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**GREEN SYNTHETIC METHODOLOGIES FOR RADICAL
GENERATION**

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1. INTRODUCTION

A radical is an atom, molecule, or ion that has one unpaired valence electron that makes it highly chemically reactive. They are important in reactions like combustion, polymerization, and many other chemical processes and in general in total synthesis. Total synthesis is the complete chemical synthesis of a complex molecule, often a natural product or medicinally important active ingredients, from simple and commercially available precursors. In the last decades, the use of radical methods in the synthesis of complex molecules has grown since Moses Gomberg, in 1900 discovered the triphenylmethyl radical while attempting to prepare the sterically encumbered compound hexaphenylethane from triphenylmethyl chloride via a Wurtz coupling.^[1] Carbon-centered radicals gained relevance as intermediates in complex molecule synthesis in the last few decades and now they are an integral part of many total synthesis processes. From a theoretical point of view, radicals are formed from spin paired molecules through homolysis of weak bonds or electron transfer (reduction). Homolysis makes two new radicals from a spin paired molecule by breaking a covalent bond. This process requires a lot of energy and classical methods for radical generation are often highly toxic for the environment. The increasing attention to problems of chemical pollution and resource depletion stimulates research towards green methods for radical generation. So, in the last decades, the radical generation has evolved, shifting from metal hydride methods to electrochemical and photoredox techniques.

1.1. PERSISTENT AND TRANSIENT RADICALS

For a deeper understanding of the radical usage in total synthesis is necessary the definition of radical “persistence” and “stability”. Although organic radicals are generally intrinsically stable, their existence is often transient because they tend

to dimerize. Persistent radicals are long lifetimes, and so they are used in slower reactions due to their high selectivity. Transient radicals, instead, can be useful because of their big reactivity but they need the required stability. Generally, organic radicals are stabilized by factors like the presence of atoms with low electronegativity, delocalization, and steric hindrance. Organic radicals are electron deficient, thus the greater is the electronegativity of the atom on which the unpaired electron resides the less stable is the radical. Electronegativity influences also the stability of carbon atoms of different hybridizations. Greater s-character correlates to higher electronegativity of the carbon atom (due to the proximity of s orbitals to the nucleus) and therefore gives less stability to the radical. The delocalization of electrons across the structure of a radical, also known as its ability to form one or more resonance structures, represents a factor that stabilizes the radical. Delocalization usually occurs in the presence of electron-donating groups, such as hydroxyl groups (-OH), ethers (-OR) or electron-withdrawing groups, such as C=O or $\text{C}\equiv\text{N}$. Another weaker form of delocalization is hyperconjugation. In radical chemistry, radicals are stabilized by hyperconjugation with adjacent alkyl groups. The donation of sigma C-H bonds into the partially empty radical orbital helps to differentiate the stabilities of radicals on tertiary, secondary, and primary carbons. Tertiary carbon radicals have three-sigma C-H bonds that donate, secondary radicals only two, and primary radicals only one. Therefore, tertiary radicals are the most stable, and primary radicals are the least stable. In the end, the greater the steric hindrance is the more difficult it is for reactions to take place, and the radical form is favored by default. So radicals can be stabilized by stereoelectronic factors and made persistent by their steric environment. When used with their appropriate conditions, radical intermediates can react with regio- and stereoselective control to achieve elaborate molecular architectures. Stabilized radicals can react in predictable manifolds and persistent radicals provide a means to improve

selectivity for reactions involving transient radicals that are otherwise difficult to achieve.

