Recent Advances in Deoxygenative Thioether Synthesis Using Oxygenated Sulfur Surrogates

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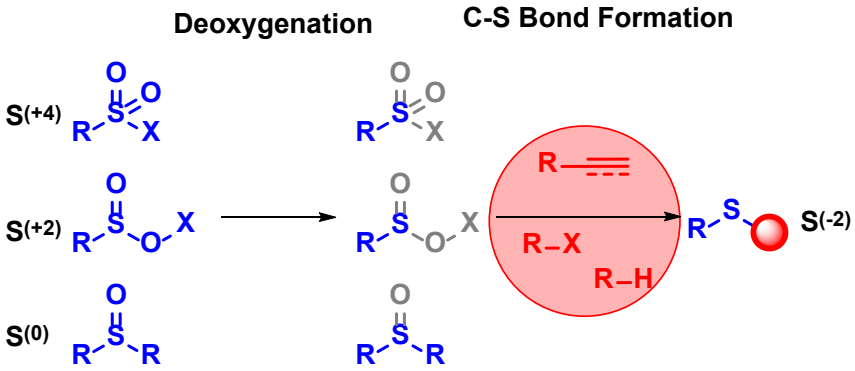

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Abstract Thioethers play a crucial role in therapeutics, diagnostics, and functional materials. Traditionally, their synthesis involved the use of thiols or their derivatives, which are associated with unpleasant odors and potential health risks. Recently, significant research has focused on employing oxygenated sulfur compounds, such as sulfinates, sulfonyl derivatives, sulfur oxyacids, and sulfoxides, as thiol surrogates for thioether synthesis. This review highlights recent advancements in deoxygenative thioether synthesis, categorizing them by reaction types, including cross-coupling reactions, C-H functionalization, and hydro/halo/oxy-thiolation of unsaturated hydrocarbons. We also discuss representative mechanisms to provide a comprehensive understanding of these innovative approaches.

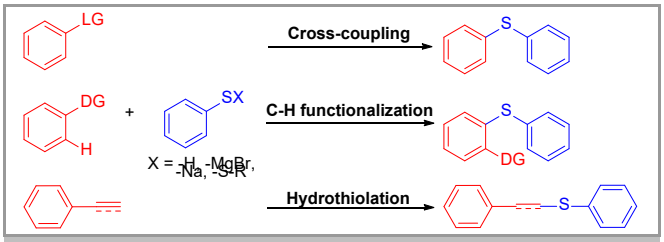
1. Introduction
2. Cross-coupling reactions
3. C-H functionalization
4. Hydro/halo/oxy-thiolation of unsaturated hydrocarbons
5. Conclusion

Key words Thioetherification, thioether, sulfonyl derivative, sulfinate, sulfoxide, sulfur oxyacid

1. Introduction

Sulfur chemistry is a pivotal area of research in modern organic synthesis due to the chemical versatility of sulfur, which is characterized by a broad range of oxidation states. Among various sulfur-containing structures, the thioether scaffold plays a significant role in fields such as material chemistry,[1] synthetic chemistry,[2] and particularly pharmaceutical development, where it is present in nearly 25% of marketed drugs.[3] Thioethers sometimes enhance bioactivity compared to other heteroatom isosteres,[4] underscoring the importance of developing methodologies for constructing thioether scaffolds and generating considerable interest among chemists.

Thioether synthesis, like other C-heteroatom bond formations, typically involves cross-coupling,[5] C-H activation,[6] and hydrothiolation of unsaturated hydrocarbons, often using thiols and their derivatives as sulfur surrogates (Scheme 1).[7] Despite the robustness of these protocols, the use of thiol derivatives is often discouraged due to their strong unpleasant odor and associated health concerns.[8] Additionally, the formation of highly stable metal-thiolate complexes can lead to catalytic poisoning,[9] prompting the search for alternative thiolate sources. Extensive research into thioetherification has identified numerous alternative sulfur surrogates, including elemental sulfur,[10] Bunte salt,[11] *N*-thiosuccimides,[12] and xanthate salt.[13] However, these alternatives can present challenges such as limited commercial availability, the need for pre-synthesis from thiols, and instability during storage, complicating their use.



Scheme 1 Conventional methods for thioether formation

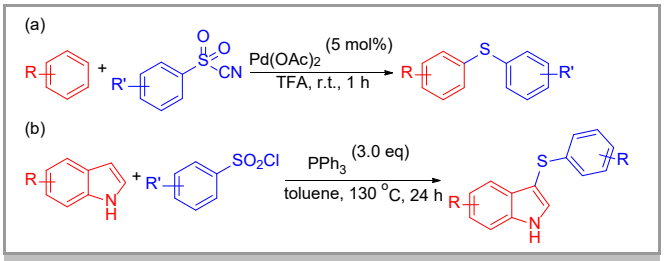
Oxygenated sulfur compounds have been widely used as sulfur donors in sulfonylation reactions[14] due to their low volatility, high stability, cost-effectiveness, and ease of purchase. Despite being ideal sulfur donors, their application in thioether synthesis has been limited, likely due to the requirement for an additional in-situ deoxygenation process prior to thiolation, which increases mechanistic complexity. In 2011, Beller and co-workers pioneered the use of oxygenated sulfur surrogates in thioetherification with their work on the C-H thioetherification of electron-rich arenes using arylsulfonyl cyanides (Scheme 2a).[15] This protocol achieved deoxygenation with trifluoroacetic acid, and similar results were obtained using sodium sulfinate

Table 1 Brief summary of the reaction

Reaction		Reactant	[S] source	Catalyst	Key additives	Ref.
Cross-coupling		Aryl halides	Sodium sulfinates	CuO	/	(18)
				$NiCl_2$•glyme + [Ir] [a]	/	(21)
				$Ni(py_4)Cl_2$	/	(19)
		gem-difluoroalkenes		Na_2Eosin Y	/	(25)
		Organoboronic acids		$Cu(TFA)_2$	/	(26)
		Sodium sulfinates		$Pd(OAc)_2$	/	(34)
		Hydrazones		/	/	(35)
		Alkyl alcohols		organophosphorus	/	(28)
			Sulfinic acids	/	NaI	(27)
		TMS-CF_3	Sodium sulfinates	$CuBr_2$	/	(31)
			Sulfonyl chlorides	CuI	/	(32)
		Allylsilanes	Sulfinic esters	/	Tf_2O	(30)
		Alkyl bromides	Sulfonyl cyanides	$Ni(acac)_2$	/	(22)
			Methyl sulfoxides	/	[Bmim][OTf]	(23)
		Halo-furanones		/	DBDMH	(24)
		4° ammonia	β-sulfinyl esters	/	KOH	(33)
C-H functionalization	Electron-rich (Hetero)aryls	Electron-rich arenes	β-sulfinyl esters	/	Tf_2O	(54)
			Sulfinic esters	/	TBAI	(37)
			Sulfonyl hydrazines	/		(38)
		Indoles		/		(39)
			Sodium sulfinates	/	HCl	(56)
				/	H_2SO_4	(61)
			Sulfonyl chlorides	/	Squaric acid	(57)
			Sulfonyl anhydrides	/	[Hmim]Br	(62)
			Methyl sulfoxides	/	DCE	(58)
		Imidazopyridines		/	KI	(41)
			Sulfinic esters	/	I_2	(42)
			Sulfonyl hydrazines	/	/	(60)
		isoquinolinones	Sulfonyl chlorides	/	I_2	(45)
		5-aminouracils	Sulfonyl hydrazines	I_2	/	(47)
		Uracils		I_2	/	(50)
		Imidazothiazoles		/	/	(60)
		Pyrazoles		/	/	(51)
	Unsaturated hydrocarbons	1,1-diphenylethenes	β-sulfinyl esters	/	Tf_2O	(66)
			Sodium sulfinates	/	HI	(64)
		Silylenol ethers		/	Triphosgene	(67)
		Enaminones		/	$POCl_3$	(70)
			Methyl sulfoxides	/	Tf_2O	(68)
		Alkene, alkynes	β-sulfinyl esters	/		(65)
		1,3-dicarbonyls				
	$C(sp^3)$-H	Benzylic amides	Methyl sulfoxides	/		(71)
		N-fluorosulfonamides	Sodium sulfinates	CuBr	/	(72)
		Alkanes		$FeCl_3$•$6H_2O$	AcCl	(73)
				/	HCl	(75)
		cyclohexanones	Sodium sulfinates	/	HI	(76)
		β-dicarbonyls	Sulfoxides	/	AcCl	(77)
Thiolation of unsaturated hydrocarbons		Arynes	Methyl sulfoxides	/	KF	(78)
		Acetylenic sulfones		/	/	(79)
		Propiolic esters		/	HI	(81)
		p-quinone methides	Sodium sulfinates	/	PPh_3	(80)
		alkenes	Sulfonyl oximes	[Ir] [a]		(83)

[a] $[Ir(dF(CF_3)ppy_2(dtbpy))PF_6$

and trifluoroacetic anhydride. In the same year, You and co-workers reported a metal-free synthesis of di(heteroaryl) sulfides using arylsulfonyl chloride as the thiolate source with triphenylphosphine as a reductant (Scheme 2b).[16] Since then, various oxygenated sulfur compounds, such as sulfonyl derivatives, sulfur oxyacid derivatives, and sulfoxides, have been reported as efficient sulfur donors in thioetherification,[17] significantly advancing synthetic routes for thioether construction. Herein, we summarize recent advancements in deoxygenative thioetherification using sulfonyl derivatives, sulfur oxyacid derivatives, and sulfoxides as sulfur donors, categorized by reaction type (Table 1).



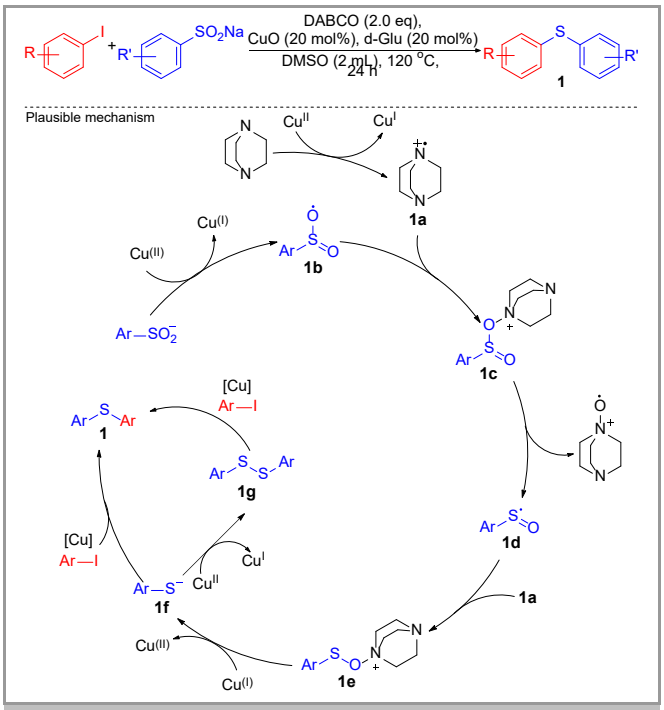
Scheme 2 Reports on thioetherification with sulfonyl derivatives in 2011

2. Cross-coupling reactions

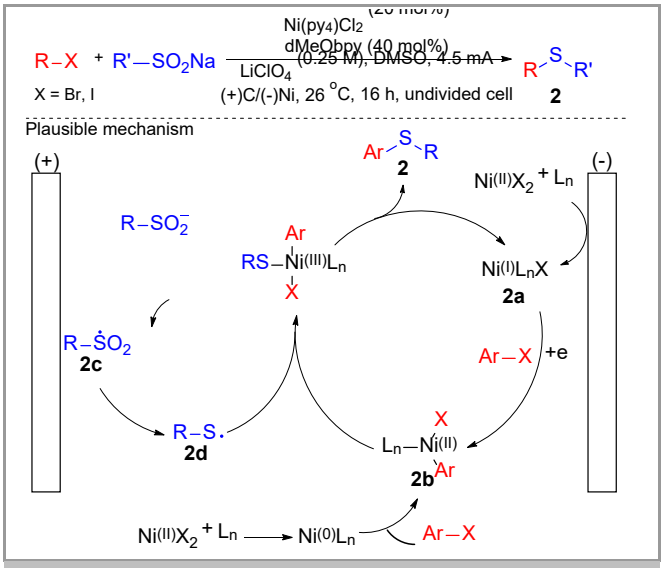
2.1 Cross-coupling with organohalides

In 2020, our group reported a Cu-catalyzed thioetherification of aryl iodides with sodium sulfinates, mediated by DABCO (Scheme 3).[18] This reaction provided a general approach for constructing thioethers, while prior to this report, thioetherification with sodium sulfinates often had a substrate scope limited to electron-rich arenes.[17] From the radical trap experiment, we observed that the formation of thioethers was completely inhibited upon the addition of 4.0 equivalents of TEMPO. Additionally, the DABCO *N*-oxide radical was trapped and detected by HRMS in the reaction mixture. Mechanistically, the reaction begins with the formation of the DABCO radical cation (**1a**) through $Cu^{(II)}$ oxidation. Concurrently, sodium sulfinate is oxidized by $Cu^{(II)}$ to generate a sulfonyl radical (**1b**), which then couples with **1a** to form intermediate (**1c**). The extrusion of the DABCO N-oxide radical leads to the formation of a sulfinyl radical (**1d**), which reacts again with 1a to produce DABCO-sulfanolate (**1e**). Upon reduction of **1e** by $Cu^{(I)}$, the resulting thiolate anion (**1f**) can either directly couple with the aryl iodide or form a disulfide (**1g**) for subsequent coupling reactions.

