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# Recent advances in alkoxy radical-promoted C–C and C–H bond functionalization starting from free alcohols

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Direct functionalization of inert C(sp<sup>3</sup>)–C(sp<sup>3</sup>) and C(sp<sup>3</sup>)–H bonds represents one of the most valuable synthetic tactics, yet large obstacles remain in terms of reactivity and selectivity. Alkoxy radicals enable C–C bond scission via β-C elimination and C(sp<sup>3</sup>)–H bond cleavage through a hydrogen atom transfer (HAT) process, thus providing an efficient method to address these problems. In view of atom- and step-economy, the direct use of abundant alcohols as alkoxy radical precursors in radical transformations is of high synthetic value. This feature article summarizes our recent achievements in (a) C(sp<sup>3</sup>)–C(sp<sup>3</sup>) bond cleavage via ring-opening of cycloalkanols and (b) site-specific C(sp<sup>3</sup>)–H functionalization of unprotected aliphatic alcohols, along with the reconstruction of various new chemical bonds, e.g. C–halogen, C–C, C–N, C–S, and C–Se bonds.

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## 1. Introduction

Owing to the ubiquity of inert chemical bonds such as C–C and C–H bonds in nature, direct transformation of inert chemical

bonds into other valuable functional groups represents an ideal synthetic tactic with the upmost atom- and step-economy.<sup>1,2</sup> The past few decades have witnessed rapid ascent in this area, regardless of the large obstacles remaining in terms of reactivity and selectivity. Complementary to transition-metal catalysis that has made remarkable progress in C–C and C–H bond activation, controllable radical reactions have also proven to be a powerful toolkit showcasing the distinct potentials to regulate the reactivity as well as chemo/regio-selectivities.

The radical translocations enabled by reactive heteroatom-centered radicals such as *N*- and *O*-radicals have long been

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Scheme 1 Generation of alkoxy radicals.

exploited in organic chemistry, such as the Hofmann–Löffler–Freitag reaction<sup>3</sup> and Barton nitrite ester photolysis.<sup>4</sup> Apart from the applications in  $C(sp^3)$ –H activation *via* hydrogen atom abstraction, *O*-radicals also display a unique feature which induces  $\beta$ -C fragmentation to cleave  $C(sp^3)$ – $C(sp^3)$  bonds. Alkoxy radicals, devoid of stabilization by inductive or delocalization effects, are a class of highly active intermediates normally hard to rein. In addition, direct formation of alkoxy radicals from free alcohols is formidably challenging due to the strong bond dissociation energy (BDE,  $\sim 105 \text{ kcal mol}^{-1}$ )<sup>5</sup> and high oxidation potential of alcoholic O–H bonds. These factors impede the wide exploitation of alkoxy radicals in synthetic chemistry. Traditionally, alkoxy radicals could be circuitously obtained from the elaborated alcohol derivatives, *e.g.* nitrite esters,<sup>4</sup> lead(IV) alkoxides,<sup>6</sup> peroxides,<sup>7</sup> sulfonates,<sup>8</sup> hypohalites,<sup>9</sup> *N*-alkoxy-pyridine-2-thiones,<sup>10</sup> and *N*-alkoxyphthalimides (Scheme 1).<sup>11</sup> From the perspective of atom/step-economy and synthetic efficiency, in comparison, the alkoxy radical-mediated reactions starting from free alcohols are of higher value, and have received much attention recently.

Over the past few years, our group has been devoted to the formation of alkoxy radicals directly from free alcohols under mild conditions and the subsequent transformations. This feature article summarizes our recent achievements in (a)  $C(sp^3)$ – $C(sp^3)$  bond cleavage *via* ring-opening of cycloalkanols and (b) site-specific  $C(sp^3)$ –H functionalization of unprotected aliphatic alcohols, along with the reconstruction of various new chemical bonds, *e.g.* C–halogen, C–C, C–N, C–S, and C–Se bonds.

