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Recent advances in direct α-C(sp^3)-H bond functionalization of thioethers

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ABSTRACT

Thioether skeletons are widely present in drugs, natural products, functional materials, and life science. In the past decade, the selective C–H functionalization of thioethers has been extensively studied to construct novel thioether derivatives. This mini-review systematically introduces the recent advances in the field of the direct α-C(sp^3)-H functionalization of thioethers.

1. Introduction

Thioethers are important structural units found in a variety of natural products, pharmaceutical drugs, and industrial materials [1–6]. In synthesis, they are notoriously used as potent transition-metal ligands and organocatalysts [7–9]. Naturally, substantial efforts have been devoted to the development of effective methodologies to prepare these compounds [10–13]. Within this research field, the directing group assisted direct C–H bond functionalization stands out as one of the most efficient and economical approaches for the construction and derivatization of thioethers. In this strategy, directing groups can enhance the efficiency and selectivity of the C–H bond functionalization reaction [14–23]. It should be noted that thioethers themselves can act as traceless directing groups in various transition-metal-catalyzed remote C–H functionalization reactions through the coordination of the internal sulfur atom to different transition metals [24–28].

Although directing group strategy provides an important protocol to construct thioether derivatives, the functionalization of C–H bonds is usually away from the thioether skeletons. In this point, the direct α-C(sp^3)-H bond functionalization of thioethers is recognized as a powerful strategy to construct novel thioether derivatives. However, it is also a challenging issue probably due to their strong transition-metal-coordination and facile oxidation ability [29–32].

The previous reviews on thioethers mainly focused on the C–S bond activation [33–37] and sulfur directed α-C-H functionalization [27,28]. In comparison, the reviews on the direct α-C(sp^3)-H functionalization are rarely. Only one example has been reported by the Phillips group in 2018 and their review mainly described the development of transition metal-catalyzed/mediated cross-dehydrogenative coupling of ethers and thioethers in the presence of peroxides [38].

In this mini-review, we will systematically introduce and discuss the significant progress made in the field of direct α-C(sp^3)-H functionalization of thioethers within the last decade, mainly including the special oxidant-, photo- and electro-mediated α-C(sp^3)-H functionalization. Furthermore, we will also provide a summarization of the recent progress in the catalytic strategy for α-C(sp^3)-H addition of thioethers with alkenes (Fig. 1).

1.1. Special oxidant-mediated α-C(sp^3)-H functionalization

The α-C(sp^3)-H bonds of thioethers are generally regarded as unreactive components, hence, selective activation of these bonds is not an easy task. Moreover, the easy oxidation and strong coordination ability of thioethers are also highly challenging to active these C–H bonds. Therefore, most of these unreactive α-C(sp^3)-H bonds can only be activated under special oxidizing conditions. The combinations of peroxides and transition metals have been firstly performed to achieve this process. In 2013, the Wu group reported a direct C-2 alkylation of quinoline *N*-oxides with cyclic thioethers and ethers *via* a Pd-catalyzed dehydrogenative cross-coupling in the presence of *tert*-butyl hydroperoxide (TBHP), tetrabutylammonium bromide (TBAB) and water (Scheme 1a and b) [39].

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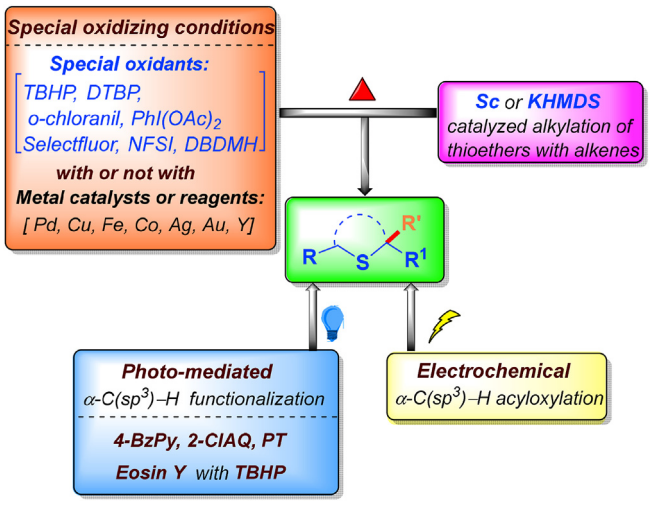
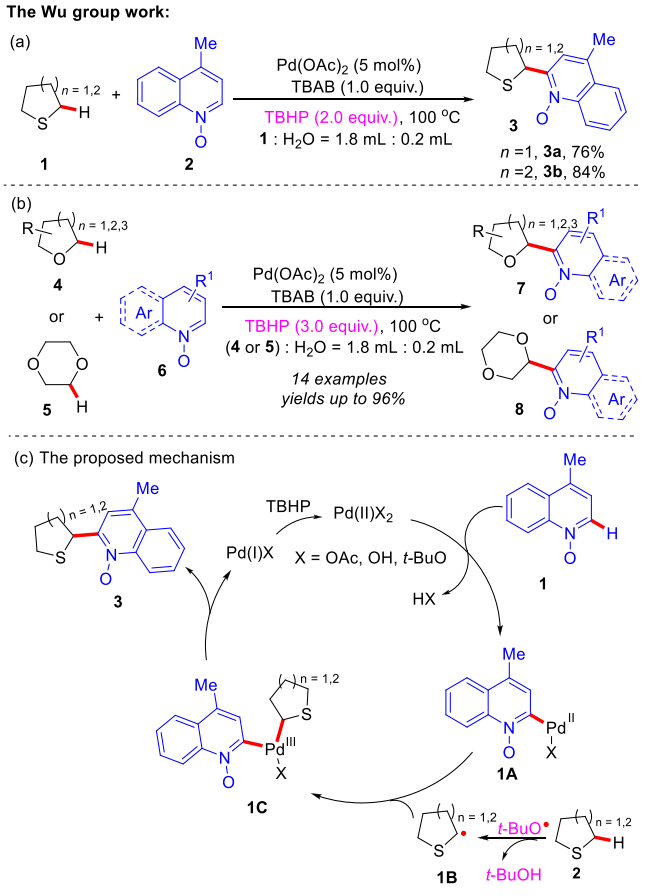


Fig. 1. Direct α-C(sp^3)-H bond functionalization of thioethers.



Scheme 1. Palladium-catalyzed dehydrogenative cross-coupling reaction of quinoline *N*-oxides with cyclic thioethers and ethers in the presence of TBHP.