In 2021, Zhang and co-workers developed an electrochemical Ni-catalyzed thioetherification of aryl halides with sodium sulfinate (Scheme 4).[19] In this process, $Ni^{(II)}$ is reduced at the cathode surface to generate a $Ni^{(I)}$ complex (**2a**), which facilitates the oxidative addition of the aryl halide to form a $Ni^{(III)}$ complex. This complex is subsequently reduced back to $Ni^{(II)}$ (**2b**) at the cathode. Alternatively, direct reduction of $Ni^{(II)}$ to $Ni^{(0)}$ at the cathode, followed by oxidative addition of the aryl halide, can also generate **2b**. At the anode surface, sodium sulfinate undergoes a single-electron transfer (SET) process to produce a sulfonyl radical (**2c**), which then disproportionates to form a thiyl radical (**2d**). The desired thioether product (**2**) is obtained through the typical Ni-catalytic cycle involving **2b**. Mechanistically, the mass transfer effect, resulting from the use of paired electrodes, governs the cascade deoxygenation of sodium sulfinate to the thiyl radical due to the slow diffusion rate of intermediates. This prevents the trapping of the sulfonyl radical by **2b**, thereby ensuring the chemoselectivity of the reaction by avoiding the formation of sulfonyl products. A similar Ni-catalyzed electrochemical thioetherification of aryl halides was reported by Pan in 2022.[20]



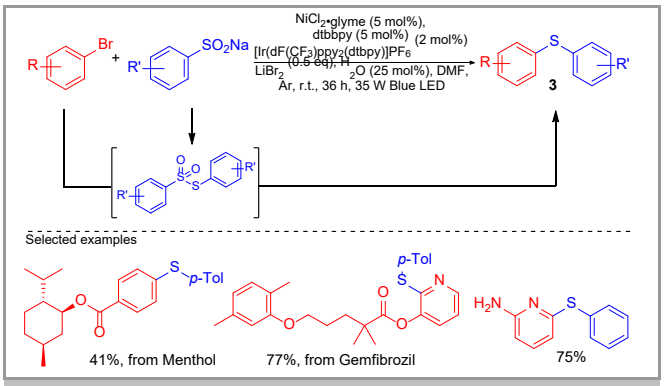
Scheme 3 DABCO promoted thioetherification of aryl iodides with sodium sulfinates



Scheme 4 Electrochemical reductive thiolation of aryl halides with sodium sulfinates

In 2022, Huang and co-workers reported a Ni/photoredox dual catalytic C-S coupling of aryl halides using sodium sulfinate as a thiolate surrogate (Scheme 5).[21] Mechanistic studies suggested that sodium sulfinate undergoes disproportionation to form thiosulfonate, which then enters the standard photo/Ni dual

catalytic cycle. This method demonstrated good functional group tolerance for the preparation of di(hetero)aryl thioethers, and a variety of pharmaceutical and natural product-derived bromopyridines were also well tolerated.

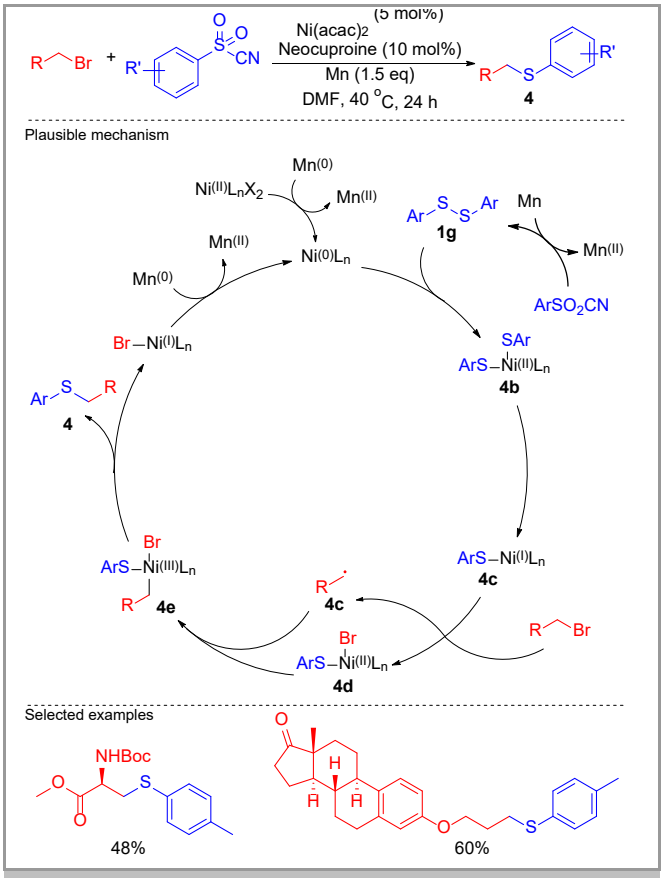


Scheme 5 Thioetherification of aryl halides under Ni/photoredox dual catalytic system

Despite sulfonyl cyanide being the first oxygenated sulfur compound used in thioetherification, further development in this area has been limited, likely due to the operational complexity involved in preparing sulfonyl cyanide. In 2021, Wang and co-workers reported a Ni-catalyzed reductive coupling between arylsulfonyl cyanide and alkyl bromide to produce alkyl-aryl thioethers (Scheme 6).[22] In this reaction, Mn is responsible for deoxygenating the arylsulfonyl cyanide to form diaryl disulfide (**1g**) and for reducing $Ni^{(II)}$ to $Ni^{(0)}$. Following oxidative addition, a $Ni^{(II)}$ complex (**4a**) is formed, which is then reduced to a $Ni^{(I)}$ complex (**4b**). This complex is further oxidized by the alkyl bromide to generate an alkyl radical (**4c**) and a $Ni^{(II)}$ complex (**4d**). The desired thioether (**4**) is formed through the standard catalytic process involving the formation of a $Ni^{(III)}$ complex (**4e**), and the Ni catalyst is regenerated via Mn reduction to complete the catalytic cycle. This protocol offers a mild and efficient method for preparing alkyl-aryl thioethers under gentle conditions; however, only a limited substrate scope for arylsulfonyl cyanide was reported.

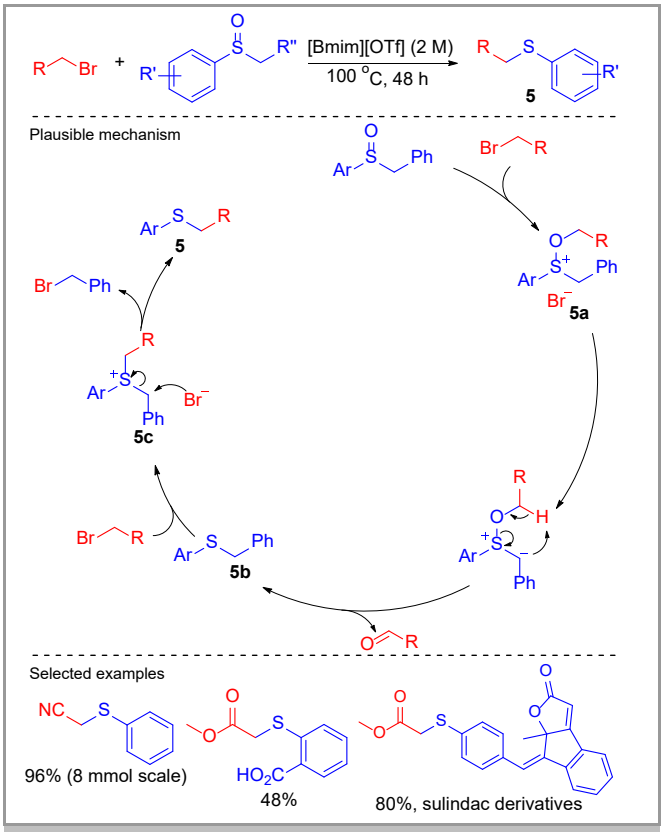
Huang, Luo, and co-workers developed a catalyst- and additive-free method for preparing thioethers from alkyl bromides and sulfoxides in an ionic liquid (Scheme 7).[23] A plausible mechanism involves sequential Kornblum oxidation and C(sp^3)-S metathesis. Initially, the alkyl bromide undergoes an S_N2 reaction with the sulfoxide to generate a sulfonium salt **5a**, which then undergoes deprotonation and a [2,3]-sigmatropic shift to form the sulfide (**5b**). **5b** subsequently undergoes metathesis with the alkyl bromide, forming a new sulfonium salt (**5c**), which undergoes nucleophilic substitution with a bromide anion to yield the desired product (**5**). Direct C(sp^3)-S metathesis between aryl methylthioethers and alkyl bromides was also effective, particularly when the solvent was changed to trifluoroethanol. This transformation demonstrated high functional group tolerance and provided an example of late-stage functionalization of sulindac. However, 6.0 equivalents of alkyl bromide were required to promote the reaction.

In 2023, Wang reported a methylthioetherification of 3,4-dihalo-2(5H)-furanones using DMSO and 1,3-Dibromo-5,5-Dimethylhydantoin (DBDMH) (Scheme 8).[24] In this protocol, DBDMH plays a crucial role in activating and deoxygenating DMSO to form dimethyl sulfide (**6a**), which then attacks the 3,4-dihalo-2(5H)-furanones to produce intermediate **6b**. Subsequent nucleophilic attack of **6b** by a halide anion yields the desired thiolated product (**6**).

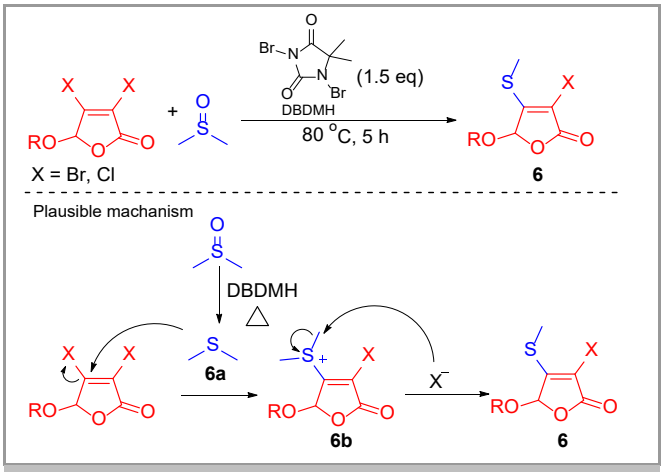


Scheme 6 Ni-catalyzed reductive thiolation of unactivated alkyl bromides with sulfonyl cyanides

Shi and co-workers described a photocatalytic thioetherification of gem-difluoroalkenes with sodium sulfinates to prepare *E*-α-fluoro-β-arylalkenyl thioethers (Scheme 9).[25] In this reaction, photoirradiation generates the excited state [Eosin Y]* (**[PC]***), which undergoes a single-electron transfer (SET) process with sodium sulfinate to produce a sulfonyl radical (**1b**). This radical undergoes cascade deoxygenation mediated by PPh_3 to generate a thiyl radical (**7a**). The thiyl radical can either be reduced by **[PC]**$^-$ to form a thiolate anion (**1f**), which then adds nucleophilically to gem-difluoroalkenes to form intermediate **7b**, or it can directly attack the gem-difluoroalkenes to yield radical intermediate **7c**, which is also reduced by **[PC]**$^-$ to form **7b**. Following β-elimination, the *Z*-product (***Z*-7**) undergoes photoinduced isomerization to convert into the *E*-configuration (**7**).



