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Illuminating Photoredox Catalysis

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Abstract

Over the past decade, photoredox catalysis has risen to the forefront of synthetic organic chemistry as an indispensable tool for selective small-molecule activation and chemical-bond formation. This cutting-edge platform allows photosensitizers to convert visible light into chemical energy prompting generation of reactive radical intermediates. In this Review, we highlight some of the recent key contributions in the field, including: the impact of the chosen light arrays; promoting fundamental cross-coupling steps; selectively functionalizing aliphatic amines; engaging complementary mechanistic paradigms; and applications in industry. With such a wide breadth of reactivity already realized, the presence of photoredox catalysis in all sectors of organic chemistry is expected for years to come.

Keywords

photocatalysis; photoredox; chemical tool; synthesis; radicals; visible light

From Classical to Modern Radical Generation

Radical intermediates are molecules that are transiently generated during a reaction and contain an unpaired electron (Figure 1A, Key Figure). Classic chemical approaches to generate these intermediates rely on hazardous radical initiators (e.g., AIBN and BEt_3), toxic reagents (e.g., Bu_3SnH), and in many cases, high temperature or high energy UV irradiation [1–3]. These modes of traditional radical generation have partly led to radical intermediates being both underexploited and underappreciated in chemical synthesis.

For nearly fifty years, photoredox catalysis has found widespread utility in the areas of carbon dioxide reduction [4], water splitting [5], and solar-cell materials [6]. Only recently, have these fundamental principles been translated to radical generation for chemical synthesis by recognizing that visible light can be converted to chemical energy for synthetic applicability in a controlled and mild fashion [7–13]. Common photocatalysts

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include Ru(II) (**1**) and Ir(III) (**2**-**3**) complexes, as well as organic dyes (**4**) (Figure 1B). Upon irradiation with visible light, metal-centered catalysts undergo a **metal-to-ligand charge transfer (MLCT)** (see Glossary) followed by **intersystem crossing (ISC)** (Box 1) revealing a relatively long-lived triplet excited-state species (e.g., for $Ru(bpy)_3^{2+*}$, τ = 1100 ns) (Figure 1C) [14–16]. From the excited state, these catalysts can engage in **single-electron transfer** (SET) events with organic substrates providing access to reactive **open-shell intermediates**. Notably, excited-state species may act as both a strong oxidant and strong reductant simultaneously (generating $Ru(bpy)_3^{3+}$ or $Ru(bpy)_3^{+}$, respectively) allowing for exceptional operator flexibility. Additional catalyst tuning (e.g., metal center and ligand sphere) allows one to predictively modify the catalyst's redox potential and thus the inherent catalyst properties. In contrast to classic chemical approaches to radical intermediate generation, methods in photoredox catalysis are exceptionally mild relying on easily accessible and bench-stable materials with ambient-temperature operation. Despite remarkable advances in classical UV radical photochemistry [17], the need for specialized equipment and lack of predictable product outcomes have ultimately skewed the perception and industrial adaptation of such methods. Fortunately, a modern era of radical chemistry dawns with photoredox catalysis (and electrocatalysis [18]), which promises to be a steadfast and translatable tool for years to come [19]. In this Review, we highlight important contributions over the last several years for visible light-mediated radical generation and synthetic utilization that supports the notion that photoredox catalysis is a lasting synthetic tool.

Evolution of Light Sources for Enhanced Reactivity and Scalability

The diverse reaction profiles accessible via photochemical approaches have reinvigorated researchers in both academia and industry to solve a host of synthetic challenges [17, 21]. Significant effort has been expended on novel reaction invention; however, there has also been significant interest in decreasing reaction times, developing standardized operating protocols to improve reproducibility, and scaling photochemical reactions for industrial applications. As revealed by the Beer-Lambert-Bouguer law, photon flux decreases exponentially with increasing path length and concentration. Thus, in large batch reactors, incomplete irradiation of reaction solutions causes the photoexcited catalyst to exist only at the reactor surface [22]. This phenomenon leads to both long reaction times and poor reaction efficiencies for larger reaction volumes. It is clear that an increase in light intensity will proportionally lead to an increase in photon capture by the photocatalyst affording a higher concentration of the excited-state species [23].

With this in mind, the synthetic photoredox community has witnessed a rapid evolution of light sources employed to improve established photochemical transformations and aid in the discovery of novel bond-forming reactions (Figure 2A). Importantly, a suite of light setups of varying intensities and wavelengths allows for modular reaction tailoring to best fit the selected photocatalyst. For example, common household compact fluorescent lightbulbs (CFL, broadband emission) can be easily converted to light-emitting diode (LED) arrays of both specific wavelengths and varying intensities. One unique development toward improving reaction efficiencies and rates has been the design of a small-scale integrated photoreactor by MacMillan and co-workers (Figure 2B) [24]. The photoreactor

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was optimized for maximum power output from the chosen LED array, electronic interface for operating simplicity, and outcome reproducibility. Of note, calorimeter measurements revealed a 10× increase in total incident radiant power with their chosen high power 450 nm LED array (>1.1 W output per LED) system relative to a standard LED lamp apparatus. This reactor was shown to provide significantly shorter reaction times in eight photoredox transformations commonly employed in medicinal chemistry, thereby supporting its further utility.

There is an increasing drive from industry to employ photoredox catalysis because it is well-suited to operate in continuous flow, allowing for more uniform light penetration, and therefore, efficient catalyst excitation relative to batch processes [25–28]. Further, continuous flow processing enhances scalability and while simultaneously reducing occupational hazards and industrial waste streams. A successful demonstration of photoredox continuous flow processing was exemplified by Beatty and co-workers radical trifluoromethylation method seeking to address the limited number of scalable trifluoromethylation protocols (Figure 2C) [29]. In collaboration with Eli Lilly, the authors identified trifluoroacetic anhydride (TFAA) as a trifluoromethyl radical source, in conjunction with pyridine *N*-oxide (PNO) as a sacrificial redox auxiliary. This low cost and operationally simple procedure uses 0.1 mol% $Ru(bpy)_3Cl_2$ as the photocatalyst and is proposed to proceed via single-electron reduction of acylated pyridine *N*-oxide, followed by fragmentation to give the reactive trifluoromethyl radical, CO_2, and pyridine. Comparison of the trifluormethylation of *N*-Boc pyrrole revealed that the reaction efficiency was significantly superior with flow processing compared with that of batch processing, generating 3.33 g (71% yield, R_t = 10 min) of product per hour (compared with 17.8 g, 57% yield over 15 hours in batch). Later, this method was efficiently performed on kilogram scale (0.95 kg isolated, 20 gh^{-1}, 50% yield) [30]. Very recently, Harper and co-workers reported on the design of a continuous flow stirred-tank reactor equipped with a high intensity laser to achieve kg/day throughput for several commonly encountered photochemical coupling reactions [31]. Using this 100 mL reactor, the authors reported tremendous reaction-time acceleration and catalysts-loading optimization. Continued advancements in light array designs will ensure optimal photocatalyst loadings, reduced waste streams, and decreased reaction times ultimately leading to a more sustainable approach to chemical synthesis.