In this reaction, the desired quinoline-containing heterocyclic compounds were isolated in good yields. The reactions between TBHP and cyclic ethers afforded the key radical intermediates. A plausible reaction pathway is proposed in Scheme 1c. First, C–H metallation of 4-methylquinoline *N*-oxide **1** with Pd(II) catalyst provides the Pd(II) species **1A**. Meanwhile, a SET between TBHP and the cyclic thioether **2** generates the radical **1B**. Next, the reaction of Pd(II) species **1A** with radical **1B** affords the Pd(III) species **1C**. The desired product **3** is formed through a reductive elimination process and Pd(I) species. Finally, the reoxidation of Pd(I) species provides the Pd(II) catalyst again for the next catalytic cycle.

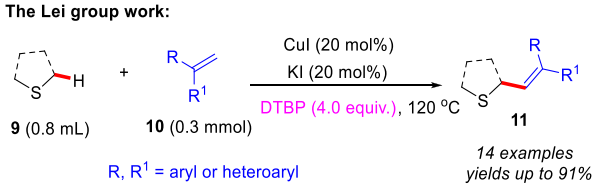
Recently, cheaper transition metal catalysts, including copper, iron and cobalt, have had a wide range of involvement in organic synthesis. When effective, these metals employment is considered more efficient compared to their precious metal counterparts due to environmental and economical factors [40–42]. In 2015, Lei and co-workers demonstrated the first example of Cu-catalyzed oxidative C(sp^3)-H alkenylation of thioethers to prepare allylic thioethers in the presence of DTBP (Scheme 2) [43]. In this novel work, a variety of 1,1-disubstituted alkenes were coupled to thioethers, providing allylic thioethers in moderate to good yields. It should be noted that linear thioethers were also shown to be effective coupling partners.

In the same year, the Liu group developed a copper-catalyzed oxidative Povarov reaction involving cyclic thioethers or ethers and *N,N*-dimethyl arylamines in the presence of TBHP through α-C(sp^3)-H functionalization (Scheme 3a and b) [44]. In addition, the proposed mechanism is also depicted in Scheme 3c.

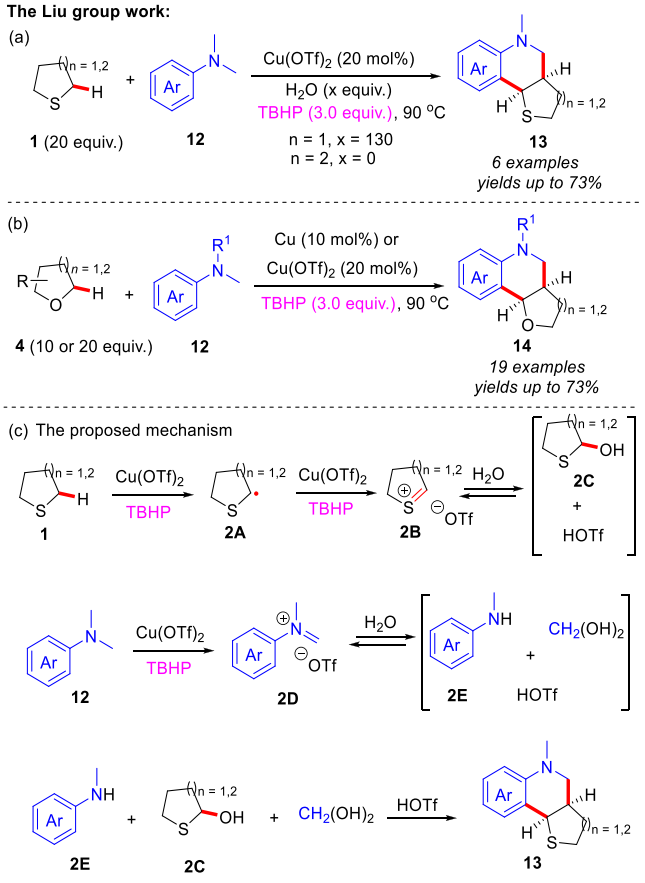
Initially, cyclic thioether **1** is oxidized by $Cu(OTf)_2$/TBHP to form the radical **2A**. The subsequent SET reaction followed by a hydrolysis process generates lactol **2C** and HOTf. Meanwhile, tertiary amine **12** is also oxidized by the same mixture *via* two SET processes, providing the iminium **2D**. The hydrolysis of the iminium **2D** affords the intermediate **2E**, $CH_2(OH)_2$ and HOTf. Finally, the condensation of intermediate **2C**, **2E** and $CH_2(OH)_2$ in the presence of HOTf produces the desired product **13**. The detailed mechanistic studies show that a $Cu(OTf)_2$-TBHP mixture can oxidize tertiary amines and ethers *via* SET processes to produce the key iminium species and ether radicals, respectively. Notably, unlike conventional Povarov reaction, this [4 + 2]-cycloaddition process did not involve [4π]- and [2π]-motifs.

In 2008, Li and co-workers reported an iron-catalyzed cross-dehydrogenative coupling of tetrahydrothiophene with 1,3-dicarbonyl compounds in the presence of DTBP (Scheme 4a) [45]. The results indicated that $Fe_2(CO)_9$ was an effective catalyst, which could selectively activate C–H bonds adjacent to heteroatoms for subsequent C–C bond formation. Next, a novel Fe-catalyzed difunctionalization of alkene was also developed by the Li group [46]. In the presence of $FeCl_3$, DBU and TBHP, the reaction of thiane **1b** and *N*-phenylmethacrylamide **17** gave the corresponding oxindoles in 52% isolated yield (Scheme 4b). A detailed reaction mechanism is represented in Scheme 4c. The initial SET process between TBHP and the Fe^{2+} species provides a *tert*-butoxy radical and the Fe^{3+}(OH) species. Next, the radical intermediate **3A** is formed through the α-C(sp^3)-H functionalization of thiane **1b** in the presence of the *tert*-butoxy radical. The subsequent addition of radical intermediate **3A** to the C=C bond of *N*-phenylmethacrylamide **17** produces the radical intermediate **3B**, which can be further converted into the radical intermediate **3C** *via* intramolecular cyclization. Finally, the desired oxindole is formed through the hydrogen abstraction of radical intermediate **3C** in the presence of Fe^{3+}(OH).