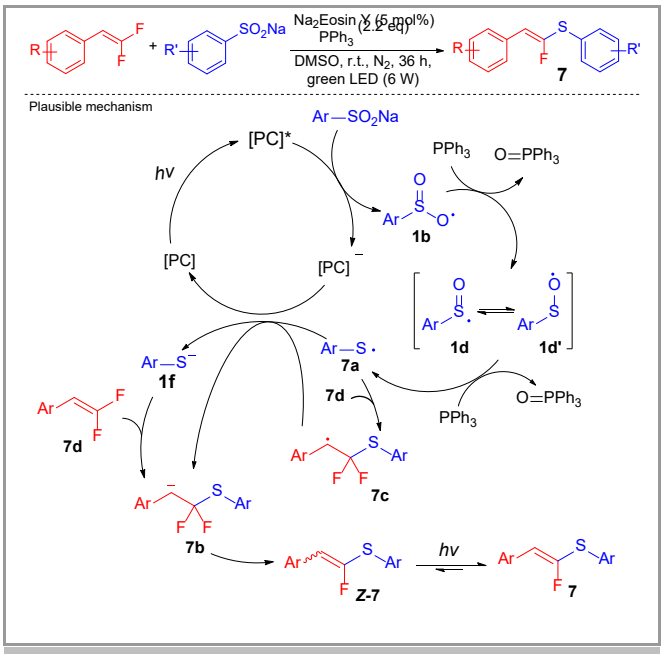
Scheme 7 Cascade sulfoxide reduction/C(sp^3)-S metathesis between sulfoxides and alkyl bromides



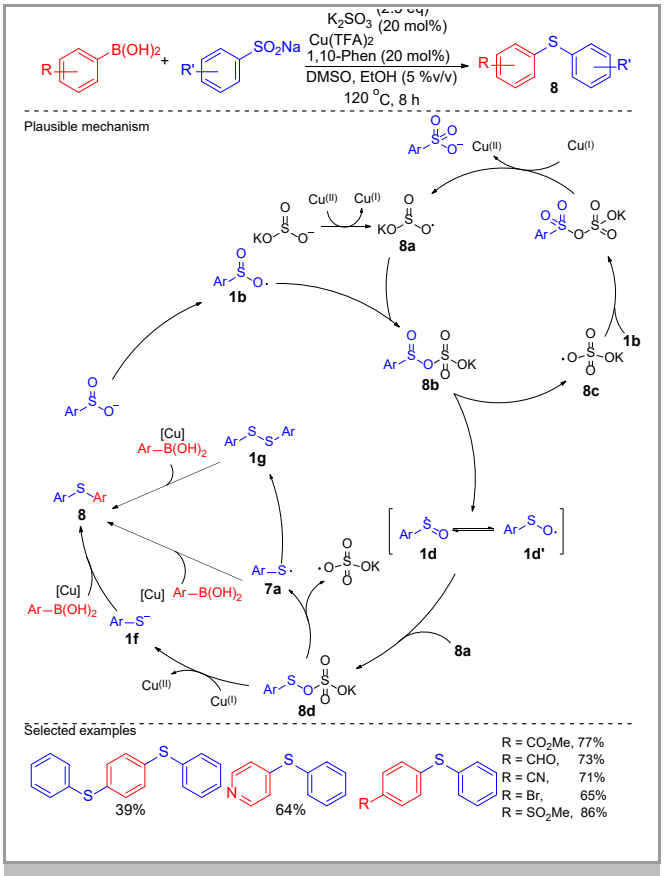
Scheme 8 DBDMH-promoted methylthioetherification of 3,4-dihalo-2(5*H*)-furanones

2.2 Cross-coupling with organoboron compounds

Building on our previous work (Scheme 2), we have developed a Chan-Lam type C-S coupling reaction between sodium arylsulfinate and organoboron compounds, mediated by K_2SO_3 (Scheme 10).[26] Based on mechanistic studies, the following plausible mechanism is proposed: The reaction begins with the sequential oxidation of K_2SO_3 and sodium sulfinate by $Cu^{(II)}$ to generate a sulfite radical (**8a**) and a sulfonyl radical (**1b**), respectively. These radicals undergo coupling to form the sulfinyl sulfonate intermediate (**8b**). Following the elimination of a sulfate radical (**8c**) and the addition of **8a**, the resulting sulfenyl sulfonate (**8d**) can undergo homolytic cleavage to form a thiyl radical (**7a**) or be reduced to yield a thiolate anion (**1f**). Intermediates **7a**, **1f**, and **1g** (formed from the radical coupling of **7a**) can react with the organoboron compound to produce the desired thioether (**8**) through a standard catalytic cycle. Notably, this reaction is compatible with various organoboron compounds, including -$B(OH)_2$, -Bpin, BF_3K and boroxine, and it also allows for di-thioetherification.



Scheme 9 Visible light-promoted thioetherification of *gem*-difluoroalkenes



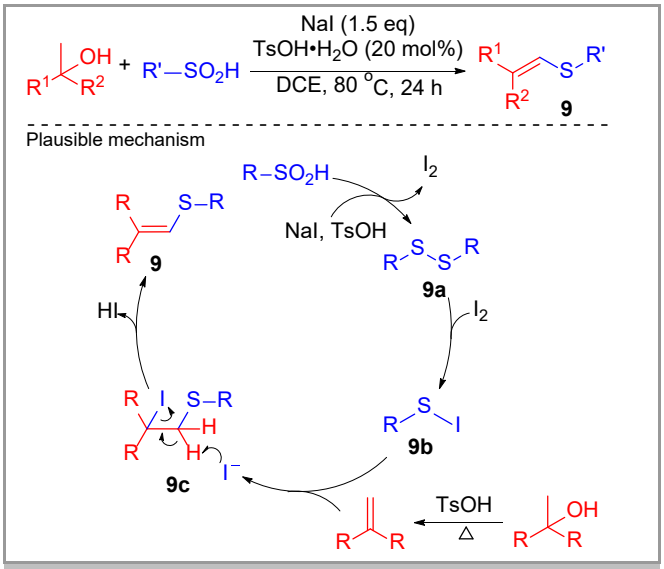
Scheme 10 Chan-Lam type thioetherification with sodium sulfinates

2.3 Dehydroxylative cross-coupling

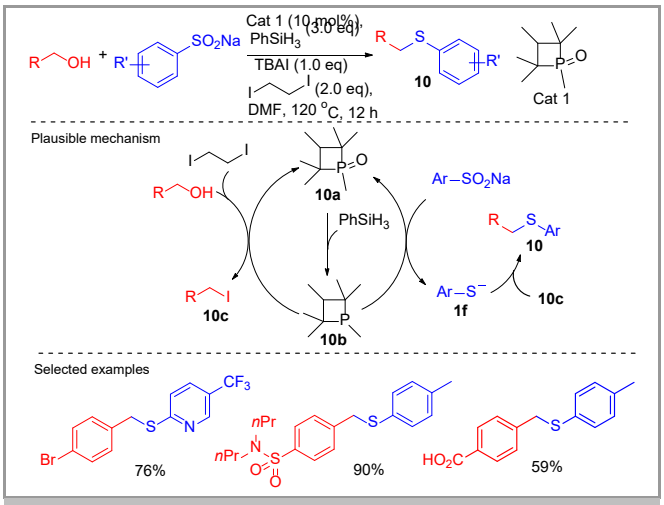
The exploration of dehydroxylative coupling of alcohols has garnered significant interest among synthetic chemists. Due to the widespread presence of hydroxy groups in pharmaceuticals and natural products, dehydroxylative coupling offers a valuable strategy for late-stage functionalization of these compounds. This approach enables the modification of complex molecules, enhancing their utility and expanding the scope of synthetic transformations.

In 2021, Wu and co-workers reported a NaI-mediated synthesis of vinyl sulfides from sulfinic acids and alcohols (Scheme 11).[27] Mechanistically, the reaction begins with the deoxygenation of sulfinic acid in the presence of a NaI/TsOH system, forming a disulfide intermediate (**9a**). This intermediate reacts with I_2, generated during the deoxygenation process, to produce sulfenyl iodide (**9b**), which acts as the active thiolating species. Concurrently, the alcohol undergoes elimination to form an alkene, which is then attacked by **9b** to yield intermediate **9c**. The desired vinyl sulfide (**9**) is formed through the elimination of HI. Notably, solvent-controlled chemoselectivity was observed, influencing the formation of either vinyl sulfide or vinyl sulfone.

In 2024, Xu and co-workers developed a dehydroxylative thioetherification of alcohols using an organophosphorus catalyst (Scheme 12).[28] Mechanistically, the reaction is facilitated by the $P^{(III)}/P^{(V)}$=O redox cycle of the phosphorus catalyst, which activates the alcohol and deoxygenates sodium sulfinate. Initially, the phosphorus catalyst **10a** is reduced to the active $P^{(III)}$ species **10b** by $PhSiH_3$. **10b** is then regenerated to **10a** through both the Appel reaction, which activates the alcohol to form an alkyl iodide (**10c**), and the cascade deoxygenation of sodium sulfinate to produce a thiolate anion (**1f**). The desired product **10** is obtained via nucleophilic substitution. This reaction is notable for its tolerance of other oxygenated sulfur compounds as reactants, particularly sulfonic acids, which are rarely used in deoxygenative C-S bond formation due to the challenges associated with their reduction.[29]



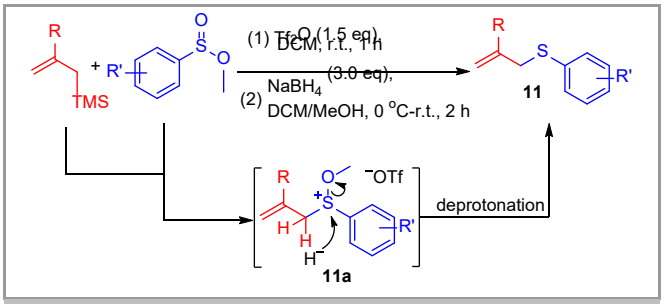
Scheme 11 NaI-mediated synthesis of vinyl sulfide from alcohols



Scheme 12 Dehydroxylative thioetherification of alcohols with sodium sulfinates

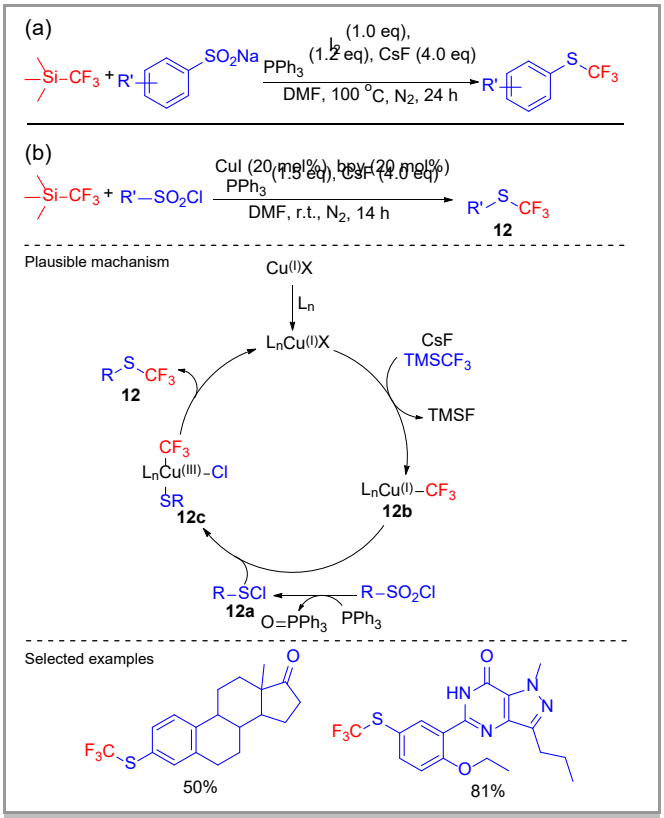
2.4 Cross-coupling with trimethylsilyl compounds

In 2020, Yoshida and co-workers reported a one-pot synthesis of allyl thioethers using sulfinate esters and allylsilanes (Scheme 13).[30] The reaction proceeds through the formation of an alkoxysulfonium triflate salt (**11a**) as a key intermediate, activated by Tf_2O. Computational and deuterated studies suggested that the deoxygenation of **11a** is initiated by nucleophilic substitution with a hydride ion, followed by subsequent deprotonation to yield the desired product (**11**).



Scheme 13 One-pot synthesis of allyl thioether from sulfinate esters and allylsilanes

Hong and co-workers described an indirect synthesis of trifluoromethyl thioethers using sodium sulfinate and $TMSCF_3$ (Scheme 14a).[31] This reaction was effective for the late-stage functionalization of natural products and pharmaceutical intermediates. Later, Hong extended this approach to a Cu-catalyzed trifluoromethylation of sulfonyl chlorides (Scheme 14b).[32] Mechanistic studies suggest that sulfenyl chloride (**12a**) is generated via a PPh_3 deoxygenation system. Concurrently, CF_3^-, generated from $TMSCF_3$ and CsF, reacts with $Cu^{(I)}$ to afford complex (**12b**). Upon oxidative addition of **12a** to **12b**, the resulting $Cu^{(III)}$ complex (**12c**) undergoes reductive elimination to yield the desired product (**12**). Compared to the previous method (Scheme 12a), this approach demonstrates the feasibility of preparing alkyl trifluoromethyl thioethers, albeit with moderate yields.