Impacting Elementary Cross-Coupling Steps with Photoredox Catalysis

Transition metal catalysis is a fundamental tool for organic chemists, allowing for simpler construction of C–C and C–X bonds [32]. Typically, these transformations operate via **oxidative addition** of an aryl halide, followed by **transmetallation**, and subsequent **reductive elimination** to furnish the new bond (Figure 3A). Photoredox catalysis has emerged as a tool to enable cross-coupling reactivity under exceptionally mild conditions by shuttling electrons to facilitate redox events, thereby promoting otherwise energetically unfavorable reaction steps [33]. In addition to facilitating reactivity, emerging methods have provided a platform to engage common chemical functionalities as suitable cross-coupling handles (e.g., carboxylic acids, alcohols, and C−H bonds). Dual photoredox/transition metal-catalyzed cross-coupling reactions have been reported with cobalt [34], copper [35], gold [36], nickel [37], palladium [38], ruthenium [39], and rhodium [40]; however, in this

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minireview, we focus on reaction manifolds utilizing only copper and nickel photoredox catalysis. Specifically, we highlight how light and photocatalysts have been strategically applied to alter the fundamental steps of typical cross-coupling reactions.

Oxidative Addition

In a traditional cross-coupling reaction, oxidative addition is often implicated as the first fundamental step of the catalytic cycle, shown by an insertion of the metal center into a polarized (pseudo)halide–carbon bond coupled with a concerted two-electron oxidation of the metal center [32]. Methods developed for copper-catalyzed cross-coupling have been limited due to difficulties associated with oxidative addition to the Cu^{I} metal center, as the resultant Cu^{III} species are unstable [41, 42]. Recent work by the Fu and co-workers employs photocatalysis to address the issues often encountered in the oxidative-addition step of copper-catalyzed cross-coupling reactions (Figure 3B). This report discloses the copper catalyzed C–N coupling of lithium carbazole and aryl halides under irradiation by a 13-W CFL lamp [35]. Catalysis is hypothesized to proceed through photoinduced electron transfer from a bis(phosphine)Cu^{I}carbazole to the aryl halide, thereby generating an aryl radical species that may react with the copper catalyst to generate a Cu^{III} intermediate and induce reductive elimination ultimately furnishing the new *N*-aryl carbazole.

Transmetallation

Transmetallation is the fundamental step that has undergone the largest advancements in photoredox- based methodologies, as a result of the contributions from the MacMillan, Doyle, and Molander groups (Figure 3C). Traditionally, transmetallation is the transfer of a ligand from one metal (e.g., $-B(OH)_2$, -MgCl, or $-SnBu_3$) to another metal [32]. For cross-couplings, the ligand is transferred to the active catalyst through a polar two-electron process. The merger of photoredox and transition-metal catalysis has been propelled by the ability to drive reactivity through formal single-electron transmetallation processes. Molander and co-workers reported use of benzylic potassium trifluoroborate salts for the preparation of bis(aryl)methanes via nickel/photoredox cooperative catalysis [43]. The reaction manifold described exploits the easily oxidized C–B bond of potassium trifluoroborate salts allowing for the generation of benzylic radicals that could be subsequently captured by the nickel catalyst. It is proposed that an aryl bromide undergoes oxidative addition with the alkyl nickel(I) species. The subsequent Ni(III) intermediate is then proposed to undergo reductive elimination furnishing the new C–C bond; reduction of the resultant Ni(I) organometallic species regenerates the active Ni(0) catalyst [44]. Since the seminal report, the scope of reactivity has been extensively evaluated [45], and the methodology has been extended to silicates for transmetallation [46].

Concurrent with the report from Molander and colleagues, the Doyle and MacMillan groups reported the coupling of aryl halides with sp^3-hybridized carbon-centered radical intermediates derived from carboxylic acids [37]. Importantly, this is not a formal transmetallation, but rather the generation and capture of carbon-centered radicals. This mechanism is analogous to that of trifluoroborate salts, and thus will be discussed in the context of being an alternative coupling handle to achieve analogous transmetallation-like reactivity. In this work, the application of a photosensitizer allowed for the oxidative

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decarboxylation of carboxylic acids. This generates a free carbon-centered radical, which is proposed to be captured by a Ni(II) species to generate a Ni(III) intermediate capable of undergoing an analogous reductive elimination to furnish the cross-coupled product [37]. This seminal publication immediately highlighted the potential for dual metal photoredox systems to revolutionize cross-coupling methodologies, as the application of stable and widely available carboxylic acids can now be used as coupling partners for the formation of C–C bonds, circumventing the need for classically employed organometallic reagents.

Reductive Elimination

Reductive elimination is the final fundamental step to a cross-coupling reaction. This reaction step is highlighted by the formation of the new bond, with the corresponding two electron reduction of the metal center (Figure 3D) [32]. One way that dual photoredox transition-metal cross-coupling has been used to enable reductive elimination of the catalytic intermediates is through oxidatively induced reductive elimination. This step has been studied by Hillhouse [47] for aryl and alkyl nickel species and likely facilitates reactivity through single-electron transmetallation of many dual photoredox transition-metal mediated cross-couplings. While this has been the most utilized mechanism to promote reductive elimination, it is not the only means to impact reductive elimination. Triplet-triplet energy transfer from the excited state photocatalyst to an organometallic intermediate has also been documented to result in the reductive elimination from an organonickel(II) to give a new C–O bond and the regeneration of the active Ni(0) catalyst [48]. Importantly, the mechanism of this transformation was thoroughly studied, and the application of time-resolved spectroscopy allowed for the assignment of energy transfer.