## 2. $C(sp^3)$ – $C(sp^3)$ bond cleavage *via* ring-opening functionalization of cycloalkanols

### a. Formation of C–halogen bonds

Despite a number of elegant synthetic methods toward  $C(sp^3)$ – $C(sp^3)$  bond cleavage, transition metal-mediated  $C(sp^3)$ – $C(sp^3)$  activation still encounters tremendous obstacles, attributed to

the fact that (a) the congested environment around the C–C  $\sigma$ -bond and the highly directed nature of the C–C  $\sigma$ -bond cause a poor interaction between the metal and the symmetric  $\sigma$ -orbital of  $C(sp^3)$ – $C(sp^3)$  bonds, and (b) the resultant alkylmetal species by metal insertion is apt to undergo a  $\beta$ -hydride elimination rather than formation of new chemical bonds.

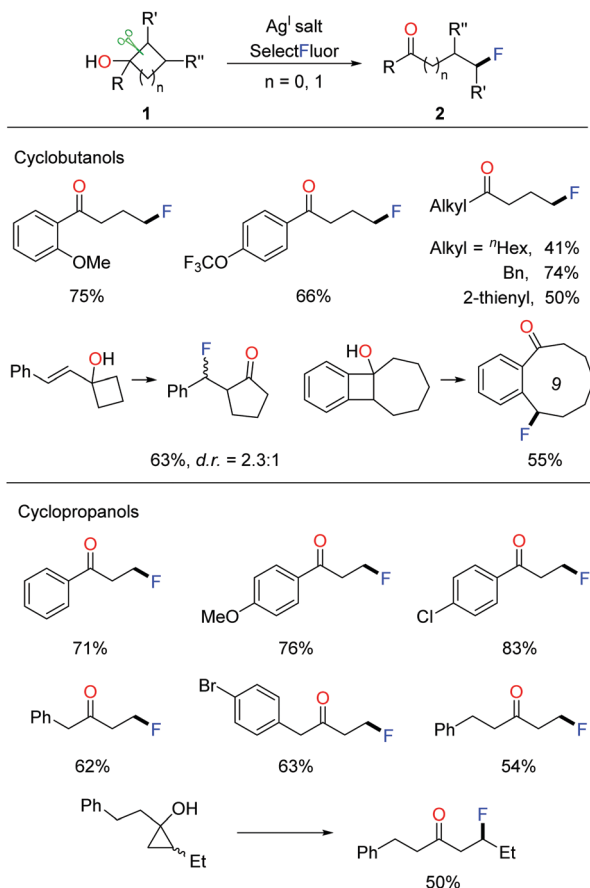
Relying on strain energy, cyclopropanols and cyclobutanols bearing small-sized rings are frequently employed as privileged precursors in radical-mediated ring opening to synthesize the distally substituted ketones. The *in situ* generated alkoxy radicals trigger  $\beta$ -C fragmentation, offering a complementary approach for  $C(sp^3)$ – $C(sp^3)$  bond cleavage to transition-metal catalysis.

Given that incorporating a fluorine atom into organic compounds remarkably improves the chemical, physical, and biological properties, the development of novel fluorination methods is crucial for multiple fields of pharmaceuticals, materials, and agrochemicals.<sup>12</sup> In 2015, we disclosed the silver-catalyzed ring-opening fluorination of cyclobutanols and cyclopropanols for the first time, affording a variety of  $\gamma$ - and  $\beta$ -fluorinated ketones respectively.<sup>13</sup> Selectfluor was used as the fluorinating agent and  $Ag^I$  salt was used as a catalyst. The investigation of substrate scope demonstrated that, regardless of electronic properties, either aryl or alkyl substituted cycloalkanols proceeded smoothly to give the corresponding products at room temperature (Scheme 2). Notably, the transformation of ring-fused benzocyclobutenols led to medium-sized cyclic fluoro-ketones, otherwise hard to make, through ring expansion.