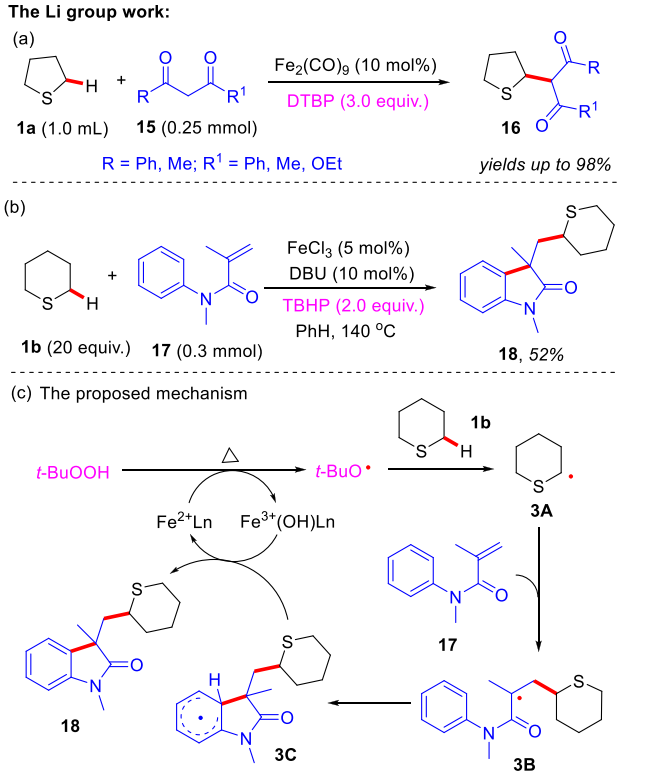
In 2017, the Lu and Li group reported a cobalt-catalyzed cross-dehydrogenative coupling reaction of aromatic carboxamide and thioethers with the assistance of a removable *N,N*-bidentate directing group (pyridin-2-yl-isopropylamine) (Scheme 5a) [47]. This process provided various important *o*-alkylated aromatic carboxamides in moderate to



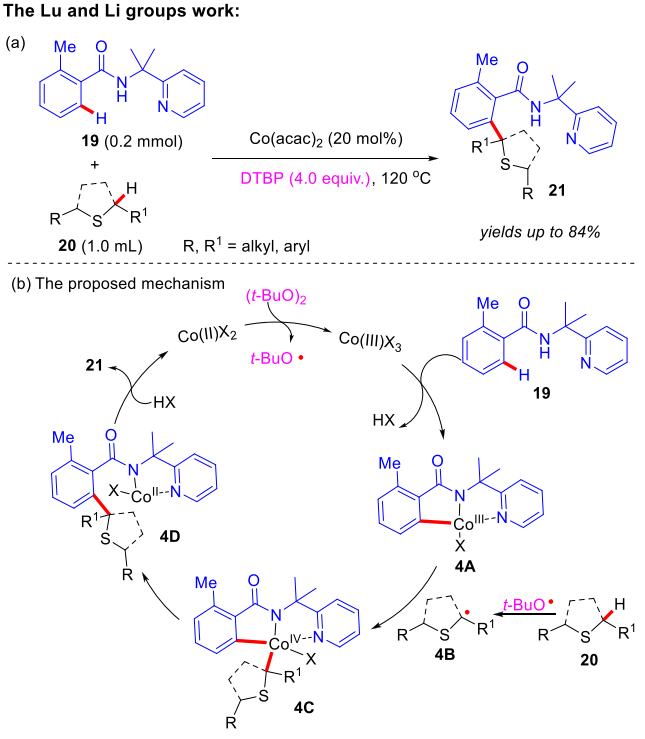
Scheme 2. Cu-catalyzed oxidative C(sp^3)-H alkenylation of thioethers to prepare allylic thioethers in the presence of DTBP.



Scheme 3. Cu-catalyzed oxidative Povarov reactions between cyclic thioethers or ethers and *N,N*-dimethylarylamines in the presence of TBHP.



Scheme 4. Iron-catalyzed cross-dehydrogenative coupling and difunctionalization reaction.

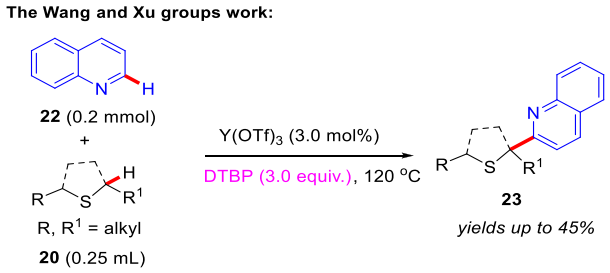


Scheme 5. Cobalt-catalyzed cross-dehydrogenative coupling reaction between unactivated C(sp^2)-H bonds of arenes and C(sp^3)-H bonds of thioethers.

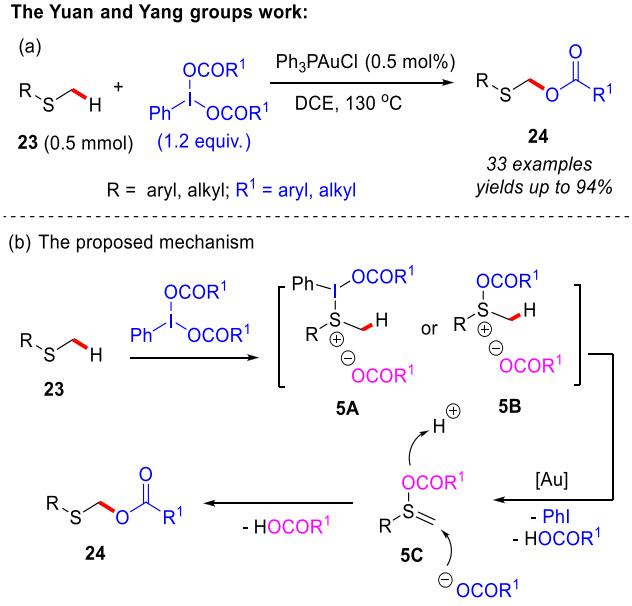
good yields. A plausible mechanism for this transformation is proposed (Scheme 5b). The initial intermolecular single electron transfer (SET) process between the Co(II) catalyst and DTBP provides a *tert*-butoxy radical and generates the Co(III) species. The subsequent coordination of the aromatic carboxamide **19** to the Co(III) species followed by a ligand exchange and C(sp^2)-H cleavage process produces the intermediate **4A**. At the same time, the *tert*-butoxy radical abstracts a hydrogen atom from the thioether **20** to form the alkyl radical **4B**. Then, oxidative addition of the intermediate **4A** with the alkyl radical **4B** yields the Co(IV) complexe **4C**. Eventually, reductive elimination of this Co(IV) complexe **4C** followed by a ligand dissociation process affords the final product.

Recently, Wang and co-workers developed a $Y(OTf)_3$-catalyzed cross-dehydrogenative coupling reaction of thioethers with quinoline in the presence of DTBP (Scheme 6) [48]. This strategy is characterized by simplicity in operation and high atom-economy, albeit while providing moderate yields. In addition to peroxides, other oxidants can also enable α-C-H functionalization of thioethers.

