Distal radical migration strategy: an emerging synthetic means

Weipeng Li, Wentao Xu, Jin Xie, Shouyun Yu and Chengjian Zhu

The remote radical migration strategy has gained considerable momentum. During the past three years, we have witnessed the rapid development of sustainable and practical C–C and C–H bond functionalization by means of long-distance 1,n-radical migration (n = 4, 5, 6) events. Its advent brings our chemical community a new platform to deal with the challenging migration transformations and thus complements the existing ionic-type migration protocols. In this review, the recent achievements in distal radical migration triggered C–C and C–H bond functionalization are summarized.

Key learning points
(1) Long-distance radical migration strategy.
(2) Selective C–C bond functionalization.
(3) Selective C–H bond functionalization.
(4) Radical rearrangement.

1 Introduction

The organic radical is one of the most notoriously reactive intermediates and thus controllable radical chemistry has earned great momentum in synthetic chemistry. A plethora of well-known radical reactions, such as the Hofmann–Löffler reaction, Barton deoxygenation reaction, Giese reaction and Minisci reaction etc., have been well exploited over the past century, providing powerful strategies for the construction of structurally diverse compounds. Typically, electrotylic, photolytic, borane oxidative homolytic, and organo-tin hydride systems can be employed to generate different kinds of radical species. In the past decade, the renaissance of radical transformation occurred along with the blooming development of transition-metal catalysis and photoredox catalysis. Radical reactions have been esteemed as an excellent complement for transition-metal-catalyzed classical ionic-type chemical bond formation between electrophiles and nucleophiles (Scheme 1).

Functionality migration, namely a functional group moving from one position to a new position, is a well-known workhorse rearrangement transformation in organic chemistry (Scheme 1). Historically, the ionic-type Favorskii, Beckmann, pinacol rearrangements have been developed with a wide range of applications. Very recently, the radical-mediated distal functionality migration has gained increasing attention and a great number of examples have sprung up like mushrooms. Radical-mediated migration is able to reconstruct the molecular structures and synthesize valuable compounds in an efficient way which are not easily available through other methods. This kind of strategy offers new synthetic protocols to organic synthesis. Although several mini-reviews have summarized the major achievements in radical-mediated 1,n-H atom transfer and in particular 1,2-aryl migration, it is still highly desirable to especially stress the breakthrough in long-distance radical migration and also its synthetic applications. In this review, the recent achievements in long-distance 1,n-radical
migration \((n = 4, 5, 6)\) induced C–C and C–H bond functionalization are discussed.

2 The C–C scission by distal radical migration

C–C bond functionalization is an important strategy to modify the skeletons of simple substrates, which can be used to construct complex molecules in an efficient and economical way. However, the high activation energy barrier of the single C–C bond renders it challenging to achieve selective C–C cleavage of non-strained compounds in the frontiers of organic chemistry. In the recent three years, the radical-mediated functionality migration offers a new choice for remote C–C bond functionalization of non-strained substrates (Scheme 2). This new C–C functionalization strategy is distinguished by the mild reaction conditions, exclusive selectivity and excellent functional group tolerance.

2.1 Recent radical aryl migration

Although the radical 1,2-arylation migration has been well studied, long-distance radical aryl migration is currently underdeveloped. In recent years, the remote aryl migration protocol was actively pursued. For example, in 2014, Liang’s group disclosed a copper-catalyzed radical trifluoromethylation/1,4-aryl migration of homo-propargylic alcohols (Scheme 3), which provided tetrasubstituted CF₃-containing alkenes in moderate yields.

Scheme 2 Remote radical C–C migration/functionalization.

Weipeng Li was born in Henan, China, in 1989. He received his Bachelor degree from Henan Normal University in 2011, and his PhD degree from Nanjing University in 2016, supervised by Prof. Chengjian Zhu. Currently, he works as postdoctoral fellow with Prof. Chengjian Zhu at Nanjing University. His current research interests are focused on visible-light induced organic transformation and gold catalysed oxidative coupling.

Wentao Xu was born in Hubei Province, China. He received his Bachelor degree from the Hefei University of Technology in 2014 and Master degree at the same university in 2017, under the supervision of Professor Huajian Xu. He is currently conducting his PhD studies under the supervision of Prof. Jin Xie and Prof. Chengjian Zhu at Nanjing University. His current research interest focuses on Au(Ⅰ)/Au(Ⅲ) chemistry.

Prof. Jin Xie was born in Chongqing, China, in 1985. He received his Bachelor degree from Northeast Forestry University in 2008, and a PhD degree in 2013 from Nanjing University working under the direction of Prof. Chengjian Zhu. From 2014–2017, he was a postdoctoral research associate in the group of Prof. A. S. K. Hashmi at Heidelberg University. In 2017, he came back to Nanjing University, as an associate professor, to start his independent career. His current research interests lie in transition-metal catalysis, biomimetic radical transformations and homogeneous gold catalysis.