A set of experiments were carried out to elucidate the mechanism. The results ruled out the pathways of electrophilic fluorination and silver-mediated reductive elimination, and supported the radical pathway. Accordingly, a plausible mechanism is depicted in Scheme 3.<sup>14</sup> Initially, coordination of cycloalkanol **1** with  $Ag^I$  salt affords the complex **a**, which is then converted to the  $F-Ag^{III}$  species **b** through the oxidation by Selectfluor. Homolysis of the intermediate **b** generates the cycloalkoxy radical **c** along with the  $F-Ag^{II}$  complex. The ring-opening of cycloalkoxy radical **c** gives rise to the ring-opened alkyl radical **d**, which interacts with the  $F-Ag^{II}$  species to furnish the fluorinated product **2** and to regenerate the  $Ag^I$  species.

Afterwards, radical mediated ring-opening fluorination of cycloalkanols was also reported by Murakami, Loh, and Lectka, respectively.<sup>15</sup>

Halogenated (Cl, Br, I) aliphatic ketones extensively serve as versatile building blocks in synthetic chemistry. However, the distally halogenated ketones are not easy to access *via* the direct halogenation at remote positions of alkyl ketones. Encouraged by the ring-opening fluorination, the silver-catalyzed protocol was further applied to the radical ring-opening chlorination.<sup>16</sup> The combination of  $AgNO_3$  and  $K_2S_2O_8$  exhibited a good catalytic efficiency. With the use of NCS (*N*-chlorosuccinimide) as the chlorinating reagent, a portfolio of distally chlorinated ketones were obtained from the corresponding cycloalkanols under mild conditions (Scheme 4). The substrate scope covered all the three-, four-, five-, six-, and seven-membered cycloalkanols. The reaction could be performed at a gram-scale, indicating the practicality of the method. In addition, a set of distally brominated ketones were



Scheme 2 Ring-opening fluorination of cycloalkanols.



Scheme 3 Proposed mechanism for ring-opening fluorination of cycloalkanols.

also afforded with the use of NBS (*N*-bromosuccinimide) in lieu of NCS.

The proposed mechanism is shown in Scheme 4. The generation of alkoxy radical **a** is probably from the single-electron oxidation of cycloalkanol by the  $\text{Ag}^I/\text{K}_2\text{S}_2\text{O}_8$  system (path a) or hydrogen atom abstraction of an O–H bond by the



Scheme 4 Ring-opening chlorination of cycloalkanols.

imidyl radical (path b). Ring opening of the cycloalkoxy radical **a** leads to alkyl radical **b**, which then interacts with NCS to afford the chlorinated ketone **3** and regenerate the imidyl radical (Scheme 5).

A similar approach to  $\gamma$ -chloroketones was also achieved by the manganese-catalyzed ring-opening of cyclobutanols (Scheme 6).<sup>17</sup> Inexpensive  $\text{MnCl}_2$  catalyst and nucleophilic chlorine source  $\text{TMSCl}$  were employed in lieu of Ag salt and NCS, affording comparable yields.

Analogous ring-opening chlorination of cyclobutanols mediated by  $\text{AgOTf}$  and  $t\text{BuOCl}$  was subsequently developed by Zhang and coworkers.<sup>18</sup>

The ring-opening functionalization of medium- and large-sized rings with low strain energy remains a formidable challenge. Recently, Knowles *et al.* disclosed the photocatalytic generation of alkoxy radicals *via* proton coupled electron transfer (PCET), and accomplished the ring opening of unstrained cycloalkanols under mild conditions.<sup>19</sup> We also applied the photocatalytic method to the ring-opening bromination of unstrained cycloalkanols (Scheme 7). Optimization of the reaction conditions revealed that by using NBS as the bromine source and PIDA (phenyliodine diacetate) as an additive the desired  $\delta$ -bromoketone was readily yielded from cyclopentanol under visible-light irradiation.<sup>20</sup>



Scheme 5 Proposed mechanism for ring-opening chlorination of cycloalkanols.



Scheme 6 The manganese-catalyzed ring-opening chlorination of cyclobutanols.