1.2. RADICAL CHAIN REACTIONS

Much of the power of free radical species stems from the natural tendency of radical processes to occur in a chain reaction. Radical chain reactions have three distinct phases: initiation, propagation, and termination. The initiation phase describes the step that initially creates a radical species. In most cases, this is a homolytic cleavage event, and it takes place very rarely due to the high energy barrier involved. Dialkylazo compounds, dialkylhyponitrites, and peroxides are classes of molecules used to thermally initiate radical processes via homolysis. The propagation phase describes the “chain” part of chain reactions. Once a reactive free radical is generated, it can react with stable molecules to form new free radicals. These new free radicals go on to generate yet more free radicals, and so on. There is a variety of propagation steps including radical-radical couplings, β -eliminations, inter- and intramolecular C-C bond formations, and more. The last phase is the chain termination that occurs when two free radical species react with each other to form a stable non-radical adduct. Although this is a very thermodynamically downhill event, it is also very rare due to the low concentration of radical species and the small likelihood of two radicals colliding with one another. The active sites of enzymes can evolve to overcome this entropic barrier by positioning two radical intermediates close to each other.

1.3. EVOLUTION OF THE USE OF RADICALS IN THE SYNTHESIS OF COMPLEX MOLECULES

The evolution of the use of radicals in the synthesis of complex molecules can be characterized into several phases (Fig. 1).

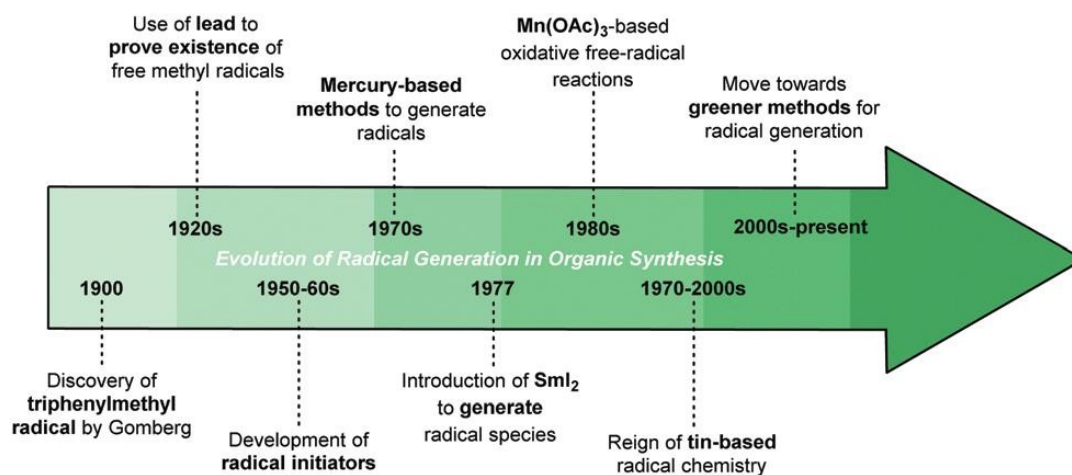


Fig. 1 Evolution of radical generation methods in organic synthesis.

The first phase of this evolution began in the late 1970's with the development of mercury-based methods to generate radicals from Bernd Giese.^[2] The Giese reaction has been used for intermolecular radical addition, but the reductive demercuration conditions responsible for the generation of carbon-centered radicals have been known for some time. However, the mercury method has been surpassed in popularity by the tin hydride method, due to the less toxic conditions than the organomercury salts. For example, Giese utilized this method in the synthesis of (-)-exo-brevicomin. Tributyltin hydride is the reagent most commonly used to conduct free-radical reactions. Simple reduction of an organic halide by tin hydride involves a controlled chain reaction with an initiator like AIBN. An example is Nagarajan's synthesis of siphinene, which relies on the use

of tin hydride and AIBN, followed by an intermolecular cyclization as the propagation step.^[3]

Other common classical methods for the generation of radical intermediates are the Markovnikov radical functionalization of olefins through metal hydride as MH HAT (metal-hydride hydrogen atom transfer) and the carbonyl reduction with samarium diiodide (SmI_2), a one-electron-transfer reagent due to the propensity for Sm(II) to revert to the more stable Sm(III) oxidation state.^[4]