Shouyun Yu obtained his bachelor degree in Chemistry from Nanjing University in 2001. After completing doctoral studies under the supervision of Prof. Dawei Ma in 2006 at the Shanghai Institute of Organic Chemistry (SIOC) in Shanghai, China, he worked as an assistant research professor in the same institute for one more year. Then he moved to Jeffrey W. Bode’s group at the University of Pennsylvania as a post-doctoral research fellow in late 2007. In September, 2010, he was appointed as an associate professor of School of Chemistry and Chemical Engineering at Nanjing University. He is currently a full professor in the same university. His current research focuses on photochemistry, radical chemistry and asymmetric synthesis and their applications in the synthesis of biologically important molecules.
to good yields. Togni’s reagent serves as a CF$_3$ radical source via a SET process with Cu$^I$. The addition of the CF$_3$ radical to the triple bond of substrate 1 forms vinyl radical 3, followed by 1,4-aryl migration to deliver radical intermediate 5. Then, oxidation of radical 5 with Cu$^{II}$ gives the desired product 2. It is of high regio- and stereo-selectivity via 5-exo ipso addition of intermediate 4, resulting in the CF$_3$ group and migrated-aryl in trans-selectivity exclusively.

In the same year, Pohmakotr and co-workers developed an enantioselective intramolecular radical cyclization/ipso-1,4-aryl migration reaction, which afforded chiral 3,3-difluoro-2-propanoylbicyclo-[3.3.0]octane products as single isomers. The authors initially synthesized starting material 6 as a mixture of diastereomers (1:1) from a chiral material with the aim of getting tricyclic radical addition product 7. Surprisingly, in the treatment of 6 with Bu$_3$SnH (1.75 equiv., 0.02 M) in the presence of a catalytic amount of AIBN, 1,4-aryl migration compound 8 was obtained instead of the expected tricyclic product 7 (Scheme 4a). A further study indicated that with a low concentration of Bu$_3$SnH, radical cyclization/ipso-1,4-aryl migration product 9 could be exclusively obtained in 78% yield as a single isomer (Scheme 4b). A suggested mechanism is shown in Scheme 4b. First, addition of the tributylstannyl radical to terminal alkyne followed by 5-exo-trig cyclization produces bicyclic radical intermediate 10. This reactive species undergoes stereospecific ipso-addition and gives intermediate 11. Then a stereoselective 1,4-aryl migration process occurs followed by elimination of the phenylsulfanyl group, leading to 12 which delivers product 9 as a single isomer after work-up with silica gel. With an excess tributylstannyl radical, intermediate 12 could be converted to 8 via a cascade defluorination process.

The radical Smiles rearrangement has been known for decades, and exhibits widespread applications in organic chemistry. Despite the great advances, the domino Smiles rearrangement remains rather elusive. In 2015, the Nevado group developed a multistep radical Smiles rearrangement reaction with the well-designed ortho-vinyl- or ortho-styryl-substituted N-(arylsulfonyl)aryl amides as substrates (Scheme 5). In this domino radical transformation, the addition of the phosphonyl or azidyl radical to activated alkenes triggers the classical Smiles rearrangement, producing 5- and 7-membered ring carboyclic products in high stereoselectivity.

As their follow-up work, the Nevado group documented another elegant example of the multi-step radical cascade reaction of N-(arylsulfonyl)acrylamides. This reaction proceeded via a radical addition/ipso-cyclization/aryl migration/intramolecular cyclization pathway, which is used for constructing four chemical bonds in a one-pot fashion. Two different scaffolds 18 and 24

---

**Scheme 3** Copper-catalyzed trifluoromethylation/aryl migration of internal alkynes.

**Scheme 4** An asymmetric intramolecular radical cyclization/ipso-1,4-aryl migration cascade.

**Scheme 5** Tandem radical Smiles rearrangement of N-(arylsulfonyl)acrylamides.

---

Chengjian Zhu was born in Henan, China, in 1966. He obtained his PhD from the Shanghai Institute of Organic Chemistry (CAS) in 1996 under the supervision of Professor Qian. Then he worked as a postdoctoral fellow successively in Universite de Bourgogne, the University of Oklahoma, and then the University of Houston from 1997 to 2000. He joined Nanjing University as an associate professor in 2000. Since 2003, he has been a professor at Nanjing University. His present research interests lie in organometallic chemistry and asymmetric catalysis.
could be obtained by changing the substrates and radical sources (Scheme 6). When N-[(2-ethynyl)aryl]sulfonyl]acylamide 17 is employed, the chemoselective radical addition to the carbon–carbon double bond could generate radical intermediate 19. Then a radical Smiles rearrangement takes place, generating amidyl radical intermediate 21 followed by intramolecular [3+2] cyclization, which finally delivers CF₃-, SCF₃-, Ph₂(O)P-, and N₃-containing indolo[2,1-a]isoquinolin-6(5H)-ones 18 in good yields catalysed by Cu₂O (R = CF₃) or AgNO₃ (R = Ph₃PO) or under other conditions (R = SCF₃, N₃) (Scheme 6a). Alternatively, with 1,3-dicarbonyl compounds as radical precursors, the authors explored Ag(I)-catalyzed radical addition to N-(aryl)(arylsulfonyl)acrylamide 22. In this process, the reactive radical intermediate 25 was proposed as an important intermediate for 1,4-aryl migration (Scheme 6b).

