

Synthesis of Bioactive Heterocycles: Photocatalysis and Computational Catalysis in Synergy

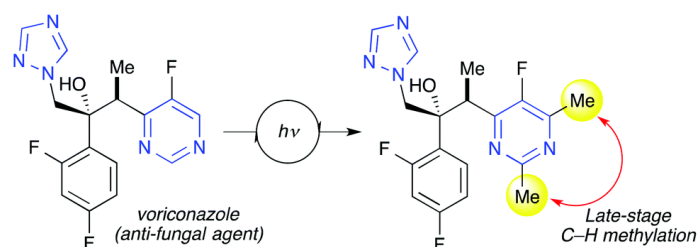
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Abstract

Small ring heterocycles form the structural basis of almost all pharmaceuticals, agrochemicals and materials. These are among the most important building blocks for the synthesis of biologically active molecules. My presentation will provide an overview of our recent efforts towards development of visible-light-mediated photoredox catalysis, which provides a powerful platform for the divergent assembly of poly-functionalized bioactive nitrogen heterocycles and late-stage modification of blockbuster drug molecules such as enoxolone (anti-ulcer), oleanic acid (hepatoprotective), gemfibrozil (lipid lowering drug), rimantadine (anti-viral), mexiletine (anti-arrhythmic), phenylbutazone (veterinary NSAID), drospirenone intermediate (oral contraceptive), avobenzone (sunscreen) and complex bioactive ergot compounds such as thevinone, nicergoline and metergoline. In addition to this, we have successfully applied our photoinduced catalysis to an efficient vinylation and allylation of electrophilic radicals, C–C and C–H bond cleavage cascades and remote functionalizations of amides and amines. Moreover, an effective synergistic role of computational catalysis in photocatalysis will be concisely presented.

materials science, agrochemistry, and medicinal chemistry. Therefore, there is continuing interest in the development of convenient, efficient, and environmentally benign synthetic methods for the construction of nitrogen containing heterocycles. Due to its natural abundance, ease of use, and promising application in industry, the use of visible light as a driving force for chemical reactions has received considerable attention in the past few years. In the context of seminal works of others in this area, a concise summary of the contributions of the authors is also offered.



The photocatalytic cycle harvests photon energy to fuel the reaction. It doesn't directly involve bond-breaking and bond-forming events (as known to date). As such, it's of broad interest to develop multifunctional catalytic systems, capable of catalyzing bond-rearranging events additionally to the sunshine harvesting process. A couple of examples exist of such catalytic systems and this field is growing rapidly.^{28–34} This is often also a neighborhood during which DFT might be utilized for design, studies of properties and development of predictive tools, particularly considering that preparation of complex catalyst systems might be highly resource and time consuming.

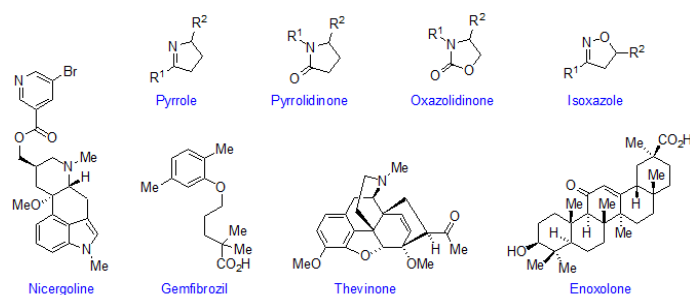


Figure 1: Representative bioactive heterocycles and drug molecules for late-stage modifications.

These Nitrogen heterocycles represent a highly important class of compounds which are widely used in

The main examples of selective intermolecular C–H functionalization of heterocycles using VLPC came from Stephenson and co-workers,⁷ who showed that indoles and other heteroaromatics readily underwent C–H

malonation under photocatalytic conditions with diethyl bromomalonate and using 4-methoxy-N,N-diphenylaniline as base. For example, the C-2 malonation of N-methylindole was achieved in 82% yield using 1 mol% of ruthenium(II) trisbipyridine dichloride as the photocatalyst (Scheme 1).⁷ In this letter, we describe our recent discovery of a photocatalytic double C–H functionalization process using indoles and diethyl bromomalonate. Our experimental efforts to understand the mechanism and scope, and to advance further development of this process, are detailed herein. Moreover, we have synergistically employed density functional theory calculations to assess a likely mechanism for the transformation.

We can conclude that, The high sensitivity of the chemical yields toward electronic effects underscores the challenges involved in achieving selective C–H multifunctionalizations. Studies to develop the photocatalytic C–H bromination chemistry further are under way and will be disclosed in the near future.