This protocol was suitable for the ring-opening bromination of less-strained five-, six-, seven-, twelve-, and fifteen-membered cycloalkanols. The brominated ketones could be easily transformed to other useful compounds, indicating the value of the protocol. Beyond these, the unprecedented ring-opening cyanation and alkynylation of large-sized cycloalkanols were also achieved under the photo-induced conditions.

According to the mechanistic studies including the Stern–Volmer experiments and cyclic voltammograms, a plausible mechanism is outlined in Scheme 8. The photo-induced generation of alkoxy radical **a** might go through two possible pathways, the photocatalytic PCET process (path a) and homolysis of the O–I bond of intermediate **c** derived from the interaction of PIDA and cycloalkanol (path b). Subsequent  $\beta$ -C fragmentation of intermediate **a** delivers the ring-opened alkyl radical **b**, which is captured by NBS to form the final product **4**.

### b. Formation of C–C bonds

Tetralone derivatives usually serve as versatile building blocks in synthetic chemistry. However, development of rapid and



Scheme 7 The photo-induced ring-opening functionalization of less-strained cycloalkanols.



Scheme 8 Plausible mechanism for the photo-induced ring-opening bromination of less-strained cycloalkanols.

efficient access to 1-tetralones still remains underexplored. In the absence of extra radical scavengers, the cascade ring-opening of cyclobutanols and intramolecular cyclization readily afforded 1-tetralones.<sup>21</sup> In the presence of  $\text{AgNO}_3$  and  $\text{K}_2\text{S}_2\text{O}_8$ , a portfolio of tetralones were obtained in synthetically useful yields at room temperature (rt) (Scheme 9, top). The DFT studies also verified the feasibility of the reaction. A plausible mechanism is postulated (Scheme 9, bottom). Single-electron oxidation of cyclobutanol with the  $\text{AgNO}_3/\text{K}_2\text{S}_2\text{O}_8$  system produces alkoxy radical **a** that then undergoes cyclic C–C bond cleavage to give alkyl radical **b**. Different from the previous works, the alkyl radical would intramolecularly add to the arene, affording the radical intermediate **c** which undergoes oxidation or hydrogen abstraction to furnish the tetralone product.





Scheme 12 Synthesis of unsymmetric 1,8-dicarbonyl compounds.

Chen *et al.* reported the reaction of cyclic and linear alkanols with cyclic iodine(III) reagent BI-OAc to furnish the alkynylated and olefinated products *via* photo-induced  $\beta$ -C scission.<sup>25</sup> The benziodoxole/alcohol complex derived from the interaction between alkanol and BI-OAc was oxidized by the  $\text{Ru}^{\text{III}}$  complex to provide alkoxy radicals that initiated the following transformation.

Zuo *et al.* disclosed a cerium-catalyzed cycloaddition of secondary cycloalkanols with electron-deficient alkenes through the synergistic cerium-mediated photocatalysis and photo-induced electron transfer catalysis, affording a variety of bridged-lactone products.<sup>26</sup> The cerium complex-mediated LMCT process proposed by the authors enabled the bond homolysis to generate an alkoxy radical that triggered the  $\beta$ -C scission and subsequent transformations. Additionally, continuous flow for scale-up synthesis of the polycyclic core of nepalactones was conducted, indicating the synthetic utility of the protocol.

Very recently, Knowles *et al.* reported a photocatalytic ring expansion of cycloalkanols enabled by the PCET process.<sup>27</sup> In the reaction, the alcoholic O-H bond was activated *via* the PCET process, leading to an alkoxy radical intermediate that undergoes subsequent  $\beta$ -C fragmentation to afford an alkyl radical. The following addition of the alkyl radical to the intramolecular alkene proceeded to afford valuable medium-sized cyclic ketones.