Selective Oxidation of Aliphatic Amines with Photoredox Catalysis

Aliphatic amines represent a ubiquitous functionality in biologically active compounds and pharmaceuticals. As such, selective and efficient functionalization of aliphatic amines has represented a major point of emphasis for organic chemists [49, 50]. The direct oxidation of trisubstituted aliphatic amines has an astounding impact on the bond dissociation energy of α-C–R bonds (Figure 4A) [51]. Initial efforts in this area focused on *in situ* generation and subsequent functionalization of imines from *N*-aryl tetrahydroquinoline core structures (Figure 4B) [52, 53]. This work served as an important proof of concept, as the reductive quenching of the photocatalyst excited state (PC*) gave rise to the radical cation of tri-substituted amine; subsequent hydrogen-atom transfer led to the formation of imines that could be efficiently trapped upon the addition of a nucleophile.

As the breadth of reactivity enabled by photoredox catalysis expanded, Stephenson and colleagues applied these methods to novel bond disconnections in organic synthesis. Based on the proposed biosynthesis of several catharanthine derived alkaloids, it was hypothesized that (+)-catharanthine would be an ideal entry point to the selective modification of complex molecular scaffolds through amine oxidation. Following amine oxidation to intermediate **5**, subsequent strain driven cleavage of the C16-C21 bond (α to the amine) led to the facile production of an imine (not shown) [54]. Trapping of the imine with an equivalent of cyanide followed by single-electron reduction and protonation of

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intermediate **6** led to α-amino nitrile **7**; a common intermediate in the synthesis of several structurally related alkaloids (Figure 4C). The synthetic utility of α-amino nitrile **7** was demonstrated as it was readily converted to (−)-pseudotabersonine, (+)-coronaridine, and (−)-pseudovincadifformine in 90%, 48%, and 55% yields, respectively [54].

New and mild tools enabled by photoredox catalysis have afforded the preparation of new saturated compounds of interest to the pharmaceutical sector because they are less prone to adverse metabolic processing. Anilines represent a common structural alert motif known to predispose a potential drug candidate to metabolism-driven toxicities [55]. However, this functionality is commonly found in modern drug discovery screening libraries due to the cornucopia of methods for its preparation [56]. 1-Aminonorbornanes represent a class of molecules that are well suited to serve as **bioisosteres** for anilines, providing a core saturated structure likely less prone to adverse metabolic processing events (Figure 4D). Although historical examples of 1-aminonorbornanes applications exist, their application to drug discovery has been precluded by limited synthetic accessibility. Recently, Stephenson and co-workers provided a solution to this need by reporting the application of photoredox catalysis to access a formal (3+2) cycloaddition of aminocyclopropanes with tethered olefins to provide the corresponding 1-aminonorbornane products [57]. In this work, the oxidation of aminocyclopropanes allows for the strain-driven homolysis of the α-amino C–C bond, and subsequent serial 6-exo-trig and 5-exo-trig radical cyclizations to furnish the desired 1-aminonorbornane core. This methodology proved general as it allowed access to a variety of C2-, C3-, C4-, and C7- substituted 1-aminonorbornanes. Metabolic stability studies supported the initial hypothesis that the saturated 1-aminonorbornanes is less prone to metabolic processing than their aniline counterparts, as in all cases, the 1-aminonorbornanes were found to outperform, or were on par, with the stability of the most robust aniline compounds.

Complementary Reaction Paradigms for *Anti*-Markovnikov Additions to Alkenes

Photoredox catalysis offers unique opportunities for developing complementary mechanistic profiles depending on how a given substrate is initially activated. For example, photocatalytic ***anti*-Markovnikov** selective hydrofunctionalization of alkenes was recently demonstrated by both Nicewicz [58] and Knowles [59] through contrasting C–nucleophile bond forming strategies while using a common photoredox catalysis cycle (Figure 5). Despite the pervasiveness of Markovnikov-selective additions (H–nucleophiles to alkenes) in organic chemistry, methods to access the opposite selectivity with the same substrates remains challenging and is limited to forcing transition metal catalysis and monosubstituted activated alkenes [60, 61].

Over the past several years, Nicewicz and colleagues have developed powerful strategies that reverse selectivity of traditional hydrofunctionalization reactions of alkenes by taking advantage of the known reactivity of transiently generated radical cations (Figure 5A) [62–65]. In these cases, polar nucleophiles selectively add to the least hindered site of radical cations generating a stabilized radical adduct. Key to the success of this

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single-electron alkene oxidation strategy is the judicious choice of a potent oxidizing photocatalyst [66, 67]. Notably, many terminal styrenes, as well as mono-, di-, and trisubstituted alkenes, have oxidation potentials outside the range of commonly employed transition-metal-based polypyridyl catalysts. Consequently, the group has spent tremendous effort on designing acridinium photocatalysts with potent redox behaviors [68]. Following mechanistic studies, the authors propose the following steps for their reported *anti*-Markovnikov hydrofunctionalization reactions of alkenes [62, 69]. Initial single-electron transfer from the alkene to an excited-state acridinium photocatalyst provides the reactive radical cation intermediate **8**. Inter- or intramolecular nucleophilic addition to the radical cation followed by a **hydrogen atom transfer (HAT)** event between a suitable donor, such as 2-phenylmalonitrile, furnishes the functionalized *anti*-Markovnikov product. The authors have successfully extended this photoredox HAT strategy to accomplish *anti*-Markovnikov hydroetherifications [58], hydroaminations [63, 70], hydroacetoxylations [71], and hydrohalogentaions [72, 73] of alkenes. Recently, Stephenson and co-workers reported an intermolecular alkene aminoarylation method from transiently generated alkene radical cations and arylsulfonylacetamides as a bifunctional reagent [74]. This report illustrates the power of alkenes radical cations to provide access to valuable chemical motifs (such as arylethylamines) in a succinct manner.