The Pummerer reaction is an elegant synthetic approach to functionalizing α-C-H bonds adjacent to sulfur atoms [49–51]. It's different from the above free radical mechanism, classical Pummerer process usually involves a sulfonium intermediate, sulfoxide substrate and harsh acidic condition. It's worth noting that the direct C(sp^3)-H bond of thioethers can also be achieved through sulfonium intermediates. In 2016, the Yuan and Yang groups reported an Au-catalyzed direct C(sp^3)-H bond acyloxylation of methyl sulfides incorporating hypervalent iodine(III) reagents (Scheme 7) [52]. In this reaction, various α-thioaryl and α-thioalkyl ester derivatives were isolated in good yields. Notably, bis(acyloxy)iodobenzenes were used as special oxidants to activate the sulfur center and proceed this α-C(sp^3)-H functionalization, which involves a sulfonium salt and sulfonyl acetate intermediates. In addition, a possible reaction pathway is proposed (Scheme 7b). Initially, thioether **23** is oxidized by hypervalent iodine to generate the sulfonium salt **5A** or **5B**. Next, the intermediate **5C** is formed through the elimination of sulfonium



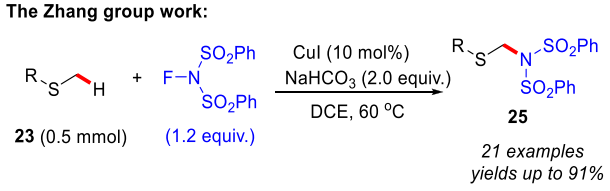
Scheme 6. $Y(OTf)_3$-catalyzed cross-dehydrogenative coupling reaction of thioethers with azaarenes in the presence of DTBP.



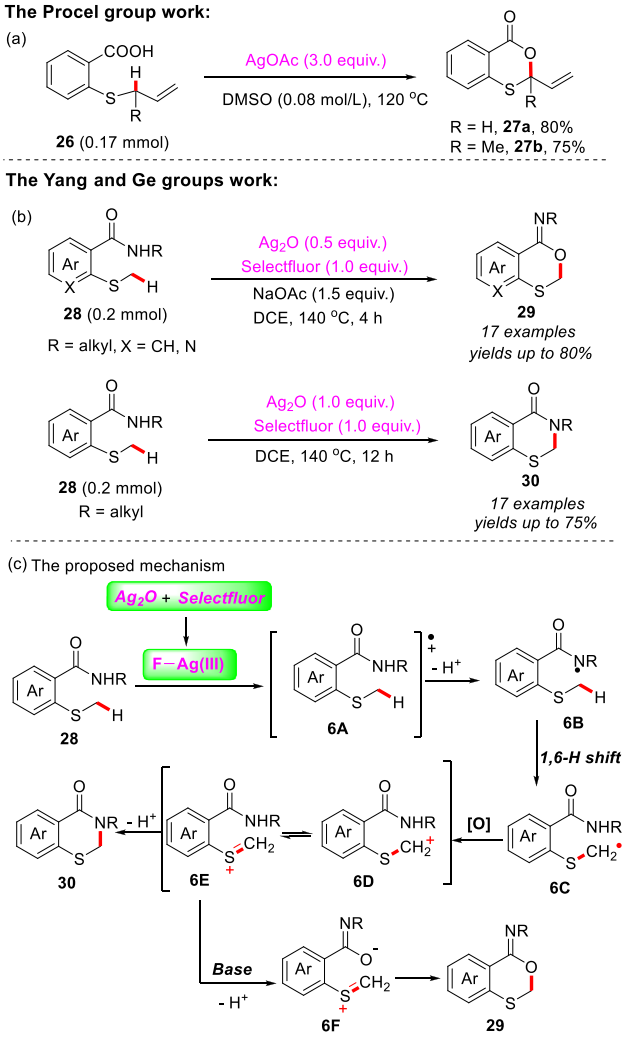
Scheme 7. Au-catalyzed direct C(sp^3)-H bond acyloxylation of methyl sulfides by using hypervalent iodine(III) reagents.

salt in the presence of a gold catalyst. Finally, a nucleophile reaction to the resulting intermediate **5C** with acid affords the desired product **24**. Very recently, the Zhang group also reported a CuI-catalyzed direct C(sp^3)-H imidation of methyl sulfides with *N*-fluorobenzenesulfonimide (NFSI) (Scheme 8) [53]. Without the use of any copper ligands, various aromatic and aliphatic methyl sulfides were converted into the corresponding products in good to excellent yields.

In 2016, the Porcel group reported a AgOAc-mediated C–H bond functionalization of alkenoic acids (Scheme 9a) [54]. In this protocol, the oxidative cyclization of alkenoic acids provided the desired products in good yields, and the oxidation of the C–H bond at the allylic position was promoted by AgOAc. Moreover, the control experiments ruled out the possibility of radical intermediacy in this process. Subsequently, the Yang and Ge group demonstrated a Ag_2O/Selectfluor-promoted α-C(sp^3)-H bond functionalization of unactivated methylthio groups (Scheme 9b)



Scheme 8. CuI-catalyzed direct C(sp^3)-H imidation of methyl sulfides with *N*-fluorobenzenesulfonimide.



Scheme 9. Silver-mediated C–H bond functionalization of the unactivated methylthio groups in the presence of Selectfluor.

[55]. Various kinds of sulfur-based heterocycles including benzooxathiin-4-imines, benzooxathiin-4-ones and benzothiazin-4-ones, were isolated in moderate to good yields *via* this transformation. It should be noted that this was the first report leading to the construction of the novel benzooxathiin-4-imine skeletons.

A plausible reaction mechanism is depicted in Scheme 9c. In the first step, the F–Ag(III) species are formed through the oxidation of Ag_2O by Selectfluor. Next, a single electron oxidation process takes place between the F–Ag(III) species and 2-methylthiobenzamide **28** producing the radical cation **6A**. The subsequent deprotonation of the radical cation **6A** gives rise to the corresponding amidyl radical **6B**, which can be further transformed into the radical **6C** through a 1,6-H radical shift. Then, the carbocation **6D** and its resonance **6E** are generated *via* the oxidation of the radical **6C**. Afterwards, the desired benzothiazin-4-one **30** is obtained through a sequential intramolecular cyclization and deprotonation process. In the presence of a base, intermediate **6E** can be converted into the intermediate **6F** which can produce benzooxathiin-4-imine **29** through an intramolecular cyclization step. Additionally, the imine group on benzooxathiin-4-imine was easily removed to yield 4*H*-benzooxathiin-4-one under acidic conditions.