The turning point in the radical production evolution has been the development of the principles of green chemistry. Green chemistry is defined as the “design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances”.^[5] The principles of green chemistry have as their goal to limit the use of toxic reagents and to minimize the generation of waste products. From this point of view both organomercury and organotin reagents are toxic for human and aquatic life, a reason that has driven the field to find alternative methods for radical genesis. Despite the versatility of organotin reagents, their application has been strongly hampered by the difficulty to remove organotin residues from final products combined with the high toxicity of some of them. Recently, the development of new electrochemical and photoredox catalysis approaches allowed the generation of radicals through milder methods, fueling resurgence of interest in radical chemistry. These new radical strategies have been applied to the total synthesis of complex molecules. Electrochemistry has historically been used for bulk chemical production. Improvements to chemoselectivity have permitted the use of electrochemistry in the synthesis of complex molecules, where chemoselectivity is often a challenge. Similarly, developments and improvements to photoredox catalysis have allowed its use in total synthesis. When applied to net-redox neutral transformations, stoichiometric reductants and oxidants can be avoided. Both of these fields offer new ways to

generate radicals in simpler, milder, and greener ways that differ from the classical methods mentioned above.

To provide context for the development of these greener methods, this review highlights the application of “classical” radical methodologies in modern total synthesis. Then this review will highlight the use of greener electrochemical and photoredox-mediated catalytic strategies for generating radical intermediates in total synthesis.

2. AIM OF THE THESIS

To provide context for the development of these greener methods, my thesis will highlight the application of “classical” radical methodologies in modern total synthesis. The organomercury hydride technique has been chosen among the various classical methods mentioned in the introduction, with the example of the Kozikowski’s synthesis of malyngolide. This synthesis and the organomercury method in general are useful to describe the generation of radicals in C-C bond forming reactions. The main focus of this thesis is the research of greener methods for radical generation in total synthesis and, about that, it will highlight the use of greener electrochemical and photoredox-mediated catalytic strategies. The chosen examples are both very recent and significant in the modern total synthesis based on the two greener methods above mentioned. In particular, the Chiba’s electrochemical total synthesis of pyrrolophenantridone alkaloids and the Smith’s total synthesis of danshenspiroketallactones are useful examples to explain how the use of respectively electrochemistry and photoredox catalyst replaced classical methods due to their better selectivity and less toxicity. In fact, the frequency of radical-based strategies in natural product synthesis has grown as greener methods have been developed and these two examples are proof of this.

3. CLASSICAL METHODS FOR RADICAL SYNTHESIS

One of the earliest methods for radical synthesis has been the mercury-based method. In general, the method based on the hydroxymercuration of olefins, with the help of sodium borohydride as reductant agent, followed by Markovnikov addition of water can be used for the synthesis of alcohols. At the same time, organomercurial compounds (R-HgX) can produce alkyl radicals by reductive demercuration. The usage of borohydride allows ligand substitutions to produce R-HgH (mercuric hydride) that can decompose easily to the carbon-centered radical and mercury metal. The alkyl radical often undergo HAT termination via mercuric hydride, and so, due to this behavior and due to the big toxicity of the intermediates, mercury has been replaced by tin, which is overall better for intermolecular chemistry. Organotin hydrides are often used as intermediates for reduction of organic compounds such as halides, aldehydes, or ketones. This reductive method involves organic free radicals as intermediates and it is possible to isolate initially formed radicals before they undergo secondary reactions. Tin hydrides like Bu₃SnH, are still used in radical transformations despite the push to find greener alternatives. The free radical compounds produced by the organotin methods have usually more stability and longevity and so they are used to propagate radical chain reactions. The propagation state starts when Bu₃Sn- goes through hydrogen or halogen atom transfer (HAT or XAT) or atom transfer radical additions (ATRA) that form carbon-centered radicals that can then undergo intra- or intermolecular reactions. Another method includes organoboranes, a class of molecules used frequently as initiators upon reaction with oxygen. The most common initiator is triethyl borane, which reacts with oxygen producing a peroxyboronate ester, which decomposes to the peroxy radical and alkyl radical species. Using this method, high temperatures are unnecessary, but the oxygen may cause auto-oxidation of radical intermediates.

