

Cluster Preface: Radicals – by Young Chinese Organic Chemists

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Chen Zhu (left) received his B.S. degree from Xiamen University in 2003 under the supervision of Prof. Pei-Qiang Huang, and his Ph.D. degree from the Shanghai Institute of Organic Chemistry in 2008 under the supervision of Prof. Guo-Qiang Lin. After postdoctoral research at Gakushuin University, Japan with Prof. Takahiko Akiyama, he moved to the University of Texas Southwestern Medical Center, working as a postdoctoral fellow with Prof. John R. Falck and Prof. Chuo Chen. He was appointed as a professor at Soochow University, China in December 2013. He is currently the Head of the Organic Chemistry Department at Soochow University. His current research interests include radical-mediated transformations, in particular radical rearrangements, and their applications in the construction of natural products and biologically active compounds.

Xin-Yuan Liu (right) obtained his B.S. degree from Anhui Normal University (AHNU) in 2001. He continued his research studies at both the Shanghai Institute of Organic Chemistry (SIOC), CAS and AHNU under the joint supervision of Prof. Dr. Shizheng Zhu and Prof. Dr. Shaowu Wang, obtaining his master's degree in 2004. After a one-year stint in Prof. Gang Zhao's laboratory at SIOC, he joined Prof. Dr. Chi-Ming Che's group at The University of Hong Kong (HKU) and earned his Ph.D. degree in 2010. He subsequently undertook postdoctoral studies in Prof. Che's group at HKU and in Prof. Carlos F. Barbas III's group at The Scripps Research Institute. At the end of 2012, he began his independent academic career at the Southern University of Science and Technology (SUSTech) and was promoted to a tenured Full Professor of SUSTech in 2018. His research interests are directed towards the design of novel chiral anionic ligands to solve radical-involved asymmetric reactions.

Key words radicals, alkene difunctionalization, photocatalysis, C–H functionalization

Since the discovery of radicals by Gomberg in 1900, radical-mediated transformations, by virtue of their inherent elegance and unique glamour, have appealed to chemists for over a century. Radicals are present in many synthetically useful applications, such as the electrolytic Kolbe decarboxylation, the Hunsdiecker reaction, and the Hofmann–

Löffler–Freytag reaction. Unlike classic ionic-type transformations, radical reactions enable the homolysis of inert chemical bonds under mild conditions and the reorganization of bonds via unusual pathways. For instance, β -C–C bond cleavage is spontaneously triggered by O- or N-centered radicals but is generally difficult to achieve by transition-metal catalysis. In addition, C(sp³)–H bond activation is much more likely to take place by means of radical-mediated hydrogen atom transfer (HAT). Consequently, radical reactions are of growing importance in order to meet the contemporary challenges in the synthesis of complex structures and bioactive molecules.

Despite the great progress made in synthetic radical chemistry, radicals are still regarded as being highly reactive, uncontrollable species, and their applications are mainly restricted to radical polymerization and transformations involving radical-chain pathways. Until the 2010s, along with the prevalence of photocatalytic and electrocatalytic techniques and the innovation of ingenious strategies, a new era was brought to the forefront of radical chemistry, with chain reactions no longer playing the lead in radical chemistry. Radicals have become controllable and are extensively harnessed in catalytic reactions. A plethora of novel types of reactions have been unveiled with good regio- and stereoselectivities, and have become robust synthetic tools.

During the last decade, a surge in efforts from China has led to important contributions being made in this area. In this SYNLETT Cluster, we are delighted to feature 11 articles from young Chinese organic chemists, which are dedicated toward different themes and concepts related to synthetic radical chemistry.

Direct C(sp³)–H functionalization is one of most challenging topics in synthetic chemistry. The radical-initiated process via HAT of C(sp³)–H bonds represents a privileged strategy owing to the mild reaction conditions and good regioselectivity. The recent progress made on radical-initiat-

ed C(sp³)-H alkynylation reactions is summarized in this Cluster (Z.-L. Li and X.-Y. Liu).¹ This review emphasizes diverse alkynylating reagents and discusses the radical alkynylation in two reaction modes: intermolecular HAT and intramolecular 1,5-HAT.

Despite there being fewer investigations on 1,2-HAT compared to 1,5-HAT, the unusual 1,2-HAT reactivity of alkoxy radicals under visible-light-induced reaction conditions for α -C-H functionalization has been summarized (Y. Chen),² in which alkoxy radicals demonstrate superior HAT reactivity attributed to the strong O-H bond dissociation energy. Various mechanistic studies are discussed in Chen's account to address key questions and to validate the 1,2-HAT reactivity of alkoxy radicals.