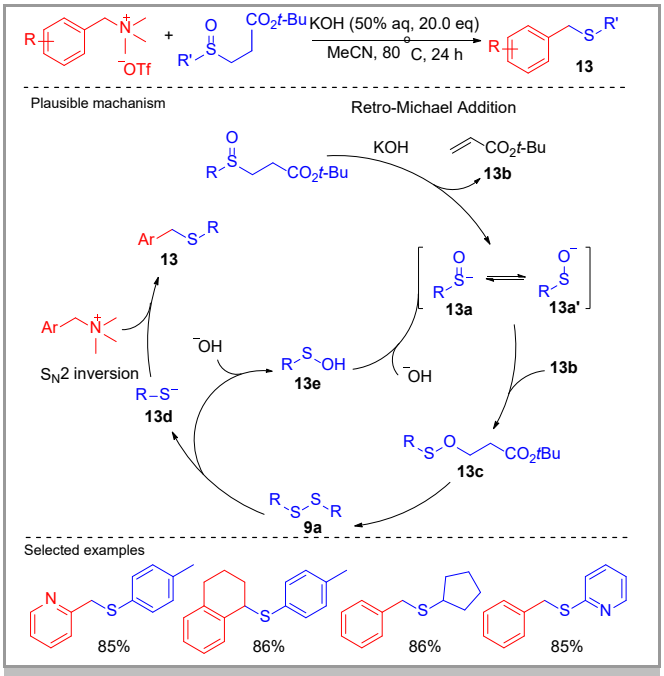
Scheme 14 Indirect trifluoromethylthiolation with $TMSCF_3$

2.5 Cross-coupling with miscellaneous reactants

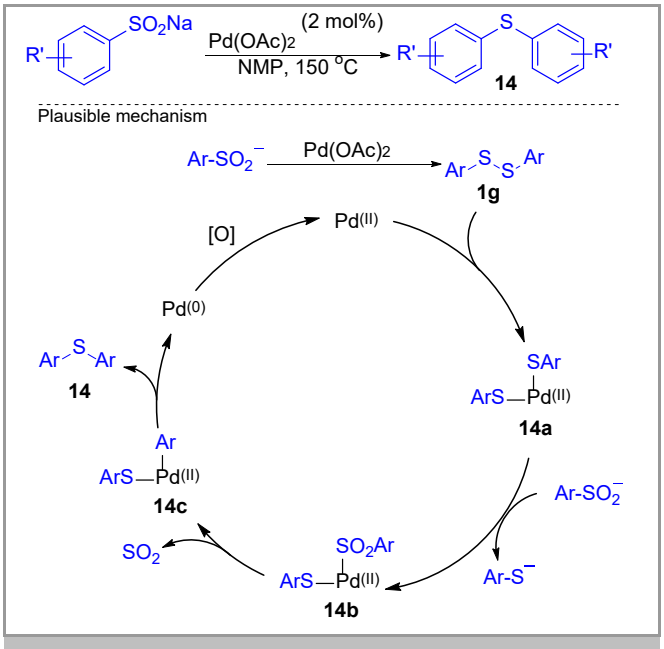
In 2021, Zeng and co-workers developed an efficient thioetherification protocol to synthesize benzyl thioethers using benzylic trimethylammonium salts as coupling partners and β-sulfinyl esters as sulfur donors (Scheme 15).[33] In this reaction, a sulfanolate anion (**13a**) is generated through a base-promoted retro-Michael addition, which involves the elimination of acrylate (**13b**). This is followed by an *O*-Michael addition of the acrylate to the tautomer (**13a'**) to form intermediate (**13c**). Disproportionation of **13c** then occurs, yielding disulfide (**9a**), which further decomposes into a thiolate anion (**13d**) as the active thiolating species in the presence of KOH. The desired product (**13**) is finally obtained via an S_N2 reaction between **13d** and the benzyl quaternary ammonium salt. This S_N2 mechanism allows the production of benzyl thioethers with reversed enantiomeric configuration and high enantiopurity.

In 2022, Gao and co-workers reported a Pd-catalyzed homocoupling of sodium sulfinate to synthesize symmetric thioethers (Scheme 16).[34] In this transformation, sodium sulfinate is initially deoxygenated to form disulfide (**1g**) in the presence of a Pd catalyst. The disulfide then undergoes insertion into the Pd catalyst to form complex (**14a**). Subsequent ligand exchange between **14a** and sodium sulfinate leads to the formation of complex **14b**. Upon liberation of SO_2, complex **14c** is formed, and the desired thioether (**14**) is obtained through reductive elimination.

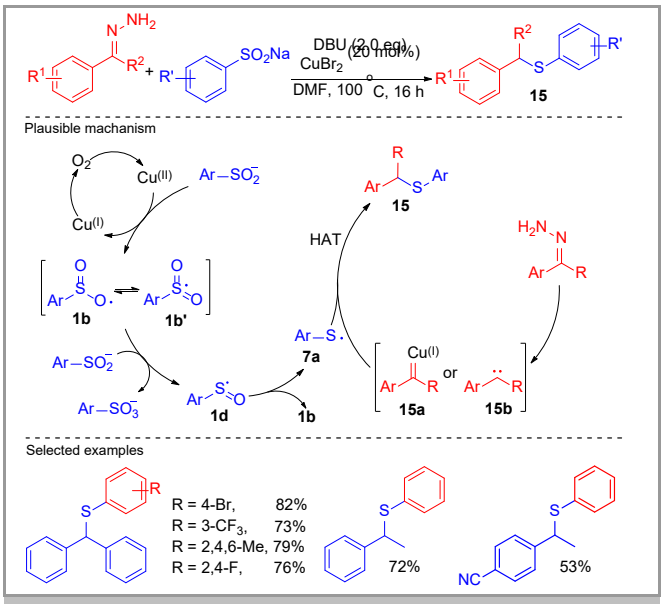
In 2023, Singh reported a Cu-catalyzed thioetherification of hydrazones using sodium sulfinate to synthesize benzylic thioethers (Scheme 17).[35] In this transformation, sodium sulfinate is oxidized to form a sulfonyl radical, which undergoes deoxygenation by excess sodium sulfinate and sequential disproportionation to produce a thiyl radical (**7a**) as the active thiolating species. Additionally, upon the elimination of N_2, the Cu complex (**15a**) or carbene intermediate(**15b**) react with **7a**, followed by a hydrogen atom transfer (HAT) process to yield the desired benzylic thioether (**15**). Following this work, Jadhao and Gaikwad reported a similar approach using sulfonylhydrazine and ketone for the in-situ generation of hydrazone to construct benzylic thioethers in the same year.[36]



Scheme 15 Deoxygenative coupling of β-sulfinyl esters with benzylic trimethylammonium salts



Scheme 16 Pd-catalyzed homocoupling of sodium sulfinates



Scheme 17 Cu-catalyzed thioetherification of hydrazones with sodium sulfinates

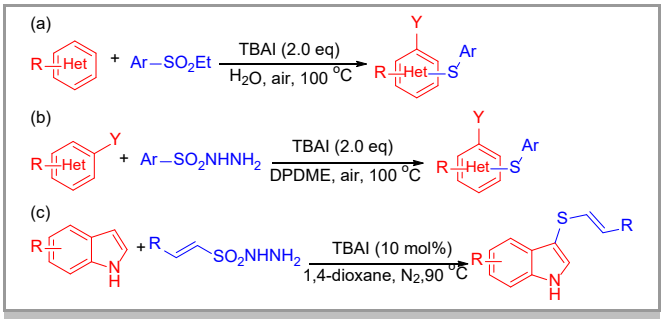
3. C-H functionalization

3.1 Functionalization of electron-rich (hetero)arenes

C-H functionalization of electron-rich (hetero)arenes is a major area in C-H thioetherification. By deoxygenating oxygenated sulfur compounds to generate active thiolating species, such as sulfenyl halides or thiosulfonates, thioetherification can be readily achieved through either electrophilic substitution or radical addition to the electron-rich (hetero)arene.

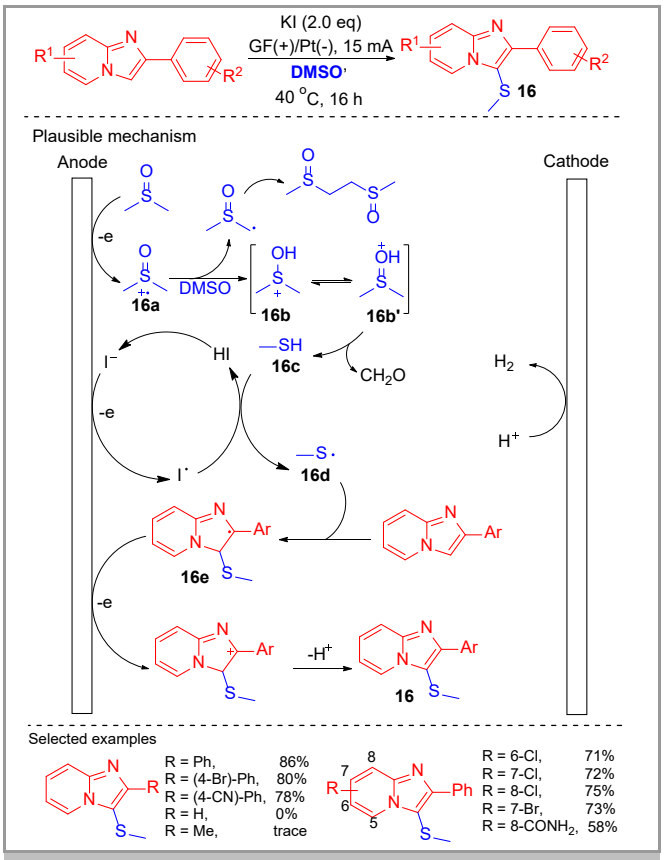
Deoxygenation of oxygenated sulfur compounds using the I_2/I^- system represents a major metal-free strategy for the effective generation of active thiolating species. In 2020, Gu and co-workers described a TBAI-mediated C-H thioetherification of arenes in water using ethyl sulfinates as the sulfur source (Scheme 18a).[37] This transformation allowed diverse electron-rich arenes, such as hydroxy/amino-substituted naphthalene, indole, and pyrrole, to be converted into the corresponding thioethers in moderate to excellent yields. Notably, the reaction was applicable for synthesizing di-thiolated products and demonstrated good scalability under green and mild conditions. In a parallel investigation, Zhang and co-workers showed that sulfonyl hydrazine could be used for the thioetherification of electron-rich arenes in dipropylene glycol dimethyl ether (DPDME) using TBAI (Scheme 18b).[38] In 2021, Saeed and co-workers successfully synthesized 3-styrylthioindole from β-*E*-styrene sulfonyl hydrazides using the TBAI deoxygenation system (Scheme 18c).[39] Additionally, in 2023, Bi and co-workers reported a similar thioetherification of arenes using a combination of HI and sodium sulfinate.[40]

In 2024, Sun, Liu, and co-workers developed an electrochemical C3-methylthiolation of imidazo[1,2-*a*]pyridine using DMSO as a methylthiolate surrogate (Scheme 19).[41] Based on mechanistic and cyclic voltammetry studies, a plausible mechanism was proposed. Initially, DMSO is oxidized to form a radical cation species (**16a**), which then reacts with another DMSO molecule to produce a cationic species (**16b**). This species decomposes into MeSH (**16c**) through the liberation of CH_2O and H^+. Concurrently, the oxidation of I^- at the anode generates an iodide radical, which undergoes a hydrogen atom transfer (HAT) process with **16c** to form a methylthio radical (**16d**). This radical is then captured by imidazo[1,2-*a*]pyridine, yielding a radical intermediate (**16e**). Upon oxidation at the cathode surface and subsequent deprotonation of **16e**, the C3-thiolated product (**16**) is obtained. Unfortunately, the reaction proceeds only with 2-arylated imidazo[1,2-*a*]pyridine, and no desired product is obtained for 2-H and 2-Me imidazo[1,2-*a*]pyridine.