There are also techniques involving metal hydrides like Fe, Co, and Mn. Olefins undergo MH HAT producing carbon-centered radical intermediate and then go through the propagation step of the chain reaction (often HAT). Moreover, this method can reduce metal waste, because transition metals can be used in substoichiometric quantities. Single-electron redox reaction can produce radicals intermediate. Metals frequently used for this method are Ferrocenium, Mn (III), Ce (IV), and also Samarium diiodide (SmI₂), often used as a stoichiometric reductant to synthesize radicals by reduction of ketone or aldehyde carbonyls. Finally, Ti(III) can be used to open epoxides by reduction, to produce more substituted radicals.

3.1. KOZIKOWSKI'S SYNTHESIS OF MALYNGOLIDE USING THE MERCURY HYDRIDE-MEDIATED RADICAL COUPLING

This synthesis is an example of one of the most common and classical methods to produce radicals: the reductive demercuration. Kozikowski and his research team, in 1982, managed to synthesize the malyngolide, a d-lactone-containing antibiotic extracted from a marine blue-green alga. ^[6] This method was based on the possibility to generate radical intermediates from hydroxymercuration products of alkenes by reduction with trimethoxyborohydride. These beta-hydroxyalkyl radicals react with electron-deficient olefins (methyl acrylate and acrylonitrile) to provide delta-hydroxy esters and nitriles which can, in turn, be cyclized to 5-substituted beta-lactones. They use the Giese method, developed few years before. Starting from an allylic alcohol Kozikowski managed to produce the organomercurial compound in 6 steps (Fig. 2). Using trimethoxyborohydride in the presence of excess methyl acrylate and the organomercurial they synthesize a 4:1 mixture of the nitrile of interest (1:1 of diastereomers) and reduction product. This is the key passage of the synthesis process that involves the formation of the organomercurial hydride that in turn

decompose to form the alkyl radical with a stoichiometric amount of mercury. This species, through an intermolecular coupling to the methyl acrylate, can produce the alpha-nitrile radical. At this point, a hydrogen atom transfer (HAT) from the alkyl radical to the nitrile radical can produce the desired nitrile, mentioned earlier. One last step lead to the desired Malyngolide from the nitrile compound. In conclusion, the Kozikowski synthesis of the malyngolide is an example of how mercury hydride can be used to generate radicals in C-C bond forming reactions. The rate of HAT is faster than the intermolecular C-C bond-forming reaction, a reason why it is essential to use a big quantity of radical trapping agent to synthesize malyngolide.

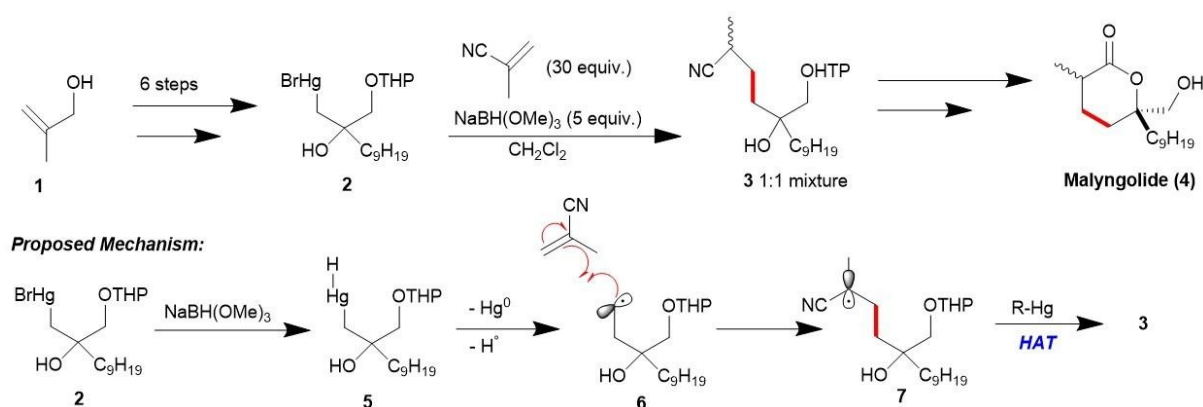


Fig. 2 Kozikowski's 1982 total synthesis of malyngolide (36) leveraging the borohydride-induced carbon-centered generation from the organomercurial 34.