In addition to the transition metal-catalyzed/mediated direct α-C(sp^3)-H functionalization of thioethers, metal-free examples have also been developed. In 2008, the Li group disclosed an *o*-chloranil-mediated C–H bond functionalization of alkyl thioethers utilizing 3-dicarbonyl

compounds (Scheme 10a) [56]. This novel Pummerer-type reaction provides a simple and efficient approach to constructing different sulfide derivatives. Recently, the Shi group demonstrated a tetra-*n*-butyl ammonium bromide (TBAB) promoted C(sp^3)-H bond acyloxylation of alkyl thioethers in the presence of hypervalent iodine(III) reagents (Scheme 10b) [57]. In this process, bis(acyloxy)iodobenzenes were used both as oxidants and reagents. The interaction of hypervalent bis(acyloxy)iodobenzenes with TBAB allows the formation of tetra-*n*-butylammonium bis(acyloxy) bromate as an important intermediate. It was also found that excess of TBAB was essential to avoiding other competing oxidation reactions.

After that, the Xu group also reported a direct NFSI-mediated C(sp^3)-H bond imidation of thioanisoles (Scheme 10c) [58]. In this reaction, NFSI was recognized as an oxidant and nitrogen source. Although this process provided moderate yields, it exhibited some advantages including metal-free, excellent functionality tolerance, high step-economy and specific regioselectivity. Finally, the control experiments indicate that thionium ion intermediates and a Pummerer-type reaction are involved in this imidation reaction.

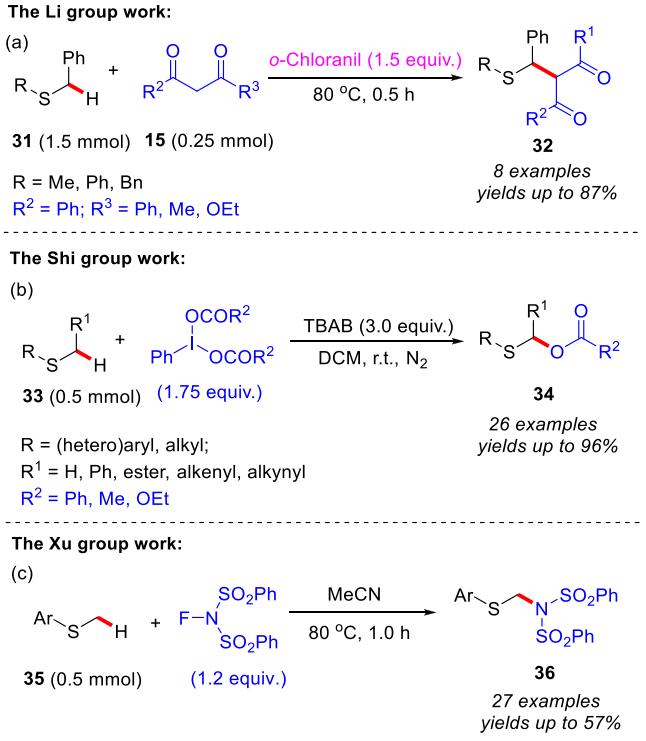
Very recently, Sun and co-workers demonstrated a 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) promoted methyl C(sp^3)-H bond azolation of thioanisoles (Scheme 11) [59]. A variety of nitrogen-functionalized thioanisoles were prepared in moderate to good yields by using benzimidazoles, 5-aryl-1*H*-tetrazoles and benzotriazoles as nitrogen nucleophiles. Unlike the previous Pummerer mechanism, a radical pathway is proposed to explain this process.

In 2019, the Yang group developed Selectfluor-promoted α-C(sp^3)-H functionalization of 2-alkylthiobenzoic acids, preparing various 1,3-benzooxathiin-4-one derivatives as a result (Scheme 12a) [60]. Control experiments demonstrate that a radical pathway may be involved in this Selectfluor-promoted process. A plausible pathway is depicted in Scheme 12b. Initially, 2-methylthiobenzoic acid **41** is oxidized by Selectfluor to generate the carbon-centred radical **7A** which undergoes subsequent re-oxidation to afford the corresponding carbocation **7B** and its resonance **7C**. The final product **42** is eventually formed through intramolecular cyclization and sequential deprotonation of intermediate **7C**.

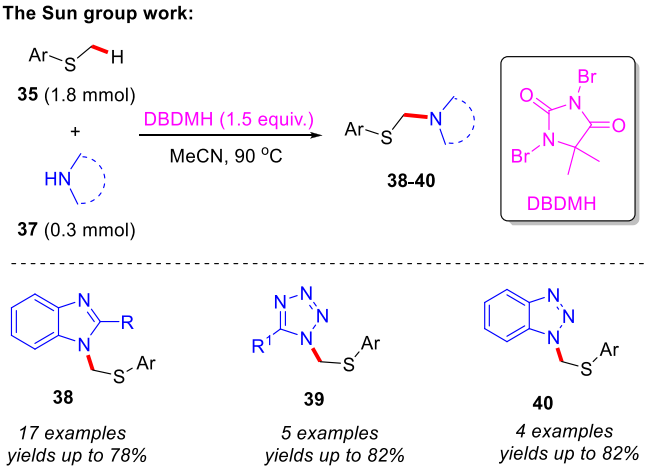
Very recently, the same group also reported an amide-directed acyloxyation of unactivated C(sp^3)-H bond of 2-alkylthiobenzamide in the presence of Selectfluor by using carboxylic acid and its corresponding salt as the acyloxy sources (Scheme 13a) [61]. Control experiments indicate the *ortho*-amide group is an indispensable directing group and amide hydrogen is also very crucial in this reaction. Further mechanism explorations demonstrate that a cyclic sulfonium salt may be involved in this process. In addition, a plausible reaction pathway is also shown in Scheme 13b. Initially, transient fluorosulfonium **8A** is formed in the presence of Selectfluor. Subsequently, the cyclic sulfonium salt **8C** can be generated by the direct cyclization of the salt **8A** or the dehydration of the sulfoxide intermediate **8B**. Next, the cyclic sulfonium salt **8C** is further transformed into the corresponding sulfonium intermediate **8D** and its resonance **8E** in the presence of NaOAc and HOAc. Finally, the combination between the sulfonium salt **8E** and the OAc anion provides the desired product **44a**. In order to illustrate the synthetic utility of this new method, a gram-scale synthesis of the anti-HIV drug **NS1040** was carried out in Scheme 13c. The target product **NS1040** was isolated with 85% yield through group-assisted purification (GAP) technology, without involving the chromatographic method.

1.2. Photo-mediated α-C(sp^3)-H functionalization

In the last decade, photo-mediated C–H functionalization has been regarded as an important green synthetic approach [62–65]. Although substantial efforts have been reported, only a few photochemistry works focused on the α-C(sp^3)-H functionalization of thioethers. In 2016, Kamijo and co-workers developed a photo-induced and 4-benzoylpyridine catalyzed non-acidic C(sp^3)-H bond functionalization strategy to incorporate an aldoxime functional group into an sp^3 carbon of thioether (Scheme 14a) [66]. In this reaction, 4-benzoylpyridine (4-BzPy) was used



Scheme 10. Metal-free direct C(sp^3)-H bond functionalization of thioethers.