Alkenes are readily available and bulk chemicals. Radical-mediated functionalization of alkenes provides a practical approach for alkene transformations, leading to numerous value-added compounds. The synthesis of boron-handled glycol derivatives is accomplished based on an NHC-boryl-radical-promoted regioselective hydroboration of glycol-protected cinnamaldehydes (F.-L. Zhang and Y.-F. Wang).³ A one-pot, two-step process is involved, in which an interesting reductive ring-opening of a glycol-derived acetal occurs by using the in situ incorporated NHC-borane unit as the hydride source.

Regioselective anti-Markovnikov hydroacylation of aryl alkenes is achieved by using neutral eosin Y as both the photosensitizer and HAT catalyst under visible-light irradiation (X. Tang and J. Wu).⁴ Aldehydes serve as acyl radical precursors arising from a direct HAT process induced by photoexcited eosin Y. A visible-light-driven redox-neutral phosphonoalkylation of alkenes is also revealed (Q. Fu, Y.-M. Yu and D.-G. Yu).⁵ Cyclopropane derivatives are synthesized from alkyl-sulfonate-substituted styrenes and H-P(O) compounds. The reduction of a benzylic radical to a carbanion is followed by an intramolecular nucleophilic cyclization as the key steps to afford cyclopropane scaffolds.

Compared to styrenes, unactivated alkenes are more common but are normally considered as challenging substrates for radical difunctionalization of alkenes. Remote functional-group migration (FGM) supplies an efficient tactic for dealing with unactivated alkenes. A radical-mediated heteroaryl functionalization of unactivated alkenes through remote *ipso*-migration of O- or S-containing heteroaryls has been disclosed (C. Zhu).⁶ Various heteroatom-centered radicals, such as azido, trifluoromethylsulfanyl and silyl radicals, trigger the migration cascade. Furyl, benzofuryl, thienyl and benzothienyl groups showcase satisfactory migratory aptitudes.

Besides aldehydes, carboxylic acids and vicinal dione oxime esters can also be employed as acyl radical precursors. Under photoredox reaction conditions, triphenylphosphine is used as a deoxygenative reagent for biarylcarboxylic acids to give acyl radicals, which rapidly participate in intramolecular radical cyclization to generate fluorenones

(C. Zhu and J. Xie).⁷ The reaction has been scaled up with continuous-flow photoredox technology, thus illustrating the practicality of the method. With the use of dual photoredox/palladium catalysis, strategically designed oxime esters serve as acyl radical sources through iminyl-radical-mediated β -C-C bond cleavage (X.-P. Liu and J.-R. Chen).⁸ Subsequently, acyl radicals participate in the palladium-catalyzed *ortho*-C-H acylation of 2-arylpyridines. This is an elegant demonstration of the compatibility of radicals by merging them into other types of reactions.

Another interesting example of the combination of radical reactions with organocatalysis is reported (S. Yu).⁹ The organocatalyzed desymmetrization of 3-substituted glutaric anhydrides and subsequent photoredox-catalyzed decarboxylative fluorination furnishes chiral aliphatic fluorides. This method offers an efficient way to access chiral fluorinated compounds in a highly enantioselective manner.

Based on a combination of electrochemical and photocatalytic technologies, so-called photoelectrocatalysis, a radical-mediated C-H alkylation reaction of heteroarenes with alkyl oxalates has been developed (H.-C. Xu).¹⁰ The Minisci-type reaction proceeds through a sequence of photocatalytic decarboxylation and electrochemical hydrogen evolution.

Unpredictability is also a charming characteristic of radical transformations. Simply heating *N*-chlorosuccinimide (NCS) analogues with azobisisobutyronitrile (AIBN) results in the formation of unexpected amidine derivatives (H. Bao).¹¹ DFT calculations suggest that intermolecular radical addition to the nitrile group of AIBN derivatives is involved, leading to structurally reorganized adducts.

The aforementioned investigations include the development of new radical reactions and efficient methods to prepare valuable functional molecules. Though this Cluster cannot cover all the endeavors from young Chinese organic chemists, these contributions clearly showcase that this generation has already played a key role in the international stage of radical chemistry. We are very grateful to all the distinguished scientists who have contributed to this SYNLETT Cluster.

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