Instead of alkene oxidation, nucleophile activation via non-covalent catalysis in conjunction with photoredox catalysis has enabled a wide breadth of fundamentally distinct transformations. Knowles and colleagues have pioneered the use of concerted proton-coupled electron transfer (PCET) in organic synthesis [75, 76]. PCETs are unconventional elementary redox processes resulting in the concomitant transfer of a proton and an electron to or from two independent donor/acceptor species. This strategy for homolytic activation of strong bonds, often in the presence of weaker ones, allows access to radical species that would be kinetically challenging to form via sequential proton and electron transfer steps. To showcase the synthetic utility of photoredox PCET, the group has developed *anti*-Markovnikov alkene functionalization methods through the oxidative generation of amidyl radicals (**9**) from the corresponding amides (Figure 5B) [59, 77–79]. Following homolytic cleavage of a redox activated amide N−H bond (BDFE = 110 kcal mol^{-1}), the generated amidyl radical is poised to cyclize onto pendent alkenes to provide a nucleophilic carbon−centered radical. Depending on the nature of the reaction conditions, the radical intermediate can (i) be trapped with a suitable Michael acceptor for a C−C bond forming event or (ii) abstract an H-atom from a HAT catalyst (such as thiophenol) to provide hydroamination products. Overall, given the exceptionally mild nature of both photoredox alkene oxidation and PCET methods, a wide range of functional groups are tolerated and will aid in accelerating the synthetic utility of these complementary approaches for substrate activation.

Recent Applications of Photoredox Catalysis

Since 2008, the field of photoredox catalysis has experienced exponential growth, providing synthetic chemists with novel bond-disconnection strategies and direct approaches to targeting native functionalities (including C−H bonds [80, 81]) under exceptionally mild conditions. Photoredox catalysis has also proven useful in the synthesis of congested

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quaternary centers through either oxidative [82] or reductive generation [83–87] of radical intermediates. Given these qualities, it is unsurprising that photoredox catalysis has served as a key bond-forming strategy in the total synthesis of complex natural products (including (+)-gliocladin C [88], heitziamide A [89], and (−)-aplyviolene) [90, 91], as well as medicinally relevant compounds (Figure 6A) [21].

The feasibility of translating small-scale photoredox reactions to large-scale flow-platforms has attracted industrial chemists for applications in late-stage drug modifications and large-scale production of key synthetic intermediates [26, 92, 93]. For example, DiRocco and co-workers have reported a direct late-stage C−H methylation, ethylation, and cyclopropanation of pharmaceutical and agrochemical agents (Figure 6B) [94]. From high-throughput experimentation, it was found that photoredox catalysis can activate organic peroxides to be suitable radical alkylating agents. Given that the method exhibits exceptional functional group tolerance, it is ideally suited for drug discovery. In a subsequent report, the Merck team in collaboration with Knowles and colleagues, reported on a photocatalytic indoline dehydrogenation as a key step in the sustainable synthesis of elbasvir, a clinically investigated inhibitor of the hepatitis C virus (Figure 6C) [95]. The photocatalyst **2** could be used in combination with *tert*-butyl perbenzoate to provide good yield and excellent ee (85% yield, >99% ee) of the dehydrogenative product. Notably, the reaction could be scaled to 100 g and processed over 5 h with a residence time of 60 min using Merck's in-house flow reactor [96]. More recently, MacMillan and colleagues reported a practical photoredox-mediated hydrogen atom transfer protocol to selectively deuterate and tritiate α-amino sp^3 C−H bonds of 18 pharmaceutical compounds (Figure 6D) [97]. Isotopically labeled molecules are essential diagnostic tools in drug discovery as they provide information about compound metabolism and biological uptake [98–100]. This single-step operation, which uses isotopically labeled water as the heavy atom source, is anticipated to be broadly enabling for interrogating the biological activity of novel drug candidates in the future.

Concluding Remarks

Modern advances in visible-light photoredox catalysis have led to myriad of novel synthetic methodologies. The ability of excited state photocatlysts to simultaneously act as both an oxidant and reductant and their ability to convert visible light into useful chemical energy have led to unprecedented reactivity, holding significant promise for enabling the continued discovery of valuable organic transformations. As the pharmaceutical sector continues to embrace photoredox catalysis, there is an ever-increasing opportunity for academic discoveries to be immediately translated to future technologies. Moreover, in an era when sustainable chemical practices are of crucial importance, further development of novel visible light-mediated methodologies and easily adaptable platforms for scaling reactions are needed for this field to continue to grow and thrive (see Outstanding Questions).

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Glossary

Aliphatic
fully saturated organic compounds composed of carbon and hydrogen atoms (hydrocarbons)

***anti*-Markovnikov**
a rule describing the regiochemical outcome of an alkene or alkyne addition reaction where a substituent becomes bonded to the less substituted carbon, rather than the more substituted carbon

Bioisostere
chemical groups with similar physical or chemical properties that produce similar biological properties to another chemical compound

Hydrogen Atom Transfer (HAT)
hydrogen atom abstraction; when a hydrogen free radical is abstracted from a substrate

Intersystem Crossing (ISC)
a radiationless process involving a transition between the two electronic states with different states spin multiplicity

Metal-to-Ligand Charge Transfer
promotion of an electron from the highest lying metal centered orbital to the lowest lying unoccupied ligand centered orbital. Typically, d→**π***

Open-Shell Intermediates
a molecule that contains singly occupied molecular orbitals which tend to be highly reactive

Oxidative Addition
a process in which the oxidation state and coordination number of a metal center increase

Proton-coupled electron transfer (PCET)
a chemical reaction that involves the concerted transfer of an electron and a proton

Reductive Elimination
a process in which the oxidation state of the metal center decreases while forming a new covalent bond between two ligands

Single-Electron Transfer
an event where an electron relocates from an atom or molecule (donor) to another atom or molecule (acceptor) resulting in a change in oxidation state of the chemical entities

Transmetallation
the transfer of a ligand from one metal center to another metal center

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Text Box 1

Light Mediated Excitation of Polypyridyl Photocatalysts

Visible light irradiation of the polypyridyl photocatalysts leads to an excitation event that ultimately furnishes a triplet excited state which is sufficiently long-lived (i.e., rate of relaxation is slower than the rate of diffusion) to allow for single electron transfer events to occur [20]. To access the triplet excited state, the photocatalyst first undergoes a metal-to-ligand charge-transfer (MLCT) event upon visible light irradiation. This photophysical process is characterized by the promotion of an electron from a metal-centered t_{2g} orbital to a ligand-centered π^* orbital, resulting in a singlet excited state (S_1) of the photocatalyst. Following MLCT, the singlet excited state undergoes intersystem crossing (ISC), which is characterized as a configurational spin flip of the electron in the ligand-centered π^* orbital, to give the lowest energy triplet excited state (T_1). The resultant triplet excited state is a long-lived excited state, capable of undergoing single-electron transfer events with organic substrates. Importantly, these processes result in the oxidation of the metal center, reduction of the ligand and a configurational spin flip of the promoted electron; but the overall charge of the complex is unchanged.