Future outlook

As progress continues into an exciting era for homogeneous photoredox catalysis, there's a continuing need for deeper understanding of catalyst properties, selectivity and reactivity to refine the chemical methods into enabling technologies. The facility of deep understanding lies in its enabling potential because it allows us to predict and streamline chemical synthesis. especially, a radical understanding of principles involved in photocatalytic late-stage functionalization would be of paramount importance for molecular design from an artificial chemistry perspective. we will be during a better position to style new chemical reactions and catalysts for the synthetic toolkit through thoughtfully employed quantum chemical calculations. DFT can provide unique and detailed insights into a spread of elementary chemical processes at relatively low cost. the advantages of enlightened, guided and streamlined experimental chemistry are too great to dismiss, and that we anticipate that the complete potential of photoredox catalysis in organic synthesis are going to be reached

through a synergistic effort of experimental and computational research.

Applications of Photocatalysis

Heterogeneous photocatalysis has been demonstrated as a coffee cost and sustainable technology for the treatment of a number of pollutants in air and water including organics and heavy metals, etc., with Japan, USA, India and China as major users of this technology as partly demonstrated by the amount of research publications during this area Unlike reverse osmosis, nano and ultrafiltration, photocatalysis may be a cheap and a possible “stand alone” technology for water treatment. As photocatalysis makes use of sunlight or UV radiation, the technology is inexpensive, environmentally friendly and may be applied worldwide. It requires minimal equipment, is very deployable and appropriate for developing countries and remote sites with no access to electricity. Photocatalysis has also been used successfully in many developing nations to destroy pathogens and algal blooms in water supplies Photodisinfection sensitized by TiO₂ has been wont to degrade the chlorophyte, treat humic substances which act as substrates for bacterial growth, inhibit bacterial degradation of impurities in natural water, and aid the transport of metals within the environment and sophisticated with Fe, Pb, Mn, making it harder to get rid of them.

Applications of Computational Catalysis

Catalysts play important roles in chemical reactions, biological processes, and industry applications. The mechanistic studies of catalysis enable the elucidation of how reactions are accelerated by the presence of a catalyst, and therefore the optimization and style of reactions or catalysts. Computational chemistry has been proven to be a strong tool for the mechanistic studies of catalysis. Computational chemistry can play fundamentally important roles in elucidating the catalytic mechanisms of such systems, by offering information about short-lived intermediates and transition states also as factors that determine catalytic properties, which isn't easily attained by experimental means. A quantum

mechanical description of a targeted catalytic system might be difficult or unfeasible in many circumstances, especially when large systems like metalloenzymes and coordination polymers are studied. Nevertheless, valuable insights can still be gained from hybrid computational techniques that allow concrete realizations of in depth reaction pathway analyses.

Recent Publications

1. Marcillo S P, Dauncey E M, Kim J H, Douglas J J, Sheikh N N, Leonori D (2018) Photoinduced remote functionalizations of amides and amines using electrophilic nitrogen-radicals. *Angew. Chem. Int. Ed.* 57: DOI: 10.1002/ange.201807941.
2. Dauncey E M, Marcillo S P, Douglas J J, Sheikh N N, Leonori D (2018) Photoinduced remote functionalizations via imminyl radical-promoted C-C and C-H bond cleavage cascades. *Angew. Chem. Int. Ed.* 57: 744-748.
3. Davies J, Sheikh N N, Leonori D (2017) Photoredox imino functionalizations of olefins. *Angew. Chem. Int. Ed.* 56: 13361-13365.
4. Reina D F, Ruffoni A, Al-Faiyz Y S S, Douglas J J, Sheikh N N, Leonori D (2017) Visible-light-mediated reactions of electrophilic radicals with vinyl and allyl trifluoroborates. *ACS Catal.* 7: 4126-4130.
5. Davies J, Syejstrup T D, Reina D F, Sheikh N N, Leonori D (2016) Visible-light-mediated synthesis of amidyl radicals: Transition metal free hydroamination and N-arylation reactions. *J. Am. Chem. Soc.* 138: 8092-8095.

Biography

Nadeem S. Sheikh is an Associate Professor of Organic Chemistry at the King Faisal University, Saudi Arabia, and his current research interests include environmentally benign catalysis to prepare bioactive molecules, computational catalysis for target-oriented organic synthesis and mechanistic investigation for synthetically significant organic transformations. He received his PhD (2008) from the University of Southampton, UK under the supervision of Prof. Richard C. D. Brown. He then moved to the laboratory of Prof. Iain Coldham at the University of Sheffield, UK, as a postdoctoral research associate (2008-2011). He has received several awards including gold medal and academic roll of honour during BSc, merit and talent awards during MSc, ORSAS award for PhD studies, EPSRC postdoctoral award and Wiley-VCH best poster presentation award at 9th ISCC in Italy.