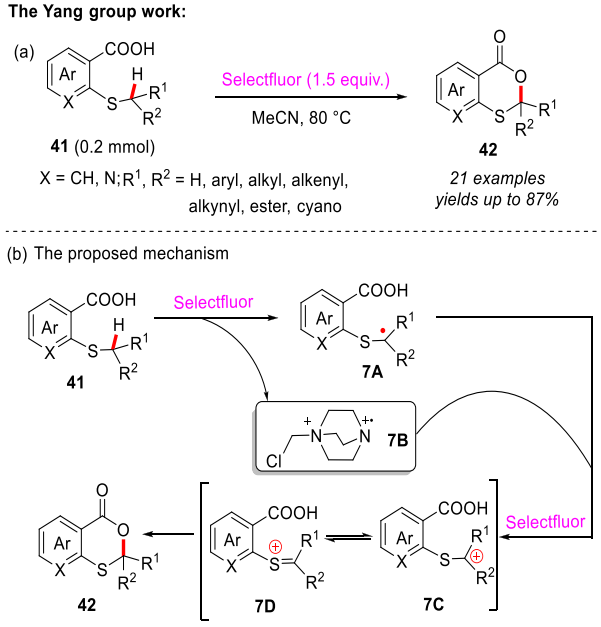


Scheme 11. DBDMH-promoted methyl C(sp^3)-H bond azolation of thioanisoles.

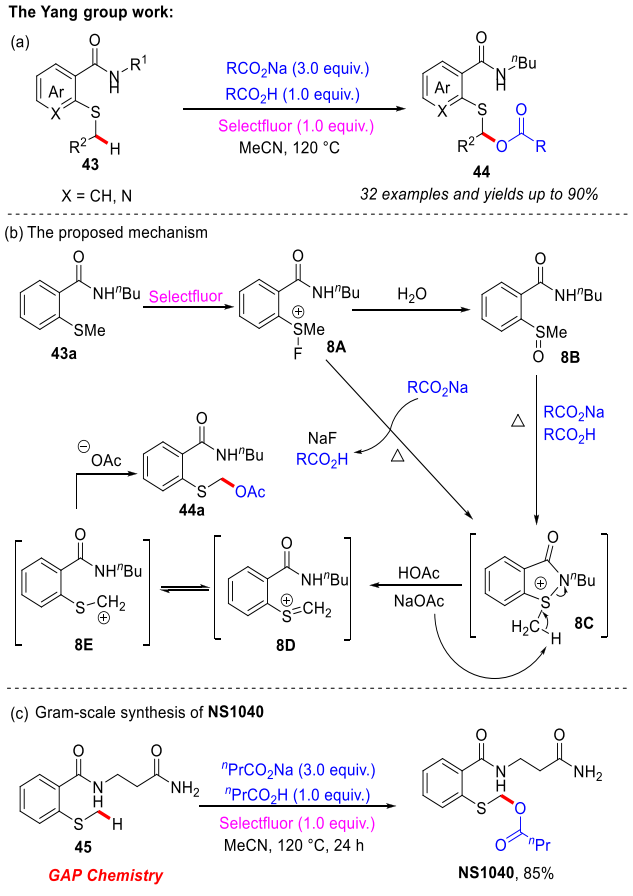
as a C–H bond activating agent, and arylsulfonyl oxime was employed as an aldoxime agent.

Furthermore, the authors proposed a plausible reaction pathway (Scheme 14b). This reaction begins with hydrogen abstraction of thioether **46** by photoexcited 4-benzoylpyridine, providing the corresponding carbon radical intermediate **9A** and radical intermediate **9B**. The subsequent addition of the radical intermediate **9A** to the sulfonyl oxime furnishes the aminyl radical intermediate **9C**. Finally, the elimination of the sulfonyl radical from the intermediate **9C** generates the aldoxime, as the leaving sulfonyl radical accepts a hydrogen atom from intermediate **9B** to regenerate the 4-benzoylpyridine catalyst.

Later, the same group also demonstrated an alkylation reaction of a nonacidic C(sp^3)-H bond of thioether through a photo-induced, 2-chloroanthraquinone (2-ClAQ)-catalzyed Michael-type radical addition reaction (Scheme 15a) [67]. Meanwhile, they also found that 5,7,12,



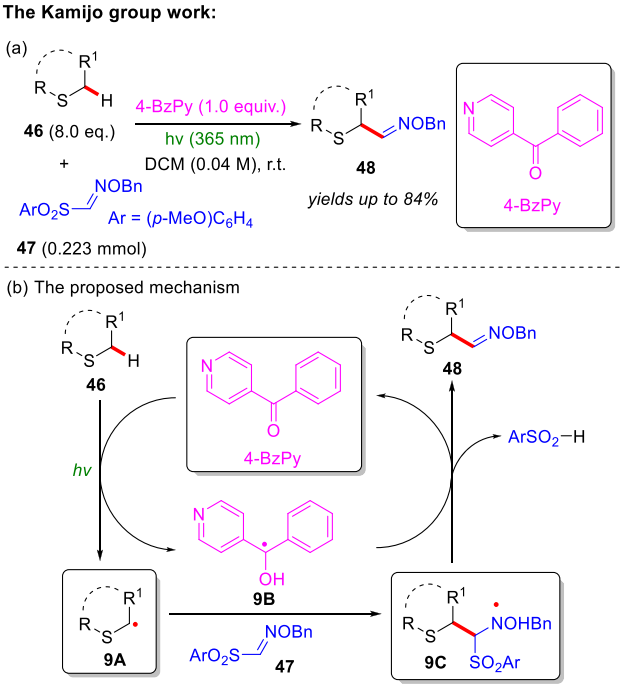
Scheme 12. Selectfluor-promoted α-C(sp^3)-H functionalization of 2-alkylthiobenzoic acids.



Scheme 13. Amide-directed acyloxyation of unactivated C(sp^3)-H bond of 2-alkylthiobenzamide in the presence of Selectfluor.

14-pentacenetetrone (PT) could be used as a visible light catalyst to achieve the allylation of C(sp^3)-H bond of thioether (Scheme 15b) [68].