In addition, aryl alkynoates can also undergo the radical 1,4-aryl migration. In 2016, Wu and co-workers reported a catalyst-free tandem sulfonyl radical addition and subsequent 1,4-aryl migration of aryl alkynoates for the synthesis of 3-sulfonyl coumarin derivatives (Scheme 7). The sulfonyl radical 30 can be generated by the treatment of easily readily available aryl diazonium salt 27 and commercially available sulfur dioxide surrogate DABCO(SO₂)₂ 28 via a single electron transfer (SET) process. As shown in Scheme 7, the radical addition of 30 to aryl propiolates 26 results in the formation of reactive vinyl radical 31, which subsequently undergoes ipso-cyclization to provide spirocyclic intermediate 32 that can be oxidized to cation 33 by DABCO radical cation 34. The resulting intermediate 33 undergoes 1,4-aryl migration and aromatization to ultimately furnish product 29.

In the same year, Wang and co-workers reported a benzyl radical initiated intramolecular 1,4-aryl migration of aryl alkynoates using TBHP as an oxidant (Scheme 8). This method is able to provide trisubstituted alkenes with toluene derivatives via a cascade C(sp³)–H bond functionalization/1,4-aryl migration/decarboxylation process.

Medium-ring skeletons are commonly found in a variety of natural products, but they rarely appear in man-made drugs and functional materials. Arguably, the synthesis of medium rings is a challenging yet attractive subject of research in organic synthesis. In 2016, Liu and co-workers established a radical induced ring expansion strategy to construct a library of benzannulated 8–11 and 14-membered cyclic ketones using readily available materials and reagents (Scheme 9). The reactions were initiated by radical azidation, trifluoromethylation, phosphonylation, sulfonylation, or perfluoroalkylation of unactivated alkenes followed by 1,4 or 1,5-aryl migration and ring expansion. More than 37 benzannulated medium-sized molecules with potential bioactivity were obtained in moderate to good yields. It was found that the reaction proceeded in a highly stereoselective manner. The medium-ring benzannulated products with a chiral carbon centre could be obtained from enantiomerically pure substrates with completely chiral transfer (Scheme 9). It is worth mentioning that the benzannulated ketones could be conveniently transferred to other complex medium-bridged scaffolds.

Lately, the same group reported another example of intramolecular remote 1,4(5)-(hetero)aryl migration of tertiary alcohols triggered by radical azidation, trifluoromethylation, or phosphonylation (Scheme 10). In some cases, heteroauration substituted substrates, such as pyridine rings, selectively underwent 1,4/1,5-migration to afford heteroaryl migrated products.

Heteroaromatic rings are prevalent structural segments distributed in natural products, medicines, and agrochemicals.
The direct incorporation of heteroaryl groups is a convenient strategy to synthesize heteroaryl-containing compounds. Although remote radical aryl migration reactions are reported by several groups, selective heteroaryl migration is still highly challenging. Zhu and co-workers realized radical-mediated heteroaryl ipso-migration of substituted tertiary alcohols with Langlois’ reagent (CF$_3$SO$_2$Na) as a CF$_3$ radical source, providing fluoroalkyl functionalized heteroarenes in good to excellent yields (Scheme 11). Most of the heteroaryl groups, including benzothiazole, benzoxazole, thiazole, imidazole and pyridine, migrated smoothly to afford the corresponding heteroaryl migration products. Notably, the electron-withdrawing heteroarene is a preferential migration functionality compared with electron-rich heteroarene and. This is completely opposite to the classical ionic-type migration rule. One limitation of the reaction was that the internal alkene failed. Control experiments also revealed that five- and six-membered cyclic transition states favoured the remote migration process and four- and seven-membered transition states disfavoured it.

The azide moiety is one useful building block, which could be readily converted to various N-containing functional groups. In 2017, Liu’s group reported an interesting copper-catalysed trifluoromethylation/1,4-aryl migration of homopropargyl azides to access trifluoromethylated nitriles (Scheme 12). Herein the CF$_3$ radical can be generated via a single electron transfer process between Cu(I) and Togni’s reagent. The addition of the CF$_3$ radical to the triple bond of substrate triggers a consecutive cascade process to generate radical which undergoes single electron oxidation and extrusion of N$_2$ to produce nitrile compound. Importantly, the products are obtained in a highly selective manner, which keeps CF$_3$ and migrated aryl groups always in the trans-position.