### c. Formation of C-N bonds

Owing to the importance of N-containing compounds and their extensive occurrence, the application of the ring-opening strategy to construct C-N bonds is of synthetic use. By means of manganese catalysis, the ring-opening azidation of cyclobutanols was achieved with the use of  $\text{TMSN}_3$  as a nitrogen source and hypervalent iodine reagent BI-OH as an oxidant (Scheme 13).<sup>28</sup> Despite electronic and steric effects, a range of structurally diverse cyclobutanols were readily converted to the corresponding  $\gamma$ -azido substituted ketones.



Scheme 13 The manganese-catalyzed ring-opening azidation of cycloalkanols.



Scheme 14 Proposed mechanism for the manganese-catalyzed ring-opening azidation of cycloalkanols.

As shown in Scheme 14, mechanistically, the interaction of  $\text{Mn}(\text{OAc})_3$ ,  $\text{TMSN}_3$ , and  $\text{BI-OH}$  gives rise to the high-valent  $\text{Mn}^{\text{V}}\text{-N}_3$  complex **a**. Incorporation of cyclobutanol **1** with the complex **a** generates complex **b** which then undergoes an SET process to furnish alkoxy radical **c** and the  $\text{Mn}^{\text{IV}}\text{-N}_3$  complex **e**. The transfer of azide from complex **e** to the ring-opened alkyl radical **d** affords the final product **9**.



Scheme 15 The manganese-catalyzed ring-opening hydrazination of cycloalkanols.

A similar strategy was further applied to the manganese-promoted ring-opening amination of cyclobutanols, in which DBAD (di-*tert*-butyl azodicarboxylate) was used as the aminating reagent (Scheme 15).<sup>29</sup> A variety of alkyl hydrazines were generated in useful yields and exclusive regioselectivity at rt. Regarding the catalytic cycle, alkoxy radical **a** is generated initially from the single electron oxidation of cyclobutanol **1** by Mn(OAc)<sub>3</sub> or the Mn<sup>V</sup> species *in situ* formed from the interaction of Mn(OAc)<sub>3</sub> with BI-OH. The radical intermediate **a** readily undergoes cyclic C–C bond cleavage to afford the alkyl radical **b** that then couples with DBAD to generate the N-centered radical intermediate **c**. Hydrogen abstraction of **c** from cyclobutanol affords the final product **10**, regenerates alkoxy radical **a**, and perpetuates the catalytic cycle.

Afterwards, Zuo *et al.* disclosed the cerium(III)-mediated photocatalytic hydrazination of less-strained cycloalkanols.<sup>30</sup> Mechanistic studies indicated that the cerium(III) chloride was assisted by a chloride anion, showing good absorption in the blue-light region and leading to more efficient photoexcitation and higher catalytic efficiency. Another function of the cerium(III) chloride complex is to coordinate with an O-atom, which promotes the β-C scission to give the ring-opened alkyl radicals.

#### d. The formation of C–S and C–Se bonds

To further exploit the practicability of the method, the formation of C(sp<sup>3</sup>)–S and C(sp<sup>3</sup>)–Se bonds *via* the manganese-catalyzed ring-opening of cyclobutanols was also disclosed (Scheme 16).<sup>31,32</sup> Commercially available reagents RS–SR (R = Ar, Me, Bn) and RSe–SeR (R = Ar, Bn) were used as the radical acceptors. The survey of the substrate scope demonstrated a good functional group tolerance; many susceptible groups such as alkynyl and alkenyl were compatible with the conditions. The protocol furnished a variety of γ-thiolated and selenylated ketones (**11** and **12**), paving a new avenue for the introduction of sulphides and selenides into organic compounds.



Scheme 16 The manganese-mediated ring-opening C(sp<sup>3</sup>)–S/C(sp<sup>3</sup>)–Se bond formation.