Next, the Wang and Miao groups demonstrated a visible-light induced



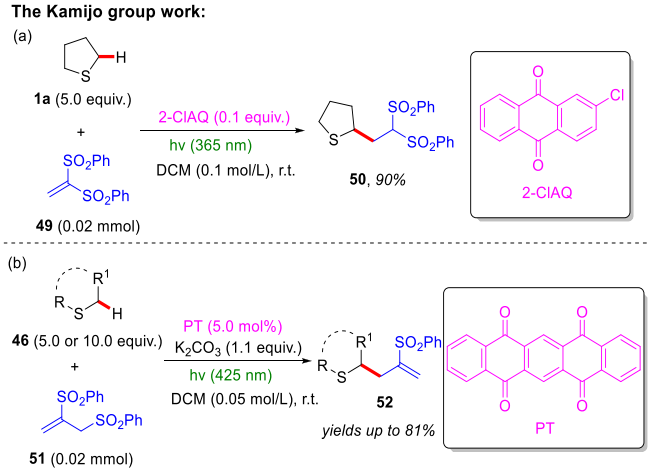
Scheme 14. Photo-mediated and 4-benzoylpyridine catalyzed non-acidic C(sp^3)-H bond functionalization strategy.

difunctionalization reaction of alkenes and thioethers (Scheme 16a) [69]. In this strategy, Eosin Y was used as a redox catalyst and photosensitizer and TBHP was used as a radical initiator. The desired alkylated oxindole was isolated in a 61% yield at room temperature. A proposed mechanism is reported (Scheme 16b): the initial blue LED irradiation of the Eosin Y catalyst provides the excited-state Eosin Y*. The subsequent SET reaction between Eosin Y* and TBHP affords a *tert*-butoxy radical and Eosin $Y^{\bullet+}$. Next, the *tert*-butyloxy radical abstracts a hydrogen atom from thiane **1a** to produce the radical intermediate **10A**, which is converted to the radical intermediate **10B** through the addition of radical **A** to the C=C bond of *N*-phenylmethacrylamide **17**. Subsequently, the radical intermediate **10B** undergoes intermolecular cyclization to generate the radical intermediate **C** which is further oxidized by Eosin $Y^{\bullet+}$ to produce the cationic intermediate **10D**. Finally, the desired alkylated oxindole **53** is formed through an aromatization process.

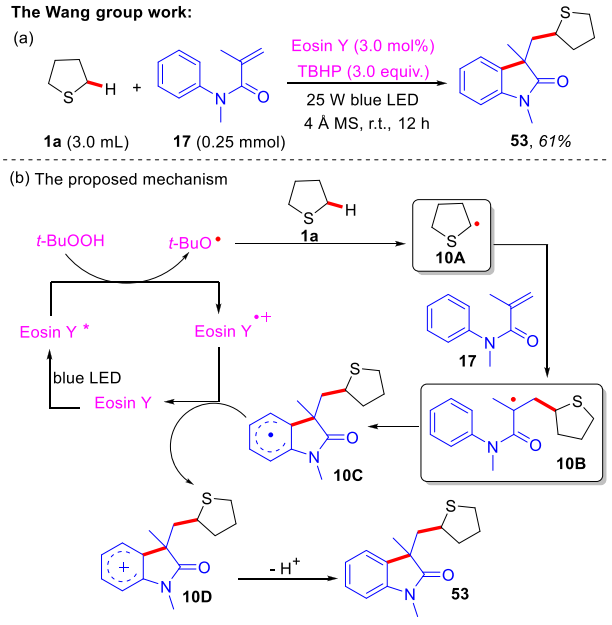
1.3. *Electro-mediated α-C(sp^3)–H functionalization*

Very recently, electrochemistry has become a powerful synthetic tool in C–H functionalization and has attracted great interest from both the scientific and engineering viewpoints due to its inherent advantages, including environmental benefits, ease of scalability, the use of cheap and/or recyclable electrodes, and the use of electricity as the traceless redox agent [70–77].

In 2021, the Lei group reported a regioselective scalable electrochemical α-C(sp^3)-H acyloxylation of sulfides (Scheme 17a) [78]. In this process, electricity, as a good alternative to chemical oxidants, was used to drive the C–H/Nu-H coupling reaction with hydrogen evolution. In addition to acyloxylation, this electrochemical method could also be used to achieve etherification and azolation reactions. Furthermore, a variety of control experiments indicate that the substrate self-assembly process is promoted by the addition of MeOH. The mechanism of this transformation is proposed in Scheme 17b. The initial self-assembly reaction of sulfide **33**, acid **54** and MeOH generates the species **11A**. Facilitated by the hydrogen bonding between the sulfur atom and the acid, a single-electron transfer process between the species **11A** and the anode produces the sulfur radical cation **11B**. Next, **11C** is formed through a



Scheme 15. Photo-mediated alkylation and allylation of nonacidic C(sp^3)-H bond of thioethers.



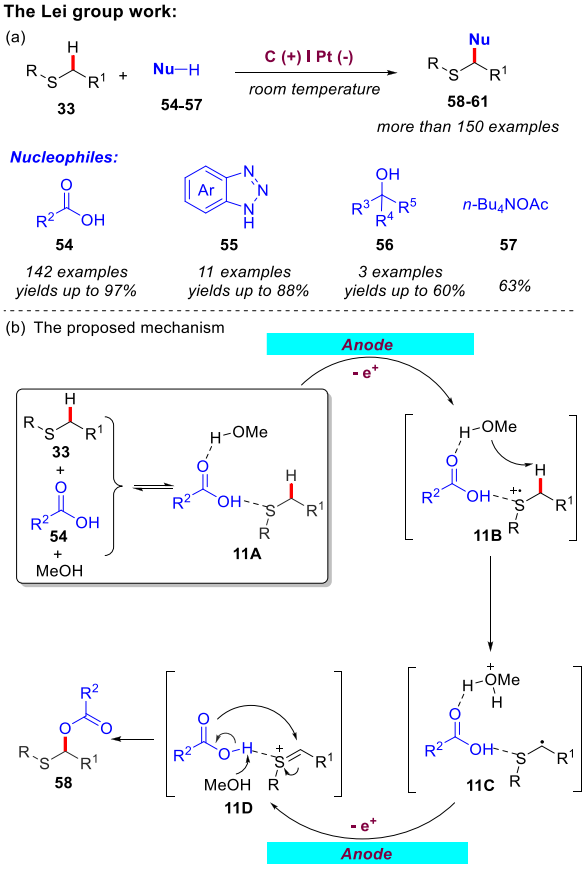
Scheme 16. Visible-light mediated difunctionalization reactions of alkenes and thioethers.

regioselective intramolecular proton-abstraction process. Subsequently, the thionium ion **11D** is formed through the loss of a proton and an electron from species **11C**. The nucleophilic addition generates the final product **58** alongside hydrogen evolution at the cathode.