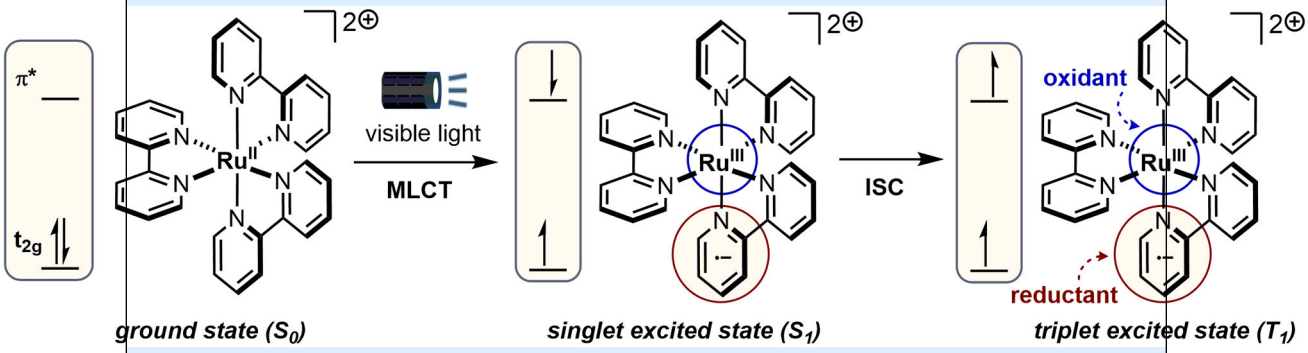

Figure I.

Metal-to-ligand charge-transfer (MLCT) and intersystem crossing (ISC) events from the ground state to the triplet excited state for the prototypical transition-metal photocatalyst, $Ru(bpy)_3^{2+}$, upon visible light irradiation.

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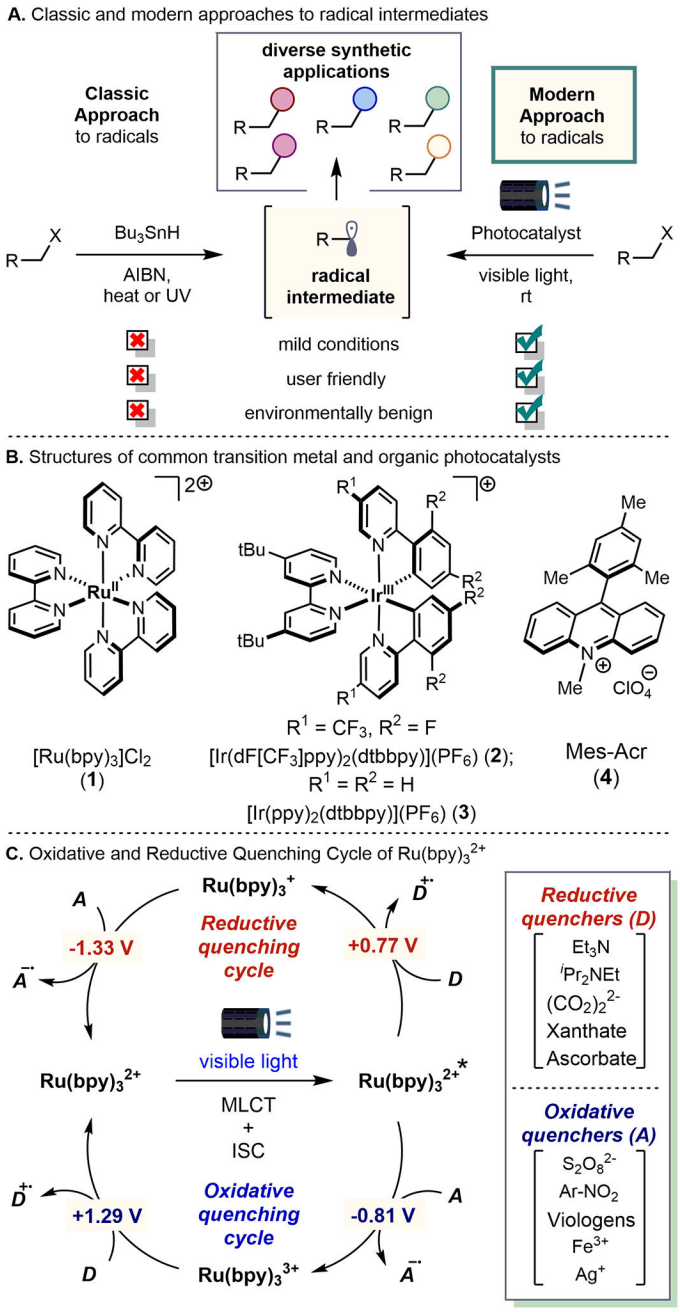

Figure 1.

Photoredox catalysis as a modern approach to radical intermediate generation.

(A) The classic (left) and modern (right; photoredox catalysis) approach to radical intermediates. (B) Commonly employed metal-centered and organic photocatalysts. (C) A general representation of the oxidative and reductive quenching cycle of $Ru(bpy)_3^{2+}$. MLCT and ISC are metal-to-ligand charge transfer and intersystem coupling, respectively.

