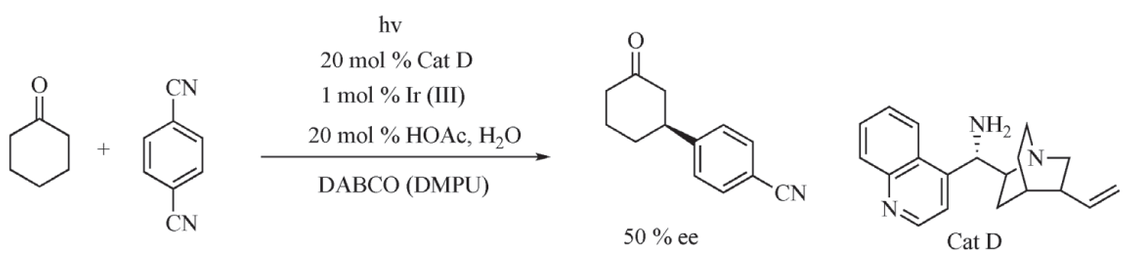

Figure 29.
Ketone β-arylation.

23. Relay visible-light photocatalysis

A relay visible-light photocatalysis strategy using formal 4+1 annulation and aromatization was achieved. Three successive photoredox cycles (one oxidative cycle and two reductive quenching cycles) were engaged in a reaction with one photocatalyst. Multiple quenching cycles could be demonstrated in a single reaction involving formal 4+1 annulation of hydrazone with 2-bromo diethylmalonate [23] (**Figure 30**).

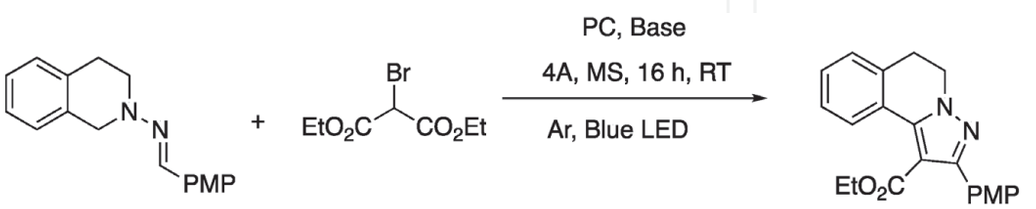

Figure 30.
Relay VLPC.

24. Conclusion

Photosynthesis has attracted biologists, physicists, and chemists for centuries; chemists by understanding how the plants synthesized chemicals using sunlight have been inspired, and that resulted in this new domain. Ultimately these new sets

of reactions under VLPC are photosynthesis mimic reactions, and the chemists brought the process into action at the laboratories.

VLPC strategies developed by chemists in recent years portrait the esthetic taste and the design of energy-saving and environmentally compatible and benign features in this innovative domain of organic synthesis.

Among all the subdisciplines of catalysis, the newly emerged gifted child, namely, visible-light photoredox catalysis, has grown rapidly and has made a great of deal of interest in both academia and industry; in the near future, we will be witnessing the process development of drug molecules.

The twin catalysis comprising a chiral agent and the transition metal catalyst brought forward the asymmetric synthesis in a one-pot synthetic fashion in this neoteric protocol which portraits the highest level of creativity of synthetic chemists. Consequently, it can be construed that from the catalytic professionals, more VPLC protocols will emerge to attain pharmaceutically active ingredients through industrial manufacturing processes, especially in enantiomerically enriched forms.

In terms of kinetics, not much work is done, and such research articles are expected in the pipeline; much work has to be done on the recyclability and reusability of catalytic materials including the studies on leaching.

It is interesting to note that only in this domain the methodology quickly reached to the stage of asymmetric synthesis in a rapid way, implying the success in the process development of drug molecules; subsequently, more process developments are expected as the industrial process.

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