Indeed, the reaction mode of radical aryl migration is not limited to radical addition to alkenes and alkynes. If the
carbon- or heteroatom-centred radical can be generated at a suitable position, the radical migration is also feasible. In 2015, one impressive radical Smiles rearrangement was disclosed from Stephenson’s group.19 The remote aryl group directly migrated to the difluoroalkyl radical which was generated in situ by means of photoredox catalysis (Scheme 13). This protocol enabled concise synthesis of a diverse range of difluoroethanoxyl-containing aryl/heteroaryl products. A series of bioactive heterocyclic substrates were compatible, and furnished the desired products in moderate to good yields (43–89%). Interestingly, both NBu3 and formic acid served as the electron and H donor. As illustrated in Scheme 13, the mechanism starts from the photoinduced SET and the generated radical \( \text{SO}_2 \) adduct, which would undergo H-atom abstraction from the NBu3 radical cation, finally leading to the desired product \( 60 \). Notably, the authors declared that a radical chain pathway might also be involved.

Different from the preceding carbon-centred radical initiated aryl migration, the distal aryl migration can also be triggered by electrophilic nitrogen radicals. For example, in 2015, Shi’s group reported an elegant Ag(I)-catalyzed 1,4-aryl migration from the carbon to nitrogen centre followed by C–O bond formation, affording \( \gamma \)-hydroxy amines or tetrahydroquinoline derivatives in satisfying yields (Scheme 14).20 During optimization of the reaction conditions, the authors found that oxidants, solvents and protecting groups on nitrogen atoms were requisite for this transformation. Among the oxidants tested, PhI(OTFA)2 was the superior one. DCE was determined to be the best solvent, and further investigation demonstrated that the addition of PhCl as a co-solvent could dramatically promote the reaction efficiency. This reaction was sensitive to protecting groups on nitrogen atoms; only the sulfonamides worked well and the other substrates, such as Boc, Ac, CO2Me, Ts or Ms-protected amides, resulted in no reaction or low conversion. The migratory aptitude of different aryl groups was also tested with unsymmetrical substrates; the results indicated that compared to electron-deficient phenyl groups, electron-rich aryl rings preferred to migrate (see Scheme 14, \( 62e \) and \( 62f \)). This point is similar to the ionic-type migration sequence.

The authors further performed several control experiments to gain insight into the mechanistic pathway. With 1.0 or 0.5 equiv. TEMPO as a radical scavenger, migration was completely suppressed. By the treatment of the modified substrate \( 64 \) with a classical radical system of triethylborane/O2, the expected migration occurred smoothly with good yield (Scheme 15a). These experiments indicated that a radical pathway should be involved. A possible mechanism was proposed in Scheme 15b. The N-centred radical \( 68 \) could be generated in the presence of a catalytic amount of Ag(l)/ligand and PhI(OTFA)2 as well as a suitable base. Then, intramolecular ipso-attack of aryl followed by C–C bond cleavage produces radical \( 80 \) which is trapped by sulfonyl acrylates \( 73 \).
or alkenes 74 to finally give carbon-to-nitrogen aryl migration products 75 or 76.

There are very few examples about the long-distance radical aryl migration between two heteroatoms. In 2016, Jana and co-workers reported a silver(i)-catalyzed 1,4-aryl migration of 2-aryloxybenzoic acids which incorporated a radical aryl migration between oxygen or sulfur and oxygen atoms.22 The carboxyl radical can be generated through SET oxidation of carboxyl acid with Ag(II) generated in situ. The 1,4-ipso attack by oxygen atom takes place with concomitant C–X (X = O or S) bond cleavage, leading to radical intermediate 88. The radical 88 could undergo a H-atom shift (X = O) or homo-coupling (X = S) to give product 84 or 85 (Scheme 17).

Very recently, Li and Cao reported a similar aryl migration between two oxygen atoms promoted by photoredox catalysis without external oxidant under mild conditions (Scheme 18).23 In this transformation, electron-rich aryls are more likely to undergo aryl migration than electron-deficient aryl groups.

### 2.2 Radical migration of other carbon-based groups

In addition, the distal migration of other carbon-based functionalities, such as –CN, –CHO, –alkynyl groups was recently developed.

In 2016, the group of Zhu reported a metal-free remote nitrile migration triggered by azidyl radical addition to give unactivated olefins (Scheme 19).24 First, the azido radical is generated from commercial available TMSN₃ in the presence of PhI(OAc)₂ as an oxidant. Then addition of the azido radical to alkene 91 leads to the formation of alkyl radical 93, which would undergo intramolecular addition at carbon atoms of nitrile groups, affording cyclic transition state 94. The resulting unstable cyclic intermediate 94 undergoes immediate C–C homolysis at room temperature to afford the CN migration intermediate 95. Finally, oxidation of 95 by PhI(OAc)₂ affords 1-azido-2-nitrile product 92. In this reaction, the 1,4- or 1,5-CN migration via a thermodynamically stable 5- or 6-membered cyclic transition state is more favourable than 1,3 or 1,6 migration.