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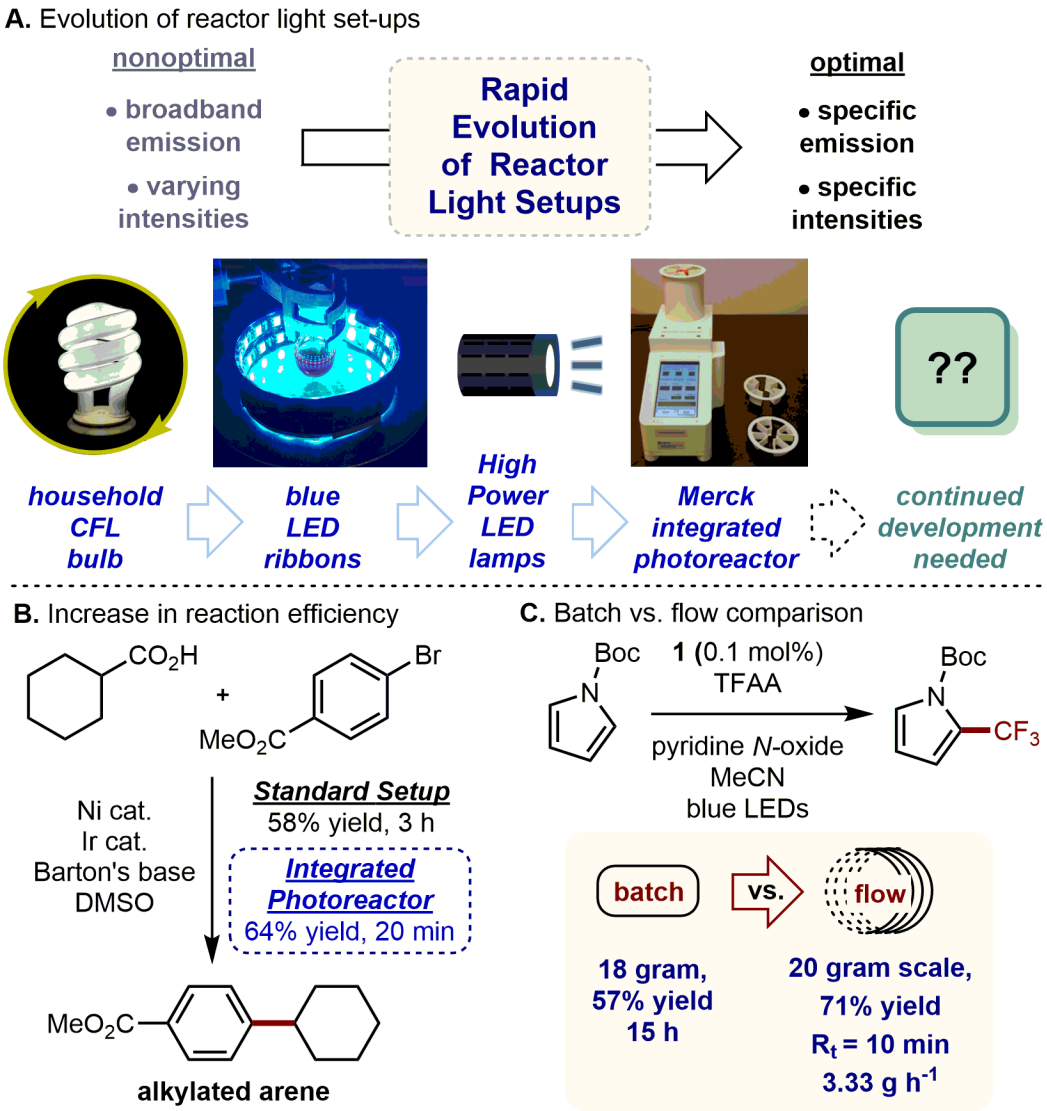

Figure 2.

Evolution of light array designs for enhanced reaction efficiency and scalability.

(A) Small library of commonly employed light array designs over the past decade. (B) The demonstration of enhanced reaction efficiency with the use of an integrated photoreactor. (C) The comparison of batch and flow processing for the trifluoromethylation of *N*-Boc pyrrole.

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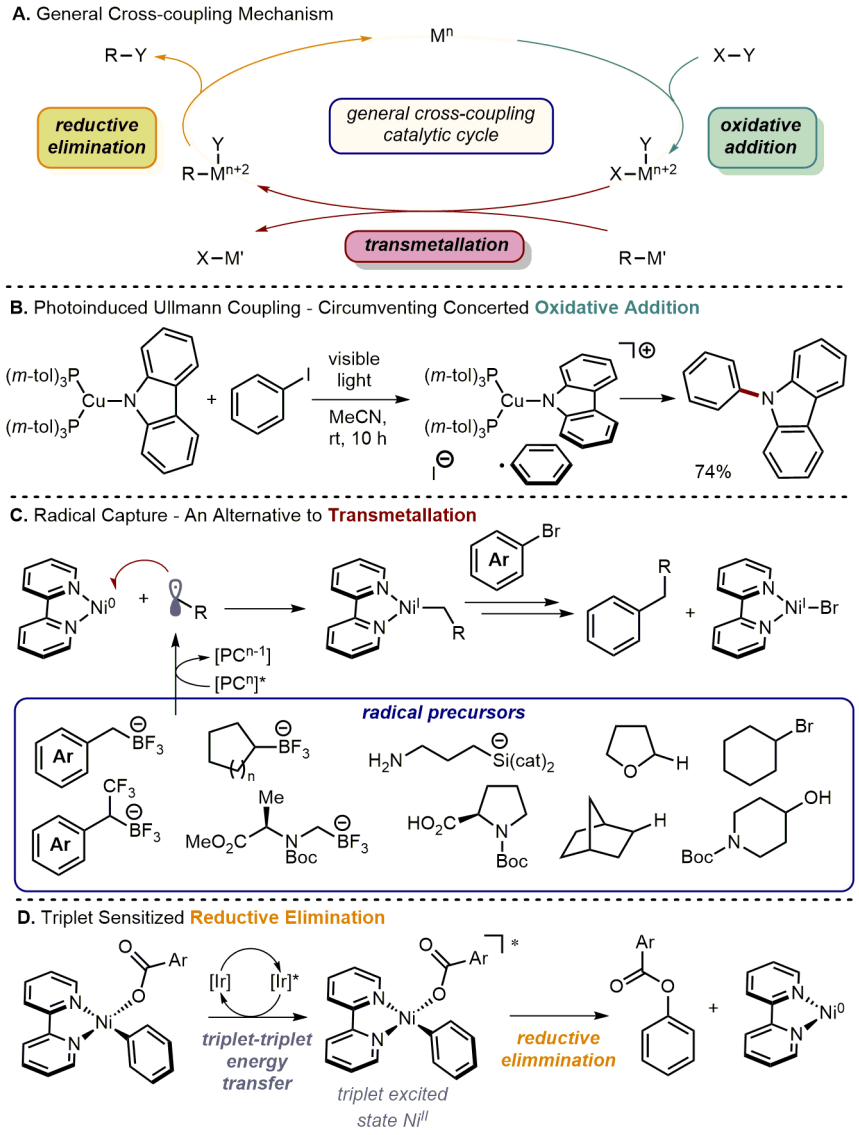