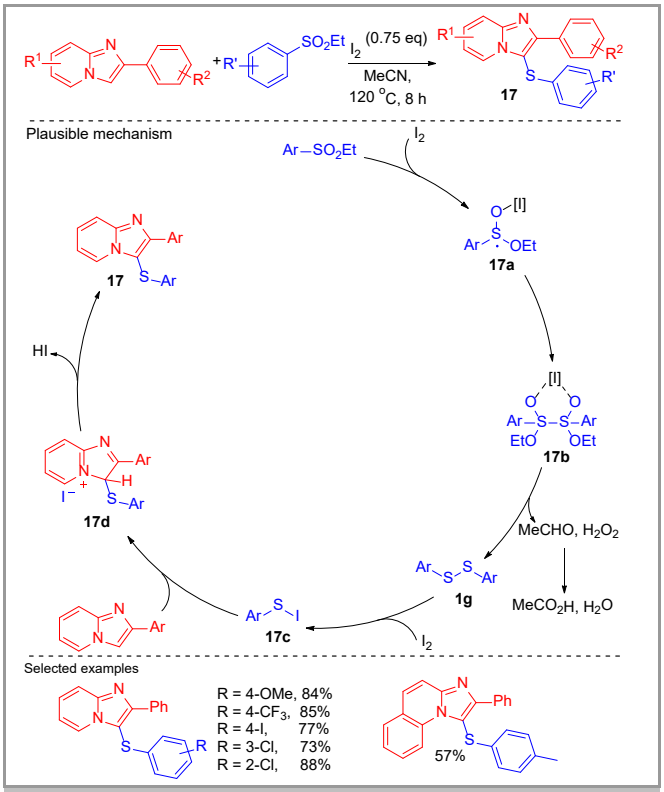


Scheme 18 Thioetherification of electron-rich (hetero)arenes using TBAI

Tang and co-workers developed a thioetherification strategy for imidazo[1,2-*a*]pyridines using I_2 as a mediator (Scheme 20).[42] The proposed mechanism suggests that the reaction begins with the activation of ethyl sulfinates to generate a radical intermediate **17a**. This intermediate undergoes radical dimerization to form a dimer **17b**, which then deoxygenates to produce disulfide (**1g**) through the elimination of acetaldehyde and H_2O_2. In the presence of I_2., disulfide **1g** is oxidized to form sulfenyl iodide (**17c**), an active thiolating species. This species undergoes electrophilic attack and elimination of HI to yield the desired product (**17**). In a parallel study, Tang also demonstrated that isoquinolin-1(2*H*)-one could undergo C4-thioetherification under similar conditions.[43] Despite the effectiveness of these methods, the reactions require high temperatures in MeCN, which can reduce applicability and increase operational complexity. In 2023, Vanelle and co-workers reported a similar thioetherification strategy for imidazo[1,2-*a*]pyridines using sodium sulfinate and I_2.[44]

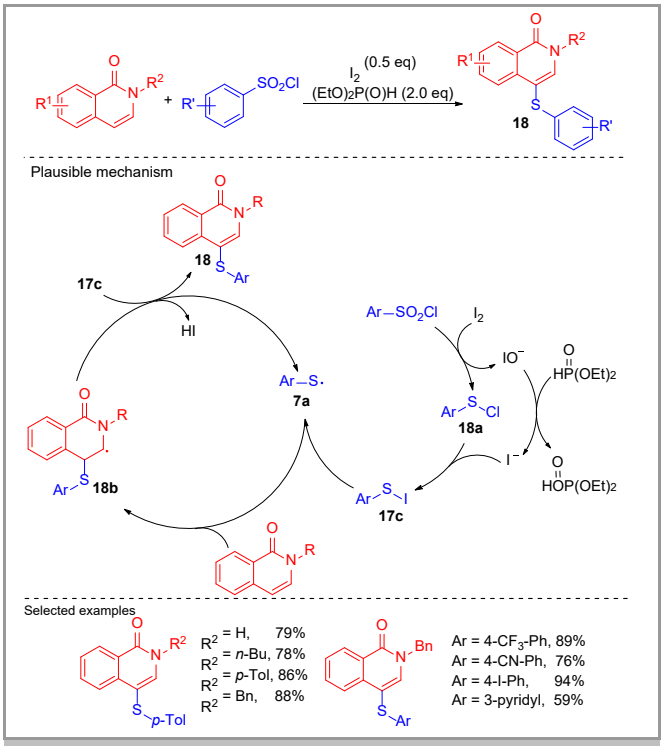


Scheme 19 Electrochemical C3-methylthiolation of imidazopyridines



Scheme 20 I_2-mediated thioetherification of imidazopyridines with sodium sulfinates

In 2021, Huang and co-workers disclosed a neat C4-thioetherification of isoquinolin-1(2*H*)-one using readily available sulfonyl chloride under an I_2/$(EtO)_2P(O)H$ deoxygenation system (Scheme 21).[45] Mechanistic studies suggested that sulfenyl iodide (**17c**), generated from the deoxygenation of sulfonyl chloride promoted by I_2 and $(EtO)_2P(O)H$, undergoes homolysis to directly produce a thiyl radical (**7a**), rather than undergoing 1,2-addition on isoquinolin-1(2*H*)-one. The thiyl radical **7a** then coupled with isoquinolin-1(2*H*)-one to form a radical intermediate (**18b**), which subsequently undergoes a HAT process with **17c** to afford the desired product (**18**). Additionally, Liu reported a C3-thioetherification of indole using sulfonic anhydride in combination with I_2 and PPh_3.[46]

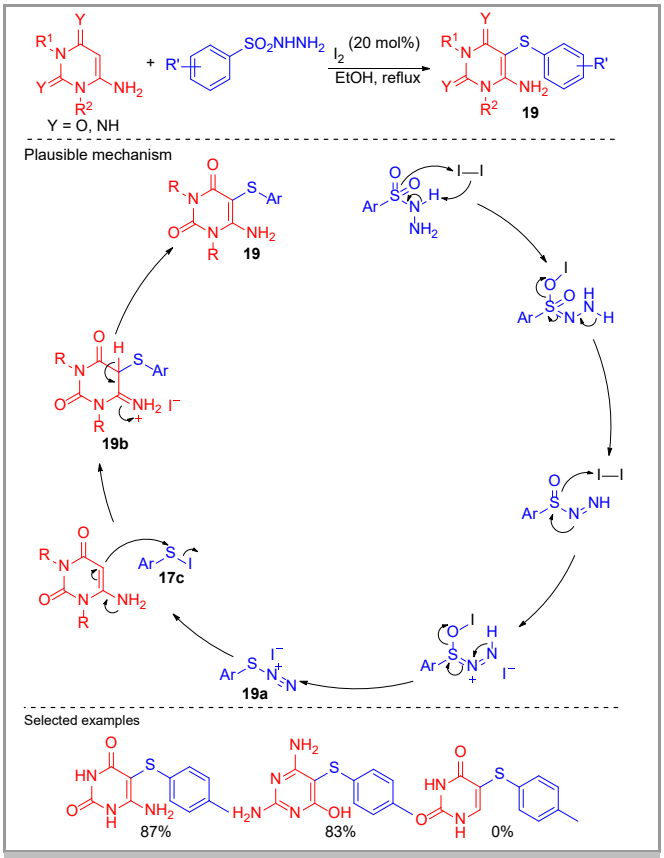


Scheme 21 I_2-promoted C4-H thioetherification of isoquinolin-1(*2H*)-ones

Deka and co-workers reported a regioselective thioetherification of C5-aminouracils using sulfonyl hydrazine as the thiolating source in the presence of an I_2 catalyst in EtOH (Scheme 22).[47] Mechanistic studies indicated that no radical intermediates were involved in this transformation, as the reaction proceeded smoothly even in the presence of TEMPO, and the 5-amino group was crucial for the reaction to occur. Under the reaction conditions, sulfonyl hydrazine is deoxygenated to form a thiodiazonium salt (**19a**) through the elimination of HOI and HI. This salt then undergoes the elimination of N_2 to afford sulfenyl iodide (**17c**). The desired product (**19**) is formed from aminouracil via nucleophilic attack on either **19a** or **17c**. The applicability of the I_2/sulfonyl hydrazine system was further expanded in 2024 to include the thioetherification of pyrrolo[1,2-*a*]quinoxalines by Nguyen[48] and indole by Liu.[49]

In 2024, Tang and co-workers also demonstrated a direct C5-thioetherification of uracil using the iodine/sulfonyl hydrazine system (Scheme 23).[50] Mechanistically, this transformation differs from the previously reported thioetherification of 5-aminouracil (Scheme 22) as it involves radical species, evidenced by the complete inhibition of the reaction in the

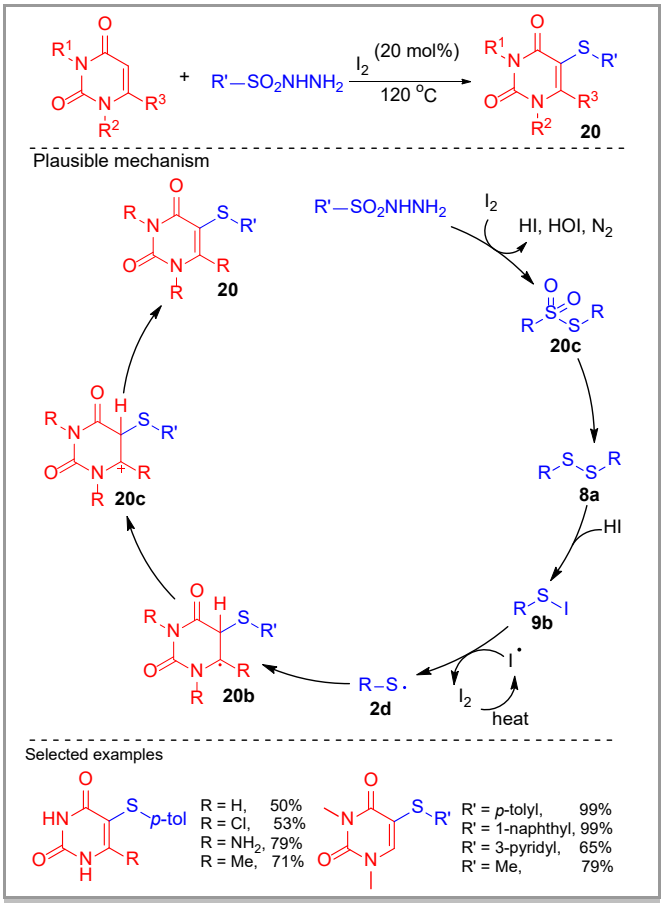
presence of TEMPO. In the proposed mechanism, sulfenyl iodide (**9b**), generated from the I_2-mediated deoxygenation, undergoes homolysis to form a thiyl radical (**2d**). This radical then attacks uracil, forming a radical intermediate (**20b**), which is subsequently oxidized by HOI and undergoes deprotonation to yield the desired product (**20**).



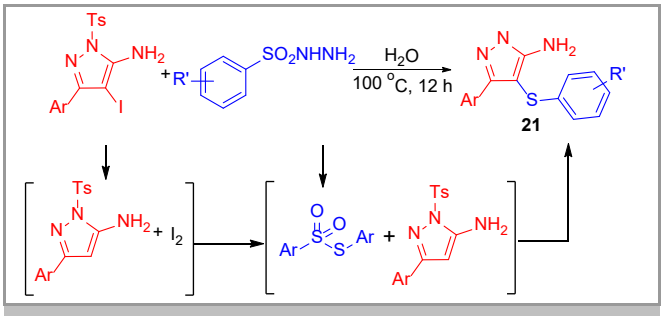
Scheme 22 I_2-catalyzed C5-thioetherification of aminouracils

Liu disclosed a C4-thioetherification of 4-iodine-1*H*-pyrazole-5-amine with sulfonyl hydrazine in water (Scheme 24).[51] Despite the presence of an iodo substituent, the reaction begins with the dehalogenation of the reactant under the reaction conditions, liberating I_2. This iodine is then used for the deoxygenation of sulfonyl hydrazine to form thiosulfonate, an active thiolating species for thioetherification, mimicking C-H functionalization mediated by I_2. The side-product, sulfinic acid, facilitates the deprotection of the tosyl group, yielding the desired thiolated product (**21**). A similar methodology can be applied to the thioetherification of 1*H*-pyrazole-5-amine by adding TBAI as an external iodine source.[52] Later, Liu reported that C3-thioetherification of 3-iodo-5-arylpyrazolo[1,5-*a*]pyrimidin-7-amine could also proceed via a similar mechanism.[53]

In 2020, Procter and co-workers described the use of trifluoromethyl sulfoxide for thiolating diverse (hetero)arenes (Scheme 25).[54] Under the reaction conditions, both halogenated and alkylated substrates could undergo trifluoromethylthiolation in moderate to good yields, a transformation that is rarely reported. The synthetic utility of this method was demonstrated through the late-stage functionalization of pharmaceutical and natural products. Based on mechanistic and computational studies, a plausible mechanism was proposed: the sulfoxide is activated by Tf_2O to generate intermediate **22a**, the active thiolating species. This is followed by an interrupted Pummerer reaction with the (hetero)arene to form a sulfonium salt (**22b**). The final product is obtained via base-promoted elimination of the R group. In 2021, Xing and co-workers reported a methylthiolation using DMSO and TsCl as the sulfoxide activator for the thioetherification of heteroarenes, following a similar mechanism.[55]