### 3. Remote C(sp<sup>3</sup>)–H functionalization *via* alkoxy radical-promoted HAT process

In the 1960s, the pioneering work on alkoxy radical-mediated HAT to achieve remote functionalization on an unreactive aliphatic site was reported by Barton and coworkers, namely the Barton nitrite ester reaction.<sup>4a</sup> Afterwards, numerous approaches were developed over the past half century for transformation of alcohols into suitable precursors to generate alkoxy radicals.<sup>4,6–11</sup> Recently, the C(sp<sup>3</sup>)–H bond allylation and alkenylation promoted by alkoxy radicals, which were generated from the preformed *N*-alkoxyphthalimides, were disclosed by Chen *et al.*<sup>33</sup> Soon after, Meggers *et al.* applied a similar strategy to the asymmetric alkylation of α,β-unsaturated *N*-acylpyrazoles.<sup>34</sup> It was found that, conventionally, the formation of alkoxy radicals mostly relied on the transformation of alcohols into various alkoxy radical precursors.<sup>35</sup> Hence, direct and efficient generation of alkoxy radicals from unmodified alcohols is in demand. Given the high BDEs and strong oxidation potential of alcoholic O–H bonds, the alkoxy radical-promoted HAT process involving free alcohols still remains challenging.

Stimulated by the previous works on radical-mediated remote functional group migration (FGM),<sup>23</sup> we disclosed tertiary-alcohol-directed remote C(sp<sup>3</sup>)–H heteroarylation *via* sequential HAT and distal heteroaryl migration (Scheme 17).<sup>36</sup> Unprotected alcohols **13** were directly employed as the alkoxy radical precursors under photocatalytic conditions. Concerning the importance and ubiquity of heteroaryls in pharmaceuticals, a series of heteroaryls, *e.g.* benzothiazolyl, thiazolyl, and pyridyl, were surveyed, which showcased the migratory aptitude in the C(sp<sup>3</sup>)–H heteroarylation. Both secondary and tertiary C(sp<sup>3</sup>)–H bonds were readily functionalized with unique regioselectivity. The reactivity of different C(sp<sup>3</sup>)–H bonds followed the order: 3° > 2° ~ benzylic > 1° C–H. Mechanistic studies suggested that the generation of alkoxy radicals might be facilitated by a PCET process, which initiated the cascade of HAT process and intramolecular heteroaryl migration.

The photocatalytic protocol was then applied to the tertiary-alcohol-directed cyanation of remote C(sp<sup>3</sup>)–H bonds. The reaction proceeded in a cascade of HAT and remote cyano migration, similarly to the above C–H heteroarylation pathway (Scheme 18).<sup>37</sup> A wide range of cyanohydrins **15** bearing various



Scheme 17 Free alcohol-directed heteroarylation of remote C(sp<sup>3</sup>)-H bonds.

functional groups were tolerated in the reaction. Mechanistic investigation such as the quantum yield ( $\phi = 4.7$ ) indicated that the overall reaction outcome might be the integration of the photocatalytic pathway and radical-chain reaction. The products **16** were further converted to many valuable compounds, *e.g.* amines, carboxylic acids, and heterocycles, manifesting the utility of alkyl nitriles.

Recently, a metal-free visible light-enabled intermolecular C(sp<sup>3</sup>)-H heteroarylation of aliphatic alcohols was disclosed (Scheme 19).<sup>38</sup> Heteroaryl was readily incorporated at the  $\delta$ -position of free alcohol with a good yield and an exclusive regioselectivity. Phenyliodine bis(trifluoroacetate) (PIFA) was used as the only reagent. This Minisci-type reaction featured mild conditions and broad substrate scope. All the primary, secondary, and tertiary alcohols were suitable substrates. A portfolio of heteroaryls, *e.g.* quinoline, isoquinoline, pyridine, phenanthridine, acridine, pyrazine, pyrimidine, quinoxaline, and 4-hydroxyquinazoline, were eligible acceptors for the alkyl



Scheme 18 Free alcohol-directed cyanation of remote C(sp<sup>3</sup>)-H bonds.

radicals generated from the 1,5-HAT process. Furthermore, this strategy could be applied to the late-stage modification of complex natural products and drugs.