4. ELECTROCHEMICAL GENERATION OF RADICALS

Traditionally, the synthesis of organic compounds has been accomplished via chemical routes. Alternatively, over the last century, the use of electrochemical methods for organic synthesis has been investigated at both the laboratory and industrial scale. Some of the benefits of electrochemical organic synthesis are higher product selectivity and purity, lower number of reaction steps, inexpensive

starting materials, less polluting byproducts, and lower consumption of energy. Due to these benefits, the electrochemistry began to be used in the process-scale generation of bulk chemicals and in the synthesis of fine chemicals and complex molecules. In the last decades, the electrochemistry developed its importance in complex molecule synthesis due to its versatility, in particular for single-electron processes that generate radical intermediates. Organic electrosynthesis constitutes a promising platform for exploiting adequately the unique reactivity profiles of radical intermediates. By the use of this greener approach, more sustainable processes with a better atom economy can be realized. The electrochemical approach offers big advantages in comparison to the use of chemical stoichiometric oxidizing or reducing agents. For example, the highly reactive and toxic agents (like transition-metal complexes) can be avoided by generating oxidant or reductant agents in situ, and adjustment of the cell potential can prevent unwanted side reactions, such as overoxidation or overreduction. Performing an electrochemical reaction with a constant potential imparts greater chemo-selectivity whereas doing so with a constant current imparts operational simplicity. Despite the benefits offered by organic electrosynthesis, its application in synthetic organic chemistry has recently been limited by the lack of standardized electrosynthetic cells and electrodes. In conclusion, the use of electricity as an alternative to stoichiometric and often toxic one-electron redox reagents constitutes a convenient, atom- and cost-efficient way to assemble molecules, and there are plenty of examples where electrosynthesis allows for more sustainable versions of classic reactions.

4.1. CHIBA'S ELECTROCHEMICAL TOTAL SYNTHESIS OF PYRROLOPHENANTHRIDONE ALKALOIDS

A recent and interesting example of how the electrochemistry can be used in total synthesis to generate radical intermediates is the Chiba's experiment of the synthesis of pyrrolophenanthridone alkaloids.^[7] This process consists of two important steps: the intermolecular cross-coupling intermediate and the indole formation. Aryl-aryl cross-coupling is a common strategy in total synthesis and drug discovery. In the field of medicinal chemistry, palladium-mediated cross-coupling is the most frequently used. However, Pd catalysts are expensive and cytotoxic; hence, alternative methods are required. An electrochemical method would be a green and clean way to prepare bioactive compounds because it can generate unique reactive intermediates without any oxidants or reductants. In this process, the starting indoline is oxidized to the arene radical cation that forms in turn a tertiary radical through a coupling with the arene group of the molecule (Fig. 3). At this point, a deprotonation and another oxidation produce the coupled indole. The optimal conditions used by Chiba's research group, for the intermolecular cross-coupling, consist in a system of MeNO₂-HFIP-LiClO₄ where Nitromethane and Hexafluoroisopropanol have the role of solvents, while the Lithium perchlorate (0,1M) is the electrolyte used for the oxidation. In particular, the HFIP has a crucial importance thanks to its ability to increase the electrophilicity of the radical cation. Once the cross-coupled indoline is formed, the second main process is the oxidation of the indoline to the final indole product. In this step, the indoline is oxidated to the radical cation and then deprotonated to generate the benzylic radical intermediate. A further oxidation is used to form the benzylic cation that through collidine (2,4,6-Trimethylpyridine) can be deprotonated to give the final indole product. In this second process, Chiba used a system with MeCN (acetonitrile) as the solvent and Bu₄NClO₄ 0,1M (tetrabutylammonium perchlorate) as the electrolyte. In conclusion, using this

approach, several pyrrolophenanthridone natural products can be synthesized in a greener and less toxic method in comparison to the classical organomercurial or organotin hydride methods.