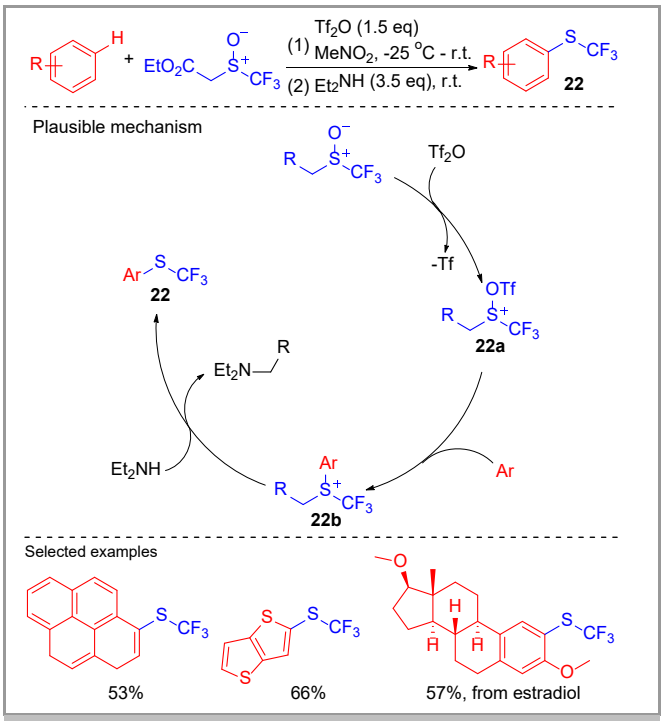
Scheme 23 I_2-catalyzed thioetherification of uracils under neat conditions



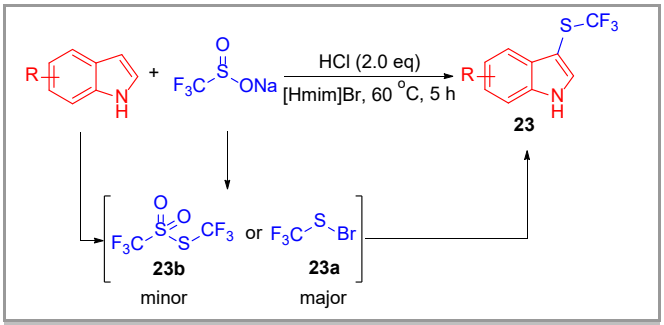
Scheme 24 C4-I thioetherification of 4-iodo-1*H*-pyrazole-5-amines in water

In 2021, Lin and co-workers developed a protocol for the trifluoromethylthiolation of indole using sodium sulfinate in an ionic liquid (Scheme 26).[56] Optimization studies revealed that the presence of Br^- from [Hmim]Br is crucial for the reaction, as the product yield decreased significantly when [Hmim]Cl or [Hmim]I was used instead. Under standard conditions, sodium sulfinate is primarily deoxygenated to form sulfenyl bromide

(**23a**) under heat and acidic conditions, with a minor pathway leading to the disproportionation into thiosulfonate (**23b**). Both **23a** and **23b** serve as active thiolating species, undergoing electrophilic substitution with indole to yield the desired product (**23**). Notably, the recyclability of the ionic liquid was demonstrated by running the experiment 10 times without significant loss of product yield.



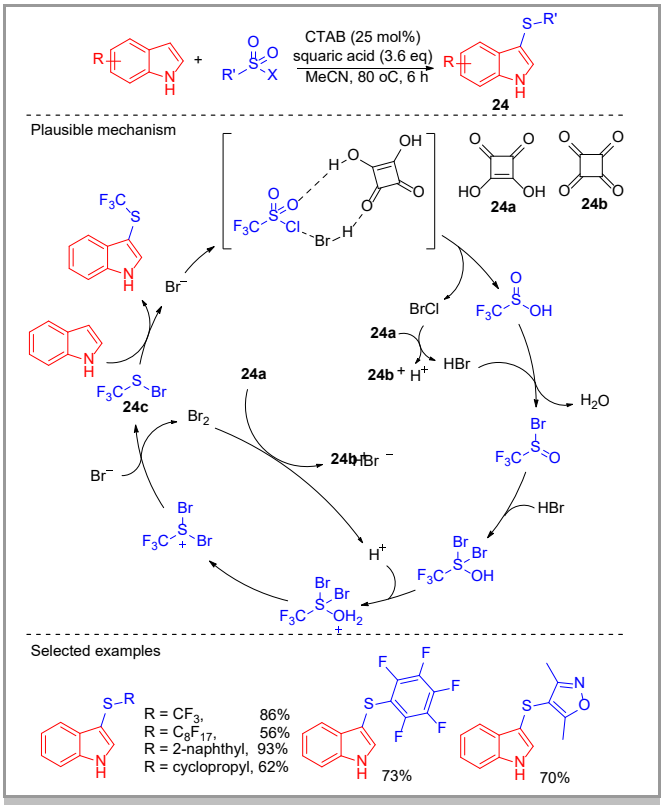
Scheme 25 Trifluoromethylthiolation of (hetero)arenes with trifluoromethyl sulfoxides



Scheme 26 Trifluoromethylthiolation of indoles in ionic liquid

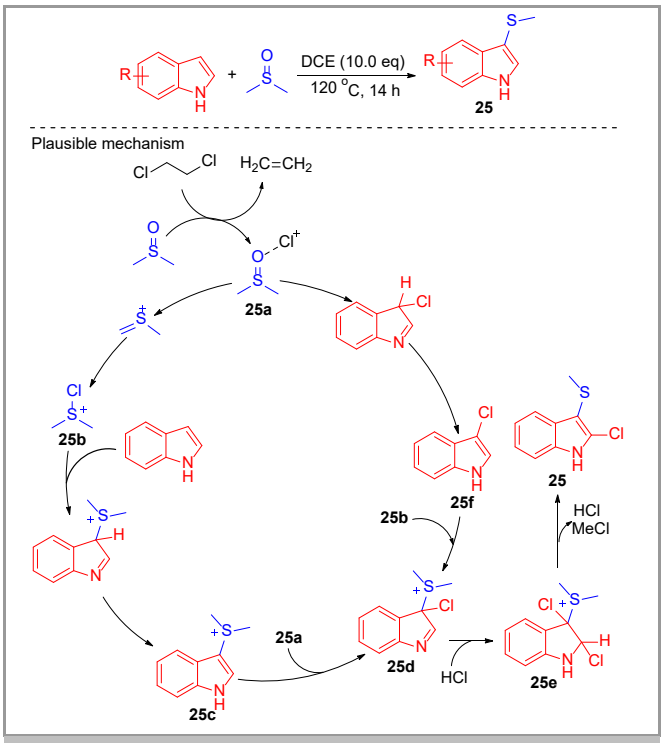
In 2022, Yi, Jiang, and co-workers reported a thioetherification method for heteroarenes using a squaric acid/bromide system (Scheme 27).[57] Based on control experiments and computational studies, squaric acid acts as a proton shuttle to facilitate the dehalogenation of sulfonyl chloride to sulfinic acid, which then undergoes further cascade deoxygenation to form sulfenyl bromide (**24c**), the active thiolating species for the thiolation of heteroarenes. This reaction demonstrates broad functional group tolerance, particularly in the preparation of polyfluoroalkylthiolated products.

In 2024, Panda and Palit described a direct chloromethylthiolation of indole using DMSO and DCE (Scheme 28).[58] Mechanistically, the reaction can proceed via two pathways. In pathway A, intermediate **25a**, formed from the reaction between DMSO and DCE, undergoes fragmentation to produce sulfonium chloride (**25b**). This intermediate then undergoes sequential electrophilic addition to indole, followed by aromatization to yield intermediate **25c**. Subsequently, **25c** can undergo electrophilic addition with **25a** to form sulfenium ion **25d**. Alternatively, **25d** can also be generated via a chloronium ion pathway, where dearomatization/ rearomatization leads to the formation of 3-chloroindole (**25f**), which then reacts with **24b** Finally, **24d** undergoes electrophilic addition with the chloronium ion, followed by the elimination of HCl, to yield the desired product (**25**).

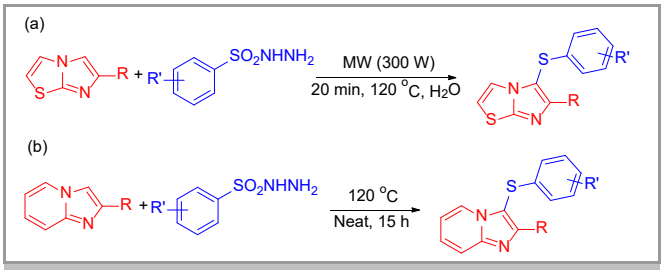


Scheme 27 Thioetherification of heteroarenes with squaric acid/Br^- system

Instead of using various external reductants to promote the deoxygenation process, disproportionation has also been found effective at high temperatures. In 2020, Liu and co-workers reported an additive-free, microwave-assisted thioetherification of imidazo[2,1-*b*]thiazoles in water (Scheme 29a).[59] Control experiments indicated that sulfonyl hydrazine undergoes disproportionation to efficiently produce thiosulfonate as the active thiolating agent under the reaction conditions. The use of microwave heating allows the reaction to be completed rapidly, within minutes. In 2022, Jana and co-workers reported a facile thioetherification of imidazoheteroarenes under neat, catalyst-free conditions by increasing the quantity of sulfonyl hydrazine to 2.2 equivalents (Scheme 29b).[60] These protocols offer a green strategy for efficiently accessing thiolated imidazoheteroarenes.

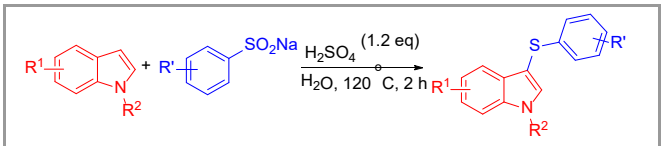


Scheme 28 Chloromethylthiolation of indoles with DMSO and DCE



Scheme 29 Reductant-free thioetherification of heteroarenes with sulfonyl hydrazines

In 2024, Zhang and co-workers disclosed an efficient and scalable protocol for preparing thiosulfonates using sodium sulfinate in water (Scheme 30).[61] Optimization studies revealed that under acidic conditions, particularly with H_2SO_4, sodium sulfinate undergoes disproportionation efficiently to yield thiosulfonates. The synthetic utility of this system was demonstrated by the direct preparation of C3-thiolated indole, showcasing its potential for practical applications in organic synthesis.

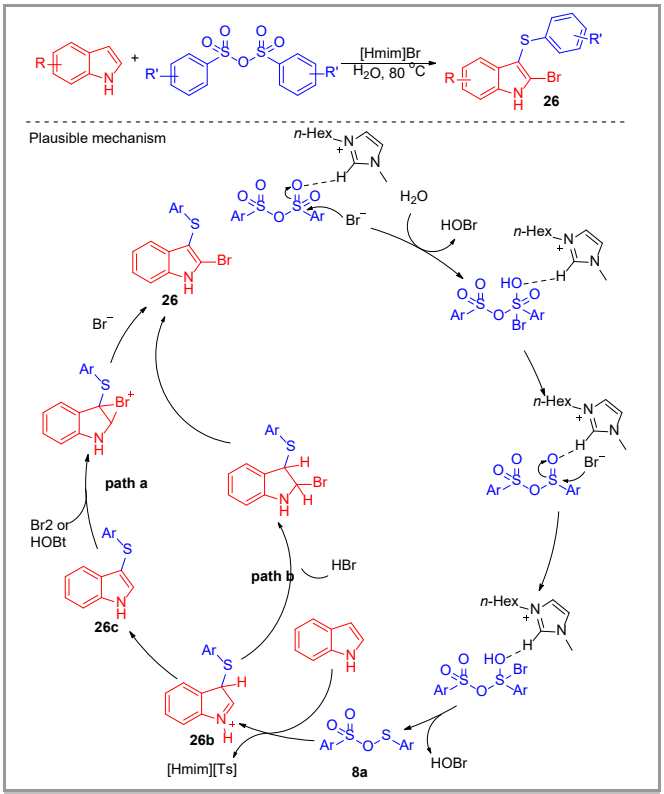


Scheme 30 Catalyst-free C3-H thioetherification of indoles under acidic conditions

In 2023, Shina and co-workers developed a sequential C-S and C-Br bond formation of (hetero)aryls using an ionic liquid with sulfonyl anhydride as the thiolate source (Scheme 31).[62] This transformation proceeds via the cascade activation of sulfonyl anhydride with the ionic liquid 1-hexyl-3-methylimidazolium bromide ([Hmim]Br) and deoxygenation through the elimination of HOBr to generate an intermediate. This intermediate then reacts with the heteroarene to afford the thiolate product (**26c**) via intermediate **26b**. In the presence of water, the bromo-thiolated product (**26**) can be obtained either through electrophilic substitution by Br_2 or HOBr, resulting from the dimerization of [Hmim]Br_2 (path a), or through nucleophilic addition of Br^- to **26b** (path b). This protocol provides a green and efficient method for a switchable cascade thiolation-halogenation reaction via temperature control. Unlike their previous report,[63] the use of sulfonyl anhydride prevents chlorination, yielding only the brominated product during the halogenation process.