Figure 3.

Impacting elementary cross-coupling steps with photoredox catalysis.

(A) A general transition metal-mediated cross-coupling catalytic cycle. (B) The use of photoredox catalysis to overcome the challenges of oxidative addition to a Cu^{I} center. (C) Photoredox catalysis has had the greatest influence on the elementary transmetallation step. (D) The demonstration of triplet-triplet energy transfer from an excited state photocatalyst to an organometallic intermediate.

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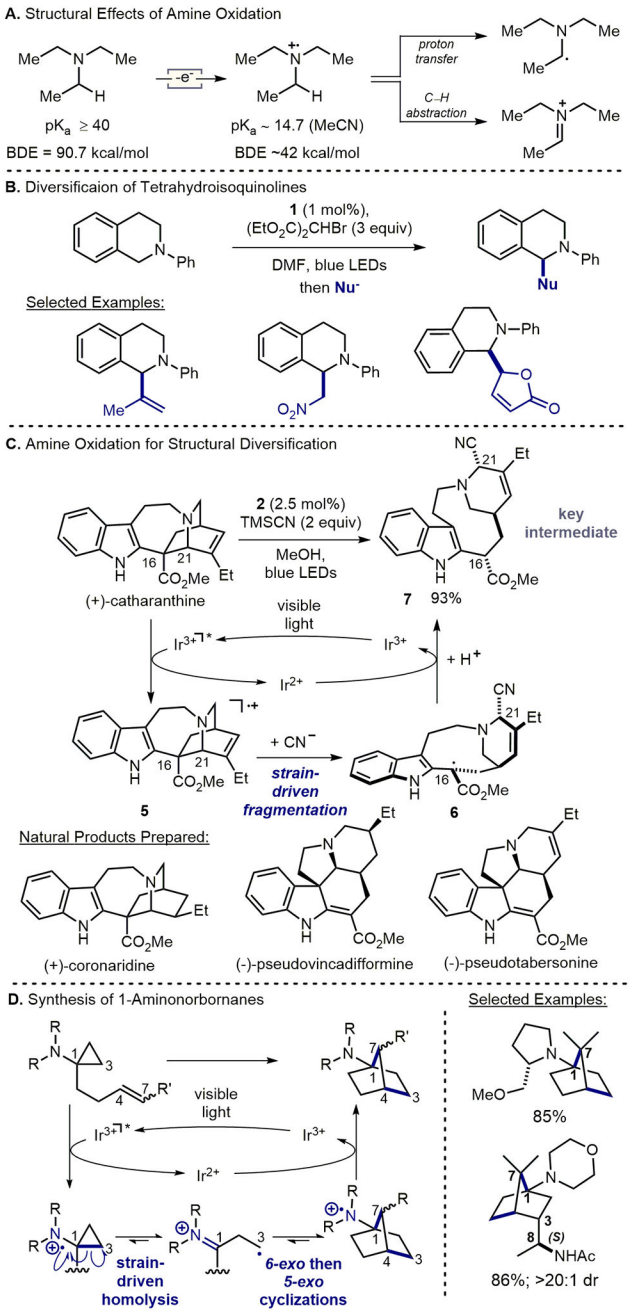

Figure 4.

Selective oxidation of aliphatic amines enabled by photoredox catalysis and subsequent synthetic applications.

(A) The resultant impact on the oxidation of aliphatic amines. (B) Initial efforts aimed at the direct oxidation of *N*-aryl tetrahydroquinoline and subsequent functionalization. (C) Amine oxidation to mimic the proposed biosynthesis of several catharanthine derived alkaloids. (D) The utility of photoredox catalysis in providing new tools for the synthesis of saturated building blocks of interest to the pharmaceutical sector.