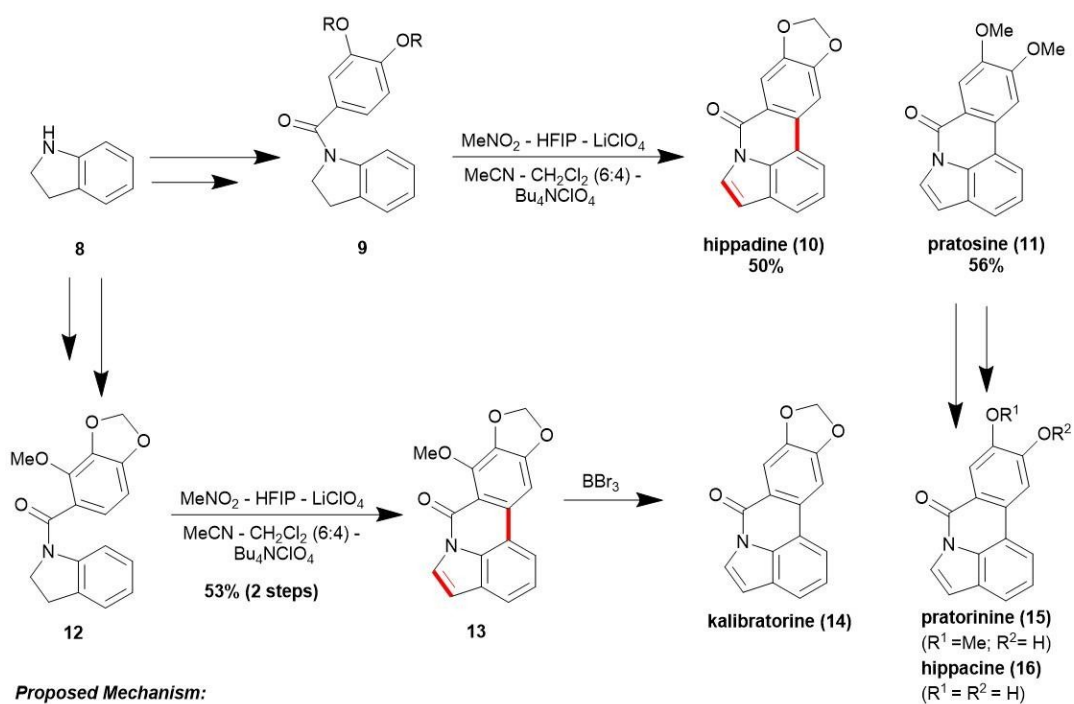


Fig. 3 Chiba's 2020 electrochemical total synthesis of pyrrolophenanthridone natural products via C(sp²) C(sp²) cross-coupling and indoline oxidation.

5. GENERATION OF RADICAL BY PHOTOREDOX CATALYSIS

The total synthesis of natural products and their derivatives continues to inspire organic chemists to identify and test new synthetic strategies and develop and explore novel methodology. In recent years, visible light photoredox catalysis has risen to prominence as a powerful technology that enables the selective formation of chemical bonds under mild reaction conditions. In a general sense, these approaches rely on the ability of metal complexes and organic dyes to convert visible light into chemical energy by engaging in single-electron transfer with organic substrates, thereby generating reactive intermediates⁽⁵⁶⁾. In particular, the use of visible light rather than UV light enables selective excitation of the photoredox catalyst in preference to most organic molecules. Consequently, the use of a low-energy light source can prevent detrimental substrate/product degradation pathways from occurring in structurally complex molecules with sensitive functionality. This approach allows the generation of radicals through reductive couplings, photocycloadditions, intermolecular C-H functionalization reactions, and more. Net-neutral redox catalytic cycles offer a “green” means to generate reactive radical intermediates for total synthesis applications while reducing the generation of excess waste. Net-neutral redox cycles circumvent the need to handle toxic reagents as substoichiometric loadings of catalyst is achievable without relying on exogenous stoichiometric oxidants or reductants to regenerate the reactive oxidation state of the catalyst.