A set of experiments were conducted to elucidate the mechanism. The NMR experiments verified that the interaction of PIFA and alcohol gave the dialkoxyiodo benzene intermediate **a** (Scheme 20). The radical-clock experiments supported the radical process. Homolysis of the intermediate **a** proceeds under visible-light irradiation, affording the alkoxy radical **b** that undergoes 1,5-HAT at the  $\delta$ -position of aliphatic alcohol to give the alkyl radical intermediate **c**. The addition of alkyl radical **c** to the protonated *N*-heteroaryl **d** gives rise to the radical cation **e**, which is oxidized by PIFA or *in situ* formed iodanyl radical to provide the final product **17**.

Afterwards, Chen and He *et al.* reported a photoredox-catalyzed C(sp<sup>3</sup>)-H heteroarylation of primary and secondary alcohols. In the reaction, Ru(bpy)<sub>3</sub>Cl<sub>2</sub> was employed as a photosensitizer and hypervalent iodine reagent PFBI-OH (perfluorinated hydroxybenziodoxole) was used as an oxidant.<sup>39</sup>

Zuo *et al.* reported a cerium salt-catalyzed  $\delta$ -hydrazination of primary alcohols under visible-light irradiation. The alkoxy radicals were generated from alcohols *via* the ligand-to-metal charge transfer (LMCT) process.<sup>40</sup> A variety of primary alcohols were efficiently functionalized with unique regioselectivity. Mechanistically, the coordination of Ce(IV) complex with alcohol excited by visible-light irradiation affords the alkoxy radical and Ce(III) complex through the homolysis of Ce(IV)-OR species. The alkyl radical generated from the alkoxy radical-mediated 1,5-HAT process is captured by DBAD to form a new C-N bond.

Jiao *et al.* disclosed a silver salt-catalyzed regioselective C(sp<sup>3</sup>)-H bond functionalization of primary and secondary alcohols.<sup>41</sup> AgNO<sub>3</sub> was used as a catalyst, and K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> was used as an oxidant. The well-designed oximonitrile-based sulfones

Scope of heteroaryls (reaction with *n*-pentanol)

Scope of alcohols (reaction with lepidine)

Scheme 19 Free alcohol-directed intermolecular heteroarylation of C(sp<sup>3</sup>)-H bonds.Scheme 20 Plausible mechanism for the alcohol-directed intermolecular heteroarylation of C(sp<sup>3</sup>)-H bonds.

functioned as the alkyl radical acceptors. A set of  $\delta$ -oximonitrile substituted alcohols were afforded at 50 °C in moderate yields.

In the reaction, an alkoxy radical was generated from the homolysis of nascent Ag<sup>II</sup>-O species.

## 4. Conclusion and outlook

Recent advances in alkoxy radical-mediated C(sp<sup>3</sup>)-C(sp<sup>3</sup>) and C(sp<sup>3</sup>)-H bond functionalization are summarized. Two parts of content are discussed: (1) C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bond cleavage *via* ring-opening functionalization of cycloalkanols, and (2) regio-selective C(sp<sup>3</sup>)-H functionalization of free alcohols. The alkoxy radicals are generated direct from the free alcohols under mild conditions, demonstrating atom- and step-economy and high synthetic efficiency. These protocols have opened new vistas for the functionalization of cyclic C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bonds and C(sp<sup>3</sup>)-H bonds.

Despite the great achievements over the past few years, there are still many challenges in this area. For example, asymmetric construction of new chemical bonds *via* the alkoxy radical mediated  $\beta$ -C fragmentation or HAT process is urgently desired. In addition, the radical-mediated ring-opening transformation based on non-strained rings is underexplored. Non-trivial synthetic strategies are needed to deal with the inherent poor reactivity. Furthermore, the combination of HAT and FGM opens a novel avenue for remote C(sp<sup>3</sup>)-H functionalization, which will attract continuous interest from the synthetic community. Future efforts are still anticipated on these aspects.

## Conflicts of interest

There are no conflicts to declare.

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