3.2 C(sp²/sp)-H activation of unsaturated hydrocarbons

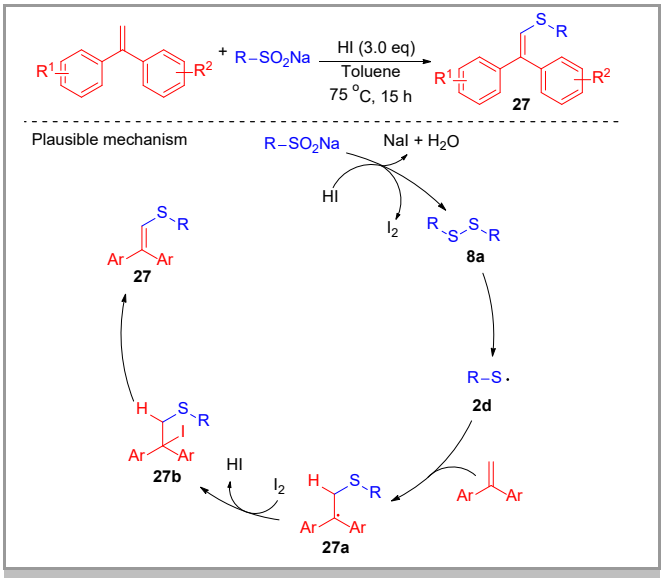
In 2020, Jiang and co-workers synthesized a series of 1,1-diphenylvinylsulfides as novel aggregation-induced emission luminogens (AIEgens) through C(sp²)-H thioetherification with sodium sulfinate (Scheme 32).[64] The incorporation of the thioether unit helps to weaken π-π stacking interactions between molecules by extending the conjugation. In this transformation, the deoxygenation of sodium sulfinate is facilitated by HI, generating a thiyl radical (**2d**) via a disulfide intermediate (**9a**). The thiyl radical **2d** undergoes radical addition with diphenylene, forming a radical intermediate (**27a**), which then couples with I_2 and undergoes sequential elimination of HI to yield the desired product (**27**).



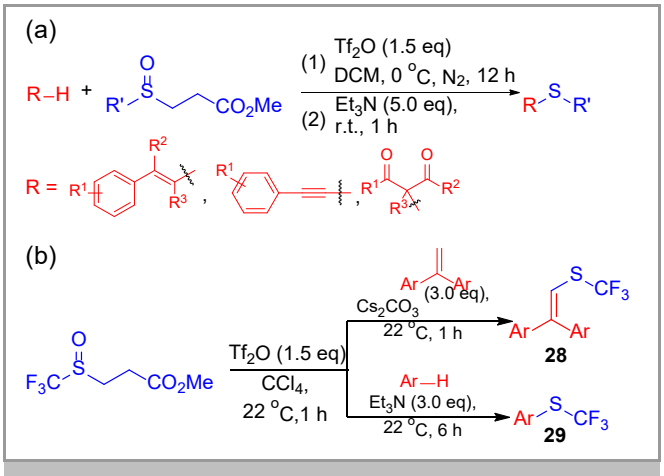
Scheme 31 Thioetherification/Bromination of indoles in ionic liquid

Later, in 2021, Cheng and co-workers reported a direct C-H thioetherification using β-sulfinylester as a thiol surrogate for alkenes, alkynes, and 1,3-dicarbonyl compounds (Scheme 33a).[65] Control experiments suggested that this transformation

proceeds via a retro-Michael reaction, as ethyl acrylate was successfully trapped via Heck coupling. In 2023, Shao and co-workers reported a trifluoromethylthiolation of 1,1-diphenylethylene and electron-rich arenes using β-trifluorosulfinylester (Scheme 33b).[66] This reaction could be scaled up to gram scale without significantly affecting product yield, and late-stage functionalization on bioactive molecules proceeded smoothly, demonstrating the high synthetic utility of this protocol. A plausible mechanism, based on control experiments, was proposed: the reaction is initiated by a Tf_2O-promoted interrupted Pummerer reaction to generate a sulfonium salt, which can be captured by styrene or an electron-rich arene. In the presence of a base, the desired product (**28** or **29**) is obtained through the elimination of the methyl ester.



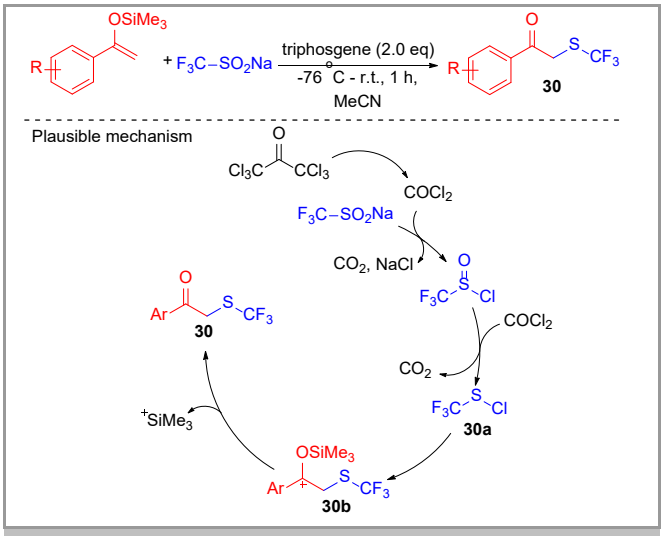
Scheme 32 C(sp²)-H thioetherification of 1,1-diphenylethene with sodium sulfinates



Scheme 33 Thioetherification with β-sulfinylesters

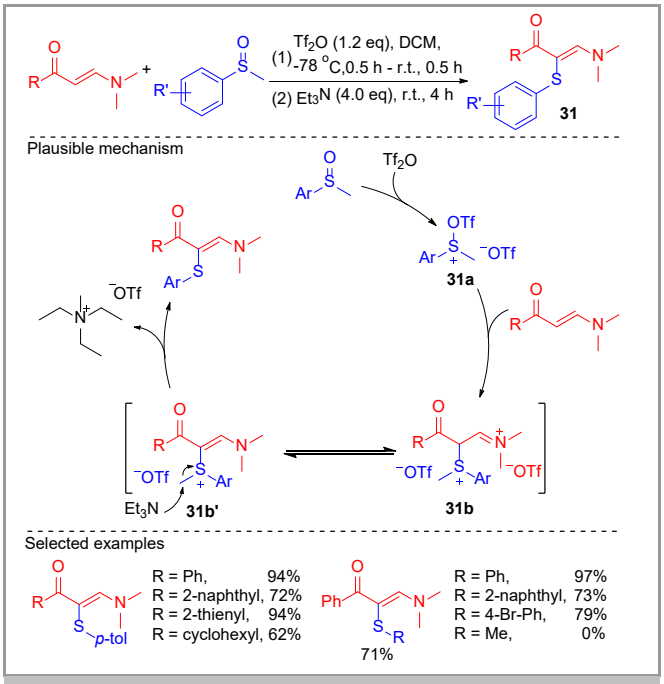
Guo and co-workers developed a thioetherification protocol for silylenol ethers using sodium sulfinate and triphosgene (Scheme 34).[67] Mechanistically, the reaction is initiated by the extrusion of phosgene, generated from the decomposition of triphosgene, which deoxygenates sodium sulfinate to form sulfenyl chloride (**30a**), the active thiolating species. Electrophilic addition of **30a** across the silylenol ether occurs, forming intermediate (**30b**), which then transforms into the desired product (**30**) through the elimination of the TMS group. Under these reaction conditions, thioetherification of electron-rich heteroarenes can also proceed efficiently. Despite its effectiveness, the use of highly toxic phosgene and the requirement for extremely low reaction temperatures (-78 °C) increase the operational complexity of this protocol.

In 2022, Zhang and co-workers reported a C(sp²)-H thioetherification of enaminones using methyl sulfoxide as a sulfur surrogate (Scheme 35).[68] Mechanistically, methyl sulfoxide is first activated by Tf_2O to form sulfonium salt **31a**, which acts as the active thiolating agent. This sulfonium salt then attacks the enaminone to generate intermediate **31b**, which undergoes rapid tautomerization to form alkenylsulfonium salt (**31b'**). The final product (**31**) is obtained through an S_N2-based demethylation between Et_3N and **31b'**. A similar system was reported by Rong and Qian for the direct C(sp)-H thioetherification of terminal alkynes using methyl sulfoxide.[69]

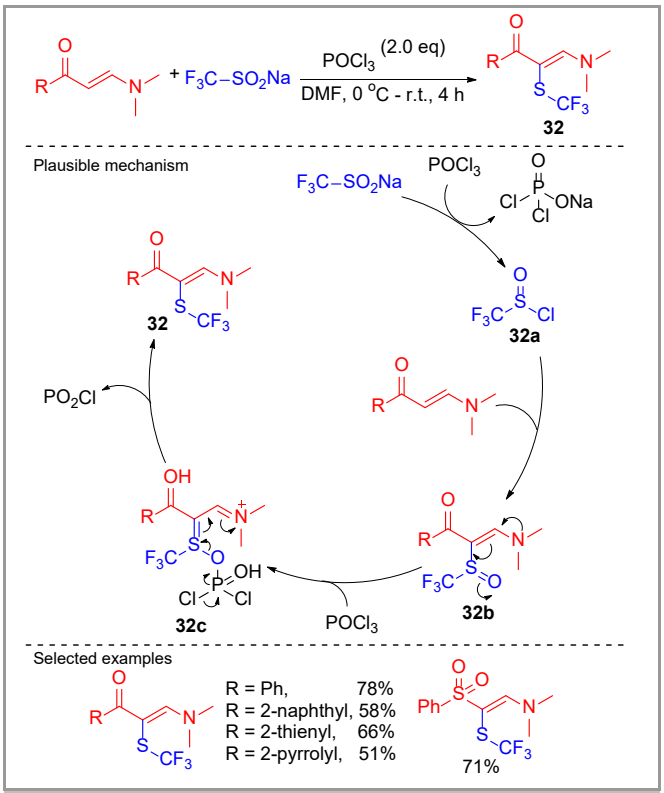


Scheme 34 Triphosgene-promoted thioetherification of silylenol ethers with sodium sulfinates

In 2024, Wan and co-workers developed a trifluoromethylthioetherification of enaminones using sodium sulfinate (Scheme 36).[70] In this process, $POCl_3$ is employed as a reducing agent to form sulfinyl chloride (**32a**), which undergoes electrophilic substitution with the enaminone to generate intermediate (**32b**). This intermediate then undergoes nucleophilic substitution with $POCl_3$, transforming into intermediate **32c**. A subsequent redox process leads to the formation of the desired product (**32**) with the elimination of sodium phosphonate. This protocol also demonstrated applicability in the trifluoromethylthiolation of ketene dithioacetals.



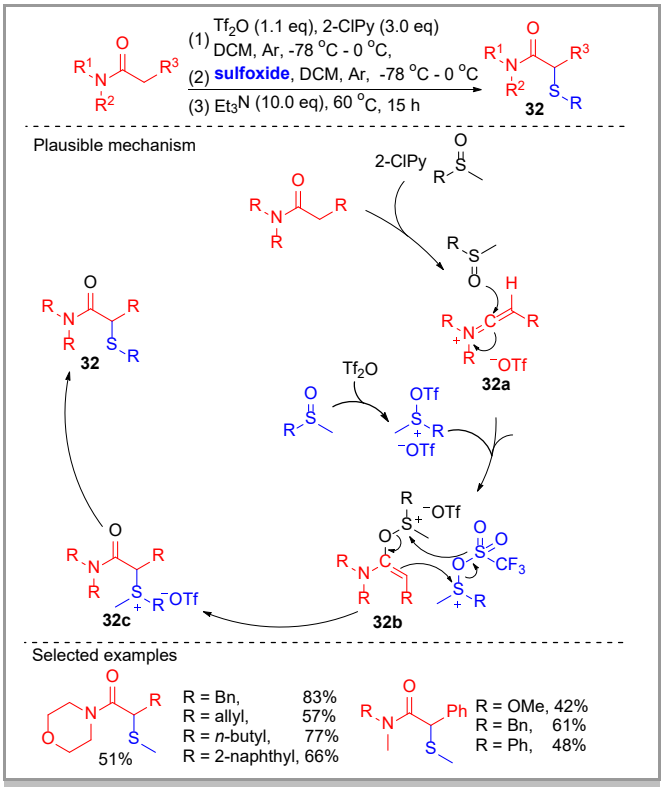
Scheme 35 Thioetherification of enaminones with methyl sulfoxides and Tf_2O