5.1. SMITH'S TOTAL SYNTHESIS OF DANSHENSPIROKETALLACTONES

In 2019, Smith and co-workers designed and validated a new visible-light-induced protocol to generate dithianyl and dioxolanyl radicals via 1,5- or 1,6-HAT.^[8] The resulting radicals engage in conjugate additions to achieve formal

allylation and alkylation. They used the catalytic method to form the precursor of the final products via direct C(sp³)-H functionalization. The starting reagent is the naphthoic acid that can be used to synthesize the first intermediate in 6 steps (Fig. 4). At this point, the photoredox catalysis (IrIII) can oxidize the Hantzsch ester and then reduce the main intermediate forming two radicals. The Hantzsch ester radical cation then reduces 34 to the corresponding alkoxy radical. 35 then undergoes [1,5]-HAT to form intermediate 36. This method is a thermodynamically favorable HAT as the electronically stabilized radical 36 is formed at the expense of the high-energy oxyl radical 35. An additional three steps led to the first synthesis of pure danshenspiroketallactones (30 and 31). These natural products are isolated from the *Salvia miltiorrhiza* plant which is used in traditional Chinese medicine as a remedy for renal failure and heart disease.

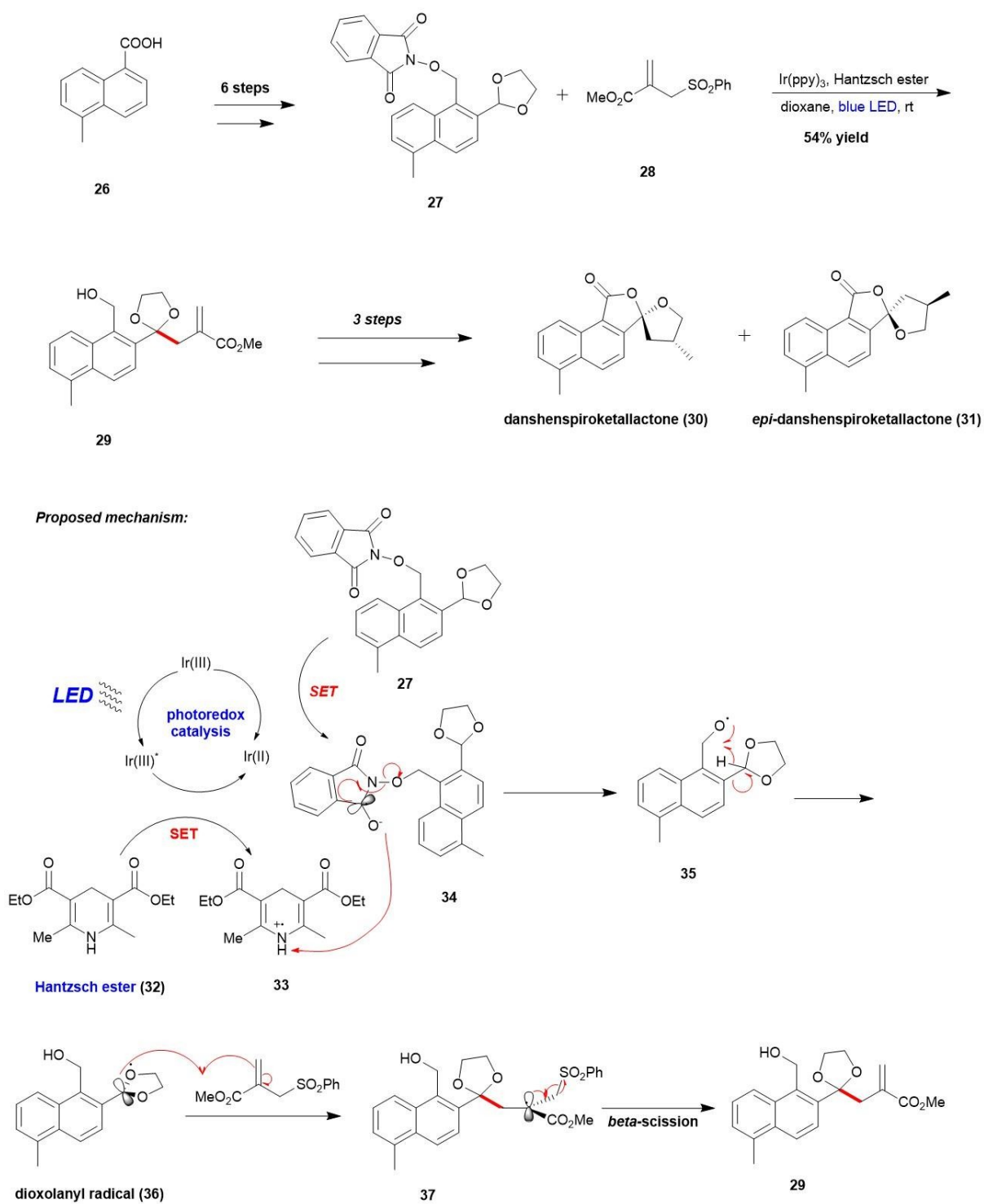


Fig. 4 Smith's approach to danshenspiroketallactones via [1,5]-radical relay chemistry.

6. CONCLUSION

The total synthesis of complex natural products remains among the most exciting and dynamic areas of chemical research. In this sense, these greener methods have paved the way for more sustainable radical chemistry, an almost essential condition in the modern chemical industry. Both electrochemistry and photoredox catalyst strategies provide several benefits in terms of selectivity, atom economy but most of all in terms of access to previously inaccessible synthetic strategies. On one side, electrosynthetic transformations utilize electricity as a cheap, versatile means to access radical species, while also allowing for high selectivity through the fine-tuning