Lately, Liu’s group extended this strategy and achieved cyanofunctionalization of terminal alkenes via distal cyano migration with diverse radical species (Scheme 20).25 The TMS-protection of hydroxyl was an essential factor for high yields.

After this disclosure, Liu and co-workers further applied the distal radical migration strategy to achieve 1,2-formylfunctionalization of alkenes through radical formyl migration (Scheme 21).26 With Togni’s reagent as a CF₃ radical source in the presence of 20 mol% CuI, radical 1,4- and 1,5-formyl migration proceeded...
smoothly to afford 1-CF₃-2-CHO products in moderate to good yields. Other radical species, such as the perfluoroalkyl radical, difluoromethyl radical and sulfonyl radical, were also able to trigger this migration under photoredox catalysis. It is noted that 1,4 and 1,5-carbonyl migration of cyclic α-hydroxyketones is also available, producing various medium-ring structures with CF₃ or N₃ groups catalysed by CuI. The possible mechanism is depicted in Scheme 21d taking Togni’s reagent as an example. The generated CF₃ radical adds to substrate 99 followed by intramolecular cyclization, yielding a cyclic transition state 101, which undergoes homolysis followed by SET to give trifluoromethylated product 100a.

Alkynes are versatile synthetic blocks in organic chemistry. Recently, Zhu and co-workers first disclosed a novel radical alkynyl migration reaction which could accomplish alkynylation of unactivated olefins promoted by visible light photoredox catalysis under mild reaction conditions (Scheme 22). With Umemoto’s reagent and a catalytic amount of fac-Ir(ppy)₃ as a photocatalyst, a highly reactive CF₃ radical and a strong oxidant Ir(IV) are generated under blue LED irradiation. The CF₃ radical reacts with the terminal alkene of 103, giving allyl radical 105, which subsequently undergoes cyclization/homolysis to afford alkynyl migration intermediate 107. Oxidation of 107 by a strong oxidant Ir(IV)-species affords the desired product 104. The control experiments showed that 5 and 6-membered cyclic transition states were much more favourable for the alkynyl migration. Various γ or δ-alkynylation alkyl ketones were constructed in good yields. Unpleasingly, 1,1-disubstituted alkenes and internal alkenes cannot undergo this transformation due to the relatively lower reactivity.

Lately, the group of Studer reported a similar radical alkynyl migration of tertiary propargylic alcohols. Different from Zhu’s work, Studer and co-workers used cheap perfluoroalkyl iodides as perfluoroalkyl radical sources in the absence of transition metal via electron catalysis (Scheme 23).

3 The C–H scission by distal radical migration
In the past decade, C(sp³)–H bond functionalization has emerged as a powerful platform to construct new carbon–carbon or
carbon–heteroatom bonds. The transition metal, such as Cu, Pd, Rh, Ru, Ir, catalyzed C–H bond functionalization has been recognized as one of the most attractive approaches to achieve C(sp³)–H bond transformation. However, these methods usually suffer from one of the following drawbacks: (1) viable for the C–H bond adjacent to N, O, S atoms; (2) the requirement of directing groups; (3) challenges in controlling the selectivity. Inarguably, the radical migration strategy offers a new chance to deal with selective and mild C–H bond functionalization (Scheme 24). In this section, hydrogen-atom transfer (HAT) triggered C(sp³)–H bond functionalization will be discussed.

### 3.1 HAT triggered by carbon centred radicals

Enantioselective functionalization of the C(sp³)–H bond is a direct and efficient manner to construct chiral sp³ carbon–carbon and carbon–heteroatom bonds. In 2014, Liu’s group developed a copper and chiral phosphoric acid co-catalyzed enantioselective α-C(sp³)–H functionalization of amides enabled by radical trifluoromethylation of unactivated alkenes concomitant with 1,5-hydrogen transfer without the need for an external oxidant (Scheme 25). It starts from the CF₃ radical addition to α-electron-poor alkenes, giving rise to alkyl radical; the resulting alkyl radical immediately abstracts the hydrogen atom adjacent to the nitrogen atom to form a more stable α-aminoalkyl radical. This intermediate is easily oxidized to generate imine compound. Interestingly, the utilization of chiral phosphoric acid could elegantly control its stereoselectivity. A diverse range of chiral CF₃-containing N,O-aminal derivatives were obtained in excellent enantioselectivity and good yields. A similar racemic phosphine catalyzed strategy was also reported from the same group.