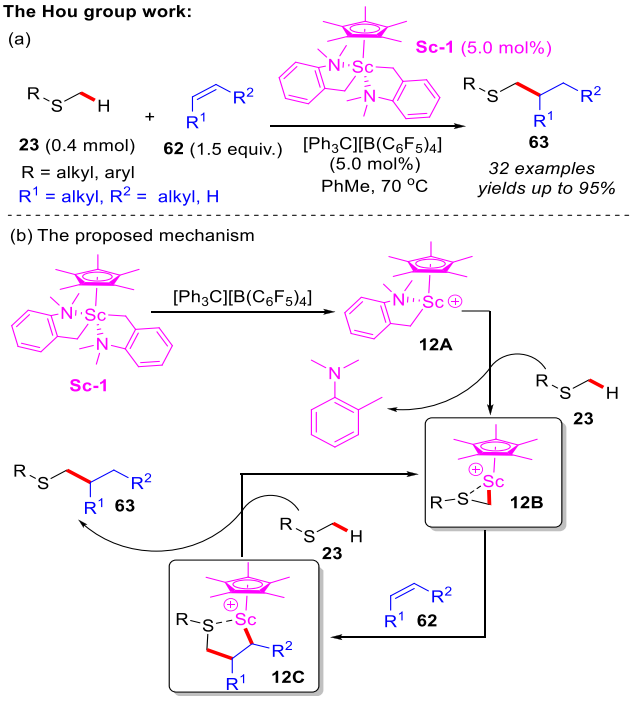
2. Catalytic strategy for the α-C(sp^3)-H addition of thioethers with alkenes

The C–H addition of sulfides to alkenes is a direct and an effective approach for the modification of sulfides, however, such transformation is very challenging. In 2018, Hou and co-workers developed the first example of Sc-catalyzed C(sp^3)-H alkylation of methyl sulfides with alkenes (Scheme 18a) [79]. A half-sandwich scandium catalyst was used to perform the unprecedented hydrothiomethylation of alkenes with methyl sulfides, providing diverse sulfide derivatives in moderate to good yields.

A plausible catalytic cycle is proposed and depicted in Scheme 18b. First, the pre-coordination of $[Ph_3C][B(C_6F_5)_4]$ to the Sc catalyst (**Sc-1**) provides the scandium species **12A**. Subsequent coordination of the

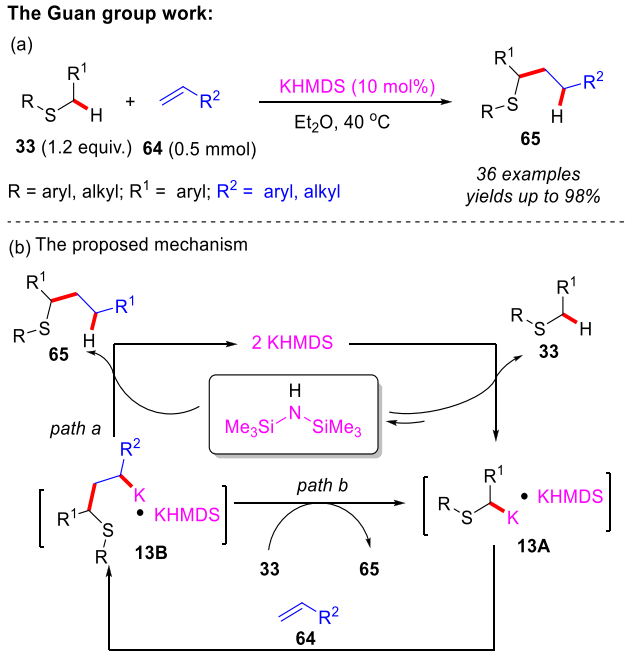


Scheme 17. A regioselective and scalable electrochemical α-C(sp^3)-H acyloxylation of sulfides.



Scheme 18. Sc-catalzyed C–H alkylation of methyl sulfides with alkenes.

sulfur atom on methyl sulfide **23** to the scandium species **12A** followed by a site-selective C–H bond activation step generates the three-



Scheme 19. KHMDS-catalyzed α-alkylation reaction of benzyl thioethers with styrenes.

membered metallacycle species **12B**. Next, the insertion of an alkene into the C–Sc bond of **12B** affords intermediate **12C**, which reacts with methyl sulfide to produce the final product **63** and releases the active species **12B** through a hydrogen abstraction process.

The aforementioned work by Hou represents a significant breakthrough in the α-C(sp^3)-H functionalization of thioethers by incorporating a cationic scandium catalyst. However, styrene substrates failed in this catalytic cycle, as scandium catalyzed polymerization of styrenes became the main reaction route instead. To resolve this scope problem, Guan and co-workers reported a Brønsted base [potassium bis(trimethylsilyl)amide (KHMDS)] catalyzed α-alkylation reaction of benzyl thioethers with styrenes (Scheme 19a) [80]. In this catalytic process, the desired alkylation products were isolated in good yields. A plausible catalytic cycle involving two equivalents of KHMDS is proposed and shown in Scheme 19b, which shows contrast to previously reported Sc-catalysis systems. First, the coordination of two KHMDS molecules to benzyl thioether **33** provides the alkyl potassium intermediate **13A**. The subsequent insertion of styrene followed by protonation produces the final alkylation product **65** and regenerates KHMDS (path a). Alternatively, there is also a possibility that the intermediate **13B** could take place with another benzyl thioethers to complete this catalytic cycle (path b).

3. Conclusion

Thioether skeletons are widely present in drugs, natural products, and industrial materials. Although the development of novel methods to prepare such skeletons is an ongoing effort, many scientific problems persist: (1) the strong coordination of sulfur's lone pair of electrons is easy to poison metals; (2) the multiple oxidation states of sulfur lead to poor reaction controllability; (3) high sulfur activity leads to poor system compatibility. Direct C–H functionalization has become an effective approach to access these skeletons in the last decade. In this mini-review, we provided a robust discussion of recent advances on the direct α-C(sp^3)-H bond functionalization, which mainly describes the direct α-C(sp^3)-H functionalization of thioethers by using different special oxidants, including peroxides, hypervalent iodine(III) reagents, electrophilic fluorinating agents, and silver salts. Moreover, both photochemical and electrochemical strategies are also developed in this field. Notably, only some special catalysts, including scandium salts and Brønsted base catalysts, could also realize the direct α-C(sp^3)-H addition of thioethers with alkenes. In spite of this significant progress, there is still room for improvement and utilization in the field of α-C(sp^3)-H functionalization of thioethers by exploring novel photochemistry and electrochemistry approaches. We hope this review will provide some insights for readers and inspire them to explore more novel strategies in the field of direct C–H functionalization of thioethers.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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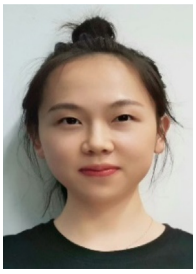

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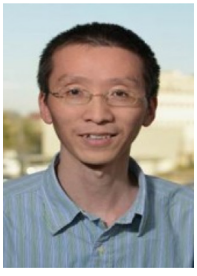

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