of the electrode potential, among other things. As mentioned above, Chiba's group was able to find a system to generate radical intermediates to accomplish an intramolecular C(sp²)-C(sp²) cross-coupling. This reaction was achieved by the generation of a strong electrophilic radical cation intermediate in the MeNO₂-HFIP-LiClO₄ system and avoiding the usage of a stoichiometric oxidant agent. This is only a single example of electrochemical radical generation, but there is indeed a wide array of electrochemical transformations that are applied in total synthesis due to all the benefits of this method. On the other side, through the generation of highly reactive intermediates in mild, controlled manners coupled with the ability of photoredox catalysts to act as both an oxidant and reductant simultaneously, photoredox catalysis gives access to previously inaccessible synthetic transformations and new forms of reactivity. As mentioned in this thesis, the importance of the photoredox catalysis is in the synthesis of highly congested quaternary centers like the Smith's synthesis of danshenspiroketallactones and epi-danshenspiroketallactones. To do This, Smith and coworkers utilize [1,5]-radical relay chemistry initiated by photoredox catalysis to generate carbon radicals via [1,5]-HAT of alkoxy radicals. This is only one of many examples in which photoredox catalysis can be leveraged to generate radicals that would be

otherwise difficult or impossible to furnish using classical radical generation methods. While classical methods for radical generation can still be leveraged in total synthesis (like the Kozikowski's synthesis of malyngolide, their biggest limitation exist in their real-world applications in the chemical industries, where photoredox catalysis and electrochemistry provides pharmaceutical, agricultural and other chemical companies the opportunity to utilize radical chemistry in the synthesis of relevant compounds while also cutting down on toxic waste and impurities.

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