In 2015, Liu and co-workers accomplished a series of remote α-C–H functionalization of carbonyl compounds via radical H-atom transfer (Scheme 26). The CF₃ radical addition to alkene followed by a 1,5-H shift and SET oxidation provided cation intermediate. This reactive intermediate could be trapped by different nucleophiles.

In 2016, Gevorgyan and co-workers reported a visible-light-mediated 1,5-H transfer reaction of hybrid aryl-Pd(II)-radical species generated via a SET process between aryl iodide and Pd(0) (Scheme 27). With the irradiation of blue LEDs, an unprecedented single electron oxidation addition of aryl iodide to Pd(0) occurs, furnishing the hybrid aryl-Pd(II)-radical species. This aryl radical complex specifically abstracts α-hydrogen adjacent to the oxygen atom, and produces alkyl Pd-radical intermediate, which finally affords silyl enols ether via SET oxidation or β-H elimination pathway.

As we discussed above, almost all the 1,5-H shift examples were focused on the functionalization of relatively weak C–H bonds. Very recently, Gagoz and co-workers developed a copper catalyzed 1,5-hydrogen shift of homoallylic alcohols with the benzyl group as a traceless hydrogen donor (Scheme 28). With CF₃- or N₃-containing hypervalent iodine reagents as radical sources in the presence of a catalytic amount of copper salts, γ-trifluoromethyl or azido substituted alcohols can be obtained in moderate to good yields.

In 2016, the group of Zhu successfully developed a copper catalyzed remote C–H amidation of aldehydes via 1,5-H transfer from C–H aldehyde groups. Both alkenes and aldehydes...
As their follow-up work, they recently documented a Pd-catalyzed difluoroalkylation and remote C–H arylation of alkenyl aldehydes through a tandem radical addition/1,5 or 1,6-HAT/Suzuki coupling process with readily available fluoroalkyl bromides and arylboronic acids (Scheme 29). Importantly, radical intermediate 138 was justified as one key intermediate for the addition of Pd(1) to undergo the traditional transmetalation with ArB(OH)2 to deliver the final product 137.

3.2 HAT triggered by nitrogen-centered radicals

Nitrogen-centred radicals serve as versatile synthetic intermediates and play an important role in many chemical transformations. Nitrogen-centred radicals have long been recognized as highly reactive intermediates that are capable of triggering distal C–H bond transfer. One of the most well-known and useful transformations is the Hofmann–Loffler reaction. Despite the great advances, the harsh reaction conditions seriously limit its synthetic applications. In 2015, the Muniz group reported a modified version. The sunlight initiated, iodine catalyzed Hofmann–Loffler reaction provided an efficient and straightforward access to a general class of saturated nitrogenated heterocycles under practical conditions (Scheme 30). Importantly, the addition of Pd(i) to undergo the traditional transmetalation with ArB(OH)2 to deliver the final product 137.

Very recently, Nagib and co-workers described a triiodide-mediated Hofmann–Loffler reaction of unactivated C–H bond for the formation of a broad range of functionalized pyrrolidines (Scheme 31). The formation of an I3– intermediate from NaI and PIDA was supposed to be one key element that could decrease the concentration of I2 in the reaction system and thus facilitate the formation of a N–I bond, which would initiate an exclusively selective 1,5-hydrogen atom transfer process through visible light induced homolysis of the N–I bond.

Although the above Hofmann–Loffler reaction proceeds well under mild conditions, stoichiometric amounts of hypervalent iodine reagents were required. In 2015, Yu's group reported the first photoredox catalyzed Hofmann–Loffler reaction of N-chlorosulfonamides without external oxidant. A variety of 5-membered ring pyrrolidines and δ-chlorinated sulfonamide were prepared in good to excellent yields. In Yu’s work, amidyl radical 151 can be generated by oxidative quenching of photoexcited *Ir(III) with N-chlorosulfonamides 149. The electrophilic N-centred radical 142 which undergoes a 1,5-H shift to give benzylic radical 143. A chain propagation between 141 and 143 can produce iodinated intermediate 144 and regenerate N-radical 142. Finally, the cyclization of 144 affords pyrrolidines or 2-pyrrolidinones with excess oxidant and I2.

Although the above Hofmann–Loffler reaction proceeds well under mild conditions, stoichiometric amounts of hypervalent iodine reagents were required. In 2015, Yu's group reported the first photoredox catalyzed Hofmann–Loffler reaction of N-chlorosulfonamides without external oxidant. A variety of 5-membered ring pyrrolidines and δ-chlorinated sulfonamide were prepared in good to excellent yields. In Yu’s work, amidyl radical 151 can be generated by oxidative quenching of photoexcited *Ir(III) with N-chlorosulfonamides 149. The electrophilic N-centred radical 142 which undergoes a 1,5-H shift to give benzylic radical 143. A chain propagation between 141 and 143 can produce iodinated intermediate 144 and regenerate N-radical 142. Finally, the cyclization of 144 affords pyrrolidines or 2-pyrrolidinones with excess oxidant and I2.