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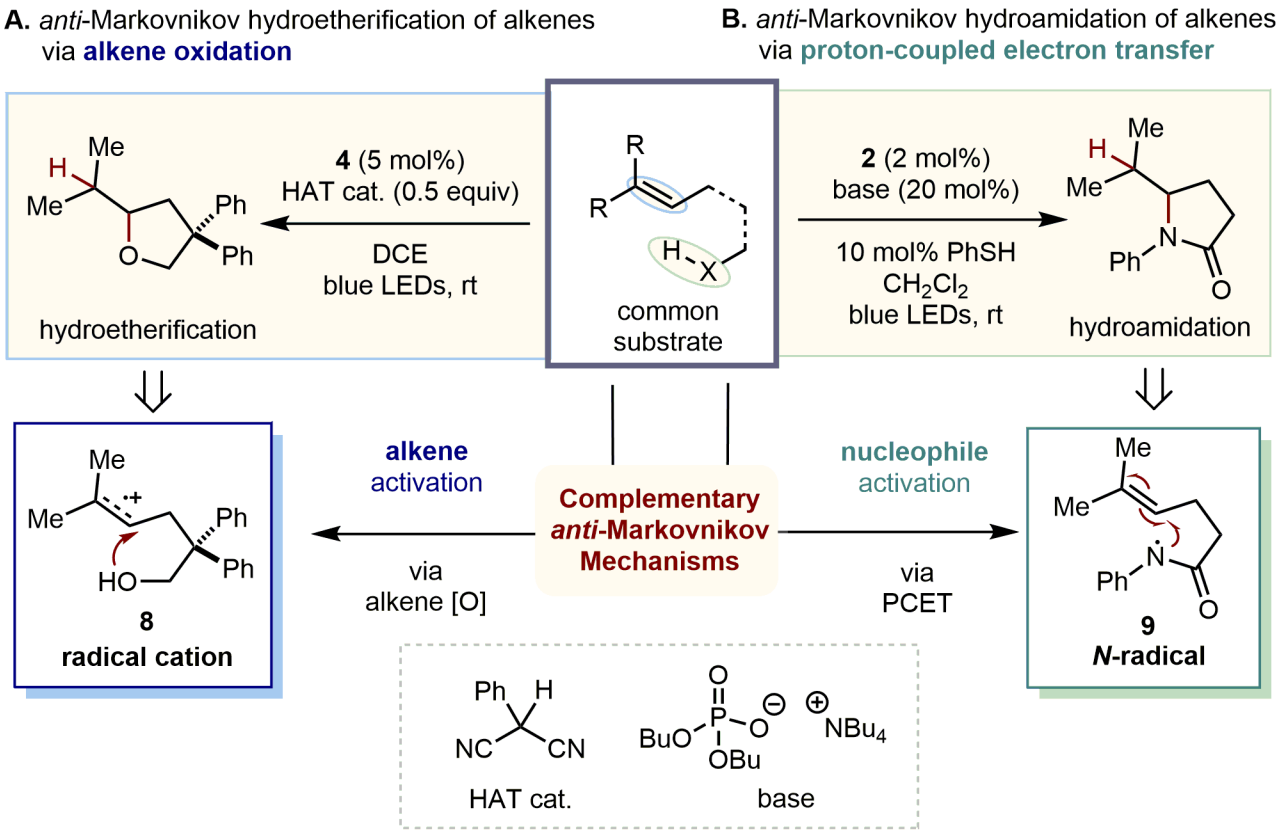

Figure 5.

Complementary mechanistic paradigms for *anti*-Markovnikov additions to alkenes.

(A) *Anti*-Markovnikov selective hydrofunctionalization of alkenes via alkene radical cations.

(B) *Anti*-Markovnikov selective hydrofunctionalization of alkenes via concerted proton-coupled electron transfer approach.

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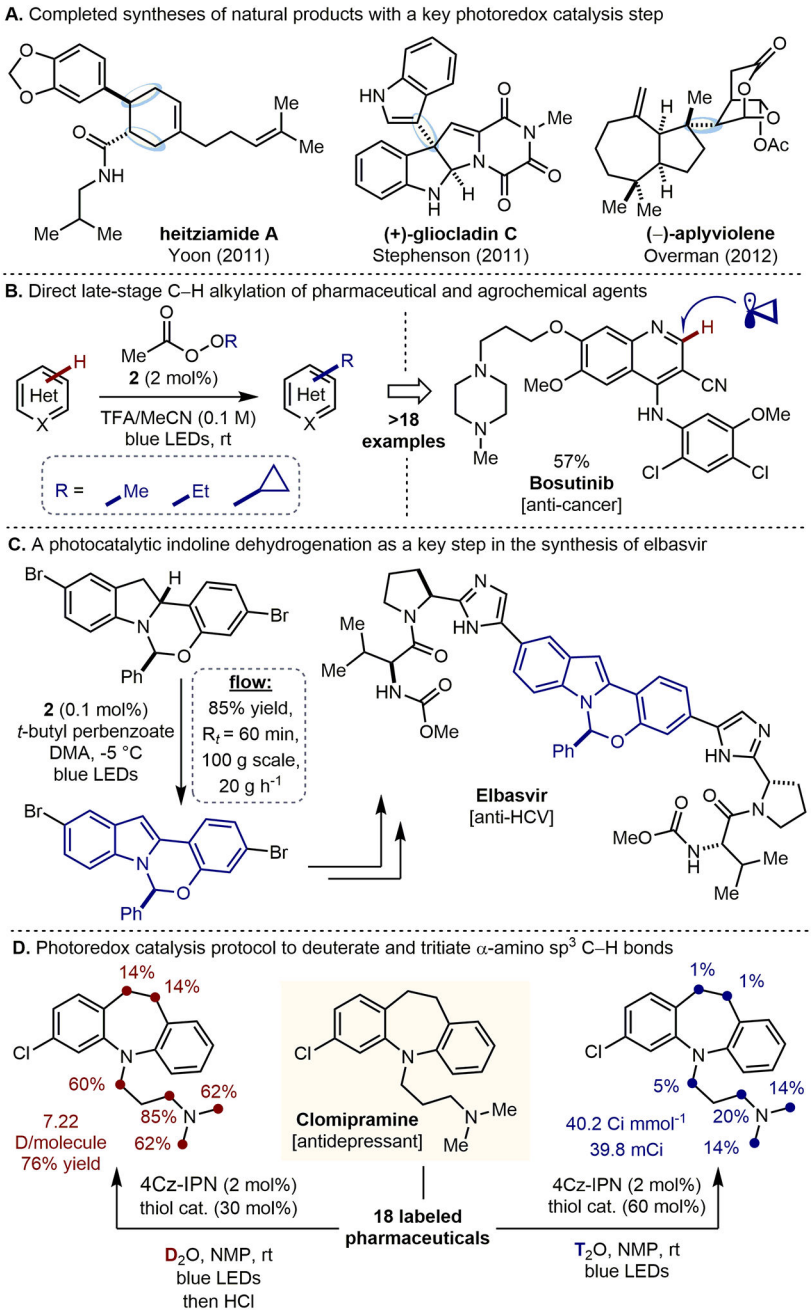

Figure 6.

Recent applications of photoredox catalysis in total synthesis and the industrial sector. (A) The use of photoredox catalysis as a key step in the synthesis of natural products. (B) The use of photoredox catalysis in the direct late-stage C−H methylation, ethylation, and cyclopropanation of pharmaceutical and agrochemical agents. (C) Photocatalytic indoline dehydrogenation as a key step in the sustainable synthesis of elbasvir. (D) A practical photoredox-mediated hydrogen atom transfer protocol to selectively deuterate and tritiate α-amino sp^3 C−H bonds of 18 pharmaceutical compounds.