Very recently, Nagib and co-workers described a triiodide-mediated Hofmann–Loffler reaction of unactivated C–H bond for the formation of a broad range of functionalized pyrrolidines (Scheme 31). The formation of an I3– intermediate from NaI and PIDA was supposed to be one key element that could decrease the concentration of I2 in the reaction system and thus facilitate the formation of a N–I bond, which would initiate an exclusively selective 1,5-hydrogen atom transfer process through visible light induced homolysis of the N–I bond.

Although the above Hofmann–Loffler reaction proceeds well under mild conditions, stoichiometric amounts of hypervalent iodine reagents were required. In 2015, Yu's group reported the first photoredox catalyzed Hofmann–Loffler reaction of N-chlorosulfonamides without external oxidant. A variety of 5-membered ring pyrrolidines and δ-chlorinated sulfonamide were prepared in good to excellent yields. In Yu’s work, amidyl radical 151 can be generated by oxidative quenching of photoexcited *Ir(III) with N-chlorosulfonamides 149. The electrophilic N-centred radical 142 which undergoes a 1,5-H shift to give benzylic radical 143. A chain propagation between 141 and 143 can produce iodinated intermediate 144 and regenerate N-radical 142. Finally, the cyclization of 144 affords pyrrolidines or 2-pyrrolidinones with excess oxidant and I2.

Very recently, Nagib and co-workers described a triiodide-mediated Hofmann–Loffler reaction of unactivated C–H bond for the formation of a broad range of functionalized pyrrolidines (Scheme 31). The formation of an I3– intermediate from NaI and PIDA was supposed to be one key element that could decrease the concentration of I2 in the reaction system and thus facilitate the formation of a N–I bond, which would initiate an exclusively selective 1,5-hydrogen atom transfer process through visible light induced homolysis of the N–I bond.
N-centred radical 151 goes through 1,5-H transfer to form radical 152. Subsequently, SET oxidation of 152 with Ir(IV) could afford carbocation 153 and regenerates the photocatalytic cycle. Finally, trapping of cation 153 by chloride anions gives chlorination product 154, which could be easily converted to pyrrolidine derivatives under base conditions (Scheme 32).

Based on their previous work on the I₂-catalyzed Hofmann–Loffler reaction and photoredox catalysis, Muniz and co-workers recently reported a dual visible-light-induced intramolecular amination of remote C(sp³)–H bonds by combination of light-activated homolysis of the N–I bond and photoredox catalysis (Scheme 33). This can avoid the use of stoichiometric amounts of hypervalent iodine reagents.

Despite the great achievements in the Hofmann–Loffler reaction, the prevalent methods usually require N–X amides as starting materials (either prepared or generated in situ). These methods are generally not amenable to the direct construction of intermolecular carbon–carbon (C–C) bonds. The direct generation of amidyl radicals from N–H bonds is a long-standing challenge. In 2016, the Knowles group and the Rovis group simultaneously made a major breakthrough in this area by means of photoredox direct generation of nitrogen-centred radicals from N–H bonds (Scheme 34). These reactions feature the formation of C–C bonds via 1,5-hydrogen atom transfer and subsequent coupling with electron deficient alkenes. Both alkyl and aryl enones were suitable coupling partners. In Knowles’s work, the strategy could also be expanded to intermolecular H-abstraction. In Rovis’s work, they also explored the possibility of cascade C–H alkylation of substrates with more than one tertiary C–H bond, and found that substrates with two adjacent tertiary C–H bonds could undergo 1,5-HAT first and then followed by 1,6-HAT, providing access to incorporating two distinct alkyls at different C–H bonds in one substrate. For both these two reactions, the nitrogen atom bearing an electron-withdrawing group was crucial for the success.

Similar to amidyl radicals, the iminyl radicals are also reactive enough to undergo 1,5-H transfer to achieve remote C–H bond functionalization. In the recent five years, oxime derivatives have been recognized as suitable precursors to produce iminyl radicals by means of photocatalysis. In 2017, the group of Nevado reported a visible light-mediated redox-neutral remote inert C(sp³)–H bond functionalization followed by intramolecular radical cyclization via an iminyl radical triggered HAT process (Scheme 35). This protocol proceeded smoothly to produce multisubstituted 3,4-dihydronaphthalen-1(2H)-ones 163 in moderate to excellent yields in aqueous media. By changing reaction conditions, C–N bonds could also be constructed in some cases to give dihydro-2H-pyrrrole scaffold 167. The iminyl radical 164 is first generated from oxime 162 by photoinduced N–O bond cleavage. Subsequently, 1,5-HAT takes place from the iminyl radical center to generate alkyl radical 166. The resulting alkyl radical immediately undergoes intramolecular cyclization/single electron oxidation followed by hydrolysis to give ketone 163. In the
absence of water, an intramolecular C(sp\textsuperscript{3})–H amination process occurs to furnish product 167.

Almost at the same time, the same group described a novel strategy for selective functionalization of the C(sp\textsuperscript{3})–H bond to access diverse dihydronaphthalen-1(2H)-ones via 1,5-H transfer to iminyl radicals (Scheme 36).\textsuperscript{46} Mechanically, iminyl radical 171 is generated from 168 and 169 by radical addition to vinyl azides and subsequent release of N\textsubscript{2} in the presence of AgI and K\textsubscript{2}S\textsubscript{2}O\textsubscript{8}. The resulting radical 171 then participates in a series of transformation involving a 1,3-H shift to give the final product 170.

The β-amino alcohol is one class of privileged substrates in pharmaceuticals, agrochemicals and natural products. Recently, Nagib’s group described a 1,5-hydrogen transfer induced intramolecular C–H amination of alcohols to get β-amino alcohol products (Scheme 37).\textsuperscript{47} The substrate 173 serves as a traceless director to generate iminyl radical 175 under a combined event of NaI and PhI(OAc)\textsubscript{2}. Intermediate 175 undergoes 1,5-H shift/intramolecular cyclization/hydrolysis, accomplishing introduction of ammonia at the β carbon of alcohols.

### 3.3 HAT triggered by oxygen-centered radicals

Owing to the high BDE of the O–H bond, alkoxyl radicals readily activate inert C–H bonds by a selective intramolecular 1,\textit{n}-hydrogen atom transfer (1,\textit{n}-HAT). However, it is still difficult to produce alkoxyl radicals under mild conditions.

In 2014, Taniguchi and co-workers reported an iron-catalyzed aerobic hydration of simple alkenes that involves hydration of the olefin, intramolecular 1,5-hydrogen shift/alkyl radical oxygenation (Scheme 38).\textsuperscript{48} A wide range of 1,4-diols were obtained in moderate yields using cheap and green reagents at room temperature. In this reaction, the structural nature of alkenes has a significant influence on the yields. Notably, it was found that additional Me\textsubscript{2}S as an electron donor ligand was essential to suppress the competing byproduct monoalcohol.

Based on the radical HAT process, in 2016, the group of Chen reported the first selective C(sp\textsuperscript{3})–H allylation and alkenylation reactions enabled by photoredox conditions (Scheme 39a).\textsuperscript{49} The oxidant and reductant were not needed. It represents an elegant redox-neutral photocatalyzed alkoxyl radical application in organic synthesis. Later, the Meggers group also reported a photoredox-mediated asymmetric C(sp\textsuperscript{3})–H activation through 1,5-hydrogen transfer (Scheme 39b).\textsuperscript{50} In both works, photoredox generation of alkoxyl radical 193 and subsequent 1,5-HAT occur to deliver alkyl radical 194 (Scheme 39c).

### 4 Conclusion

In conclusion, we have witnessed a rapid development of sustainable long-distance radical migration induced C–C and
C–H bond functionalization. Its advent brings our chemical community a new platform to deal with the challenging radical transformation and elusive rearrangement reactions. To date, this strategy has drawn great enthusiasm of organic chemists, and strongly indicates a promising application in the construction of targeted molecules beyond the transition-metal-catalyzed C–C coupling technology. With the recent three years’ efforts, the remote radical migration strategy has become a powerful method for the synthesis of intricate scaffolds.

Some challenges need to be addressed in the near future:

(1) The exploitation of asymmetric HAT transformation for enantioselective remote C–H and C–C bond functionalization.

(2) The development of novel substrate types.

(3) The application of this strategy for late-stage functionalization of complex molecules.

### Abbreviations

- **AIBN**: Azodiisobutyronitrile
- **BDE**: Bond dissociation energy
- **dbbbpy**: 4,40-Di-tert-butyl-2,20-bipyridine
- **DME**: 1,2-Ethanediol dimethyl ether
- **DABCO**: 1,4-Diazabicyclo[2.2.2]octane
- **DCM**: Dichloromethane
- **DCE**: 1,2-Dichloroethane
- **EA**: Ethyl acetate
- **HAT**: Hydrogen atom transfer
- **HFIP**: 1,1,1,3,3,3-Hexafluoropropan-2-ol
- **HE**: Hantzsch ester
- **PIDA**: PhI(OAc)2
- **mCBA**: 3-Chlorobenzoate
- **SET**: Single electron transfer
- **TBHP**: tert-Butyl hydroperoxide
- **TEMPO**: 2,2,6,6-Tetramethylpiperidine-1-oxyl

### Conflicts of interest

There are no conflicts to declare.

### Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (21732003, 21702098, 21672099, 21472084 and 21372114).

### Notes and references