Scheme 36 Trifluoromethylthiolation of Enaminones with sodium sulfinates

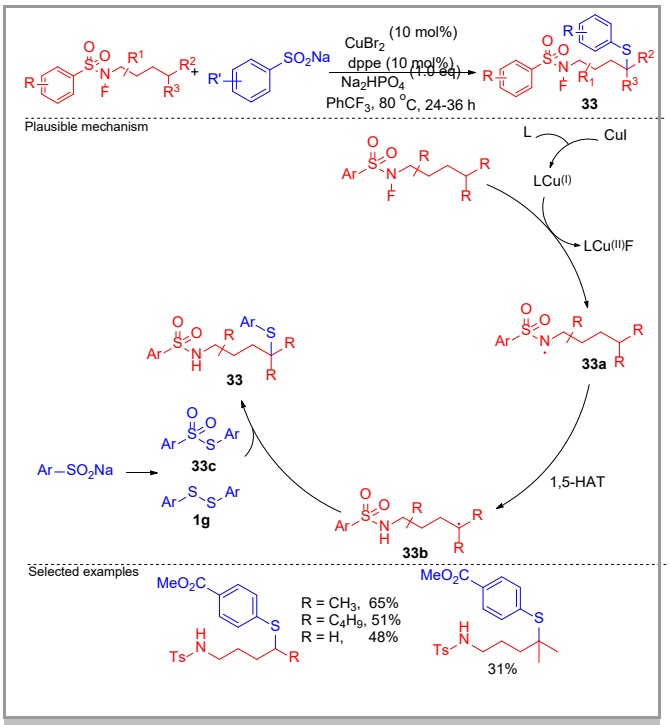
3.3 C(sp³)-H activation

In 2020, Movassaghi and co-workers disclosed an α-thioetherification of benzylic amides using sulfoxide as a thiol surrogate (Scheme 37).[71] An isotopic labeling experiment with a 1:1 mixture of DMSO and DMSO-^{18}O-d_6 suggested that the reaction proceeds via an intermolecular thioetherification process, as evidenced by the detection of a crossover sulfonium ion in mass spectrometry (MS). This finding supports the proposed mechanism involving the formation of a sulfonium intermediate, highlighting the intermolecular nature of the thioetherification. Based on isotopic labeling results and computational studies, a plausible mechanism was proposed for the reaction. The process begins with the activation of the amide by the combination of Tf_2O and 2-chloropyridine, generating a keteniminium intermediate (**32a**). This intermediate reacts with the sulfoxide to form an oxysulfonium intermediate (**32b**). The sulfonium moiety is then transferred from the activated sulfoxide to **32b** via a cyclic transition state, generating intermediate **32c**. This is followed by demethylation to yield the desired product (**32**). This protocol demonstrates broad functional group tolerance for preparing α-thiolated amides. However, the requirement for repetitive cooling of the reaction to -78 ℃ increases operational complexity and reduces system robustness.



Scheme 37 Thioetherification of amides with sulfoxides

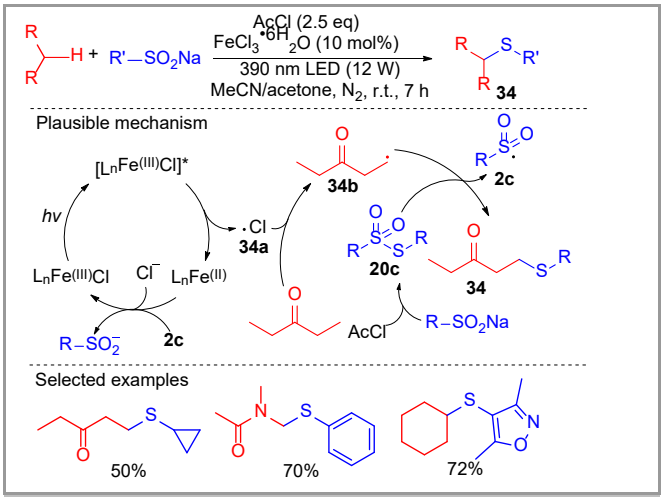
In 2021, Liu and co-workers developed a Cu-catalyzed regioselective distal thioetherification of C(sp³)-H bonds using *N*-fluorosulfonamide (Scheme 38).[72] Mechanistically, a single electron transfer (SET) process between the Cu catalyst and *N*-fluorosulfonamide generates a radical intermediate (**33a**) which undergoes a 1,5-HAT process produce an alkyl radical (**33b**). Concurrently, due to the slow generation rate of **33a**, sodium sulfinate is transformed into thiosulfonate (**33c**) and disulfide (**1g**) through cascade deoxygenation and disproportionation. The desired thioether (**33**) is then obtained through the reaction of **33c** and **1g** with the alkyl radical **33b**.



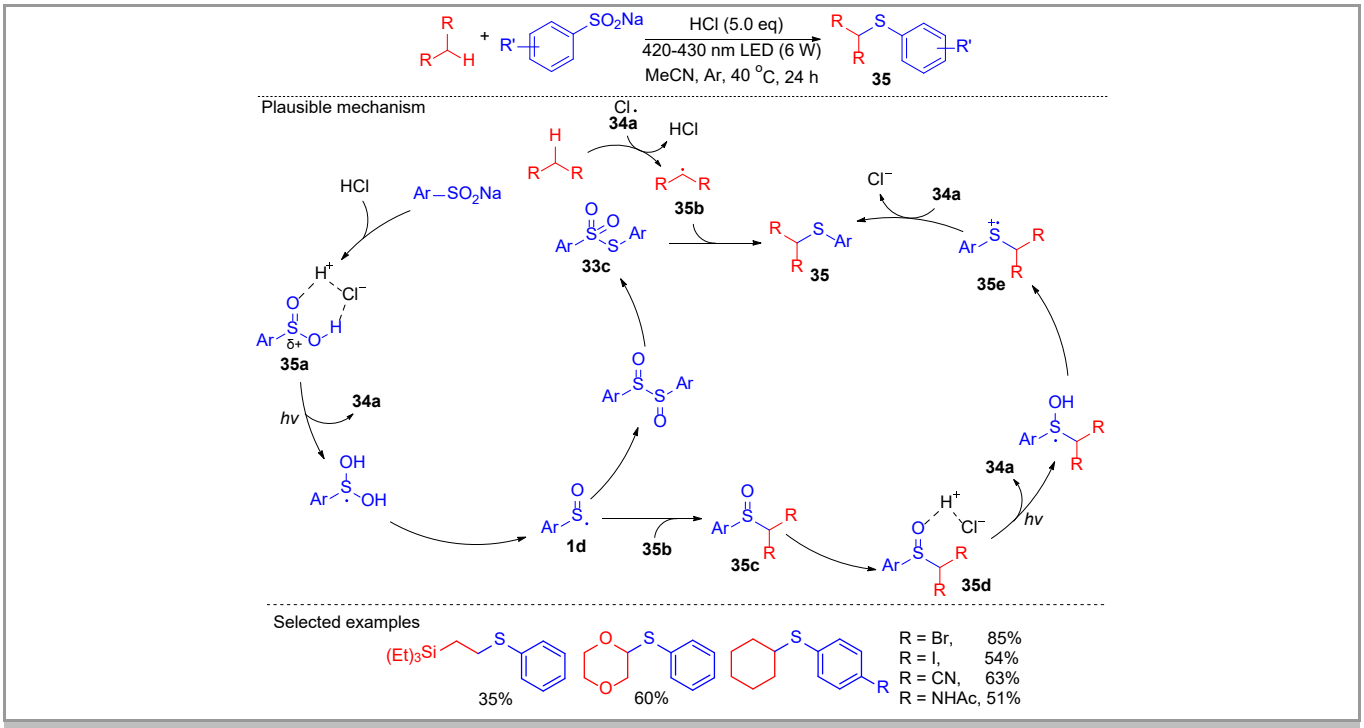
Scheme 38 Cu-catalyzed *N*-directed distal C(sp^3)-H thioetherification

In 2023, Xia and co-workers developed a C(sp^3)-H functionalization strategy for forming C-B and C-S bonds under photoirradiation (Scheme 39).[73] This protocol is notable for its broad functional group tolerance, allowing access to aryl-alkyl and dialkyl thioethers in moderate to excellent yields. Additionally, with minor adjustments to the reaction conditions, sulfoxides could also be prepared. Mechanistically, the process begins with the activation of an alkane by a chloride radical (**34a**), generated from the ligand-to-metal charge transfer (LMCT) process of [$Fe^{(III)}$]* in conjunction with $Fe^{(II)}$, to form a C-centered radical species (**34b**). Concurrently, sodium sulfinate is activated by acetyl chloride and undergoes disproportionation to produce thiosulfonate (**20c**) as the active thiolating species. The thiosulfonate is then trapped by the C-centered radical **34b** to afford the thioether (**34**), releasing a sulfonyl radical (**2c**) that oxidizes $Fe^{(II)}$ back to $Fe^{(III)}$, completing the catalytic cycle. In 2024, Xia reported that a similar transformation could be achieved using decatungstate as a photocatalyst.[74]

In 2024, Shi and co-workers described a photo-induced, catalyst-free C(sp^3)-H functionalization via an electron donor-acceptor (EDA) complex to construct thioethers (Scheme 40).[75] The reaction proceeds without a catalyst, initiated by the formation of an EDA complex (**35a**) between sodium sulfinate and HCl, which generates a sulfoxide radical (**1d**). This radical can either undergo disproportionation to form thiosulfonate (**33c**) or be directly captured by an alkyl radical (**35b**) to form a sulfoxide intermediate (**35c**). The intermediate **35c** can also form an EDA complex (**35d**) with HCl, promoting deoxygenation to yield a radical cation intermediate (**35e**). This intermediate undergoes a subsequent SET process with a chloride anion to afford the desired product (**35**).

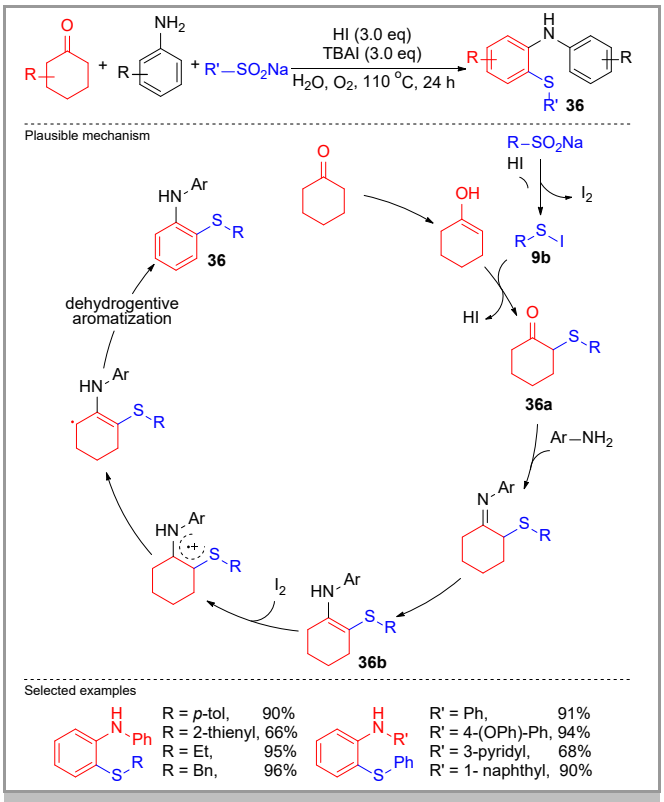


Scheme 39 Photo-induced Fe-catalyzed thioetherification of C(sp^3)-H of alkanes



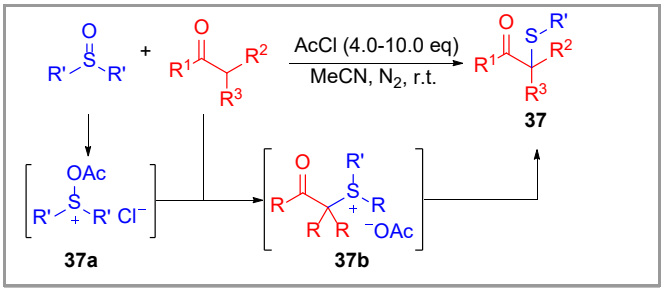
Scheme 40 Photo-induced catalyst-free C(sp3)-H functionalization for thioether synthesis

In 2023, Wu and co-workers reported the synthesis of *o*-sulfanylaniline via a three-component reaction involving a primary amine, cyclohexanones, and sodium sulfinate, proceeding through cascade thioetherification and dehydroaromatization (Scheme 41).[76] Control experiments showed that *o*-sulfanylcyclohexanone (**36a**) could be obtained in excellent yield in the absence of a primary amine under standard conditions. Mechanistically, the process begins with HI-mediated deoxygenation of sodium sulfinate to generate sulfenyl iodide (**9b**) as the active thiolating source. This is followed by nucleophilic substitution between **9b** and the *enol*-tautomer of cyclohexanone. The resulting **36a** then undergoes sequential condensation with aniline and tautomerization to form an enamine intermediate **36b**. The final product (**36**) is obtained through a cascade involving single-electron oxidation by I_2, deprotonation, and dehydroaromatization.



Scheme 41 Cascade three-component reaction towards *o*-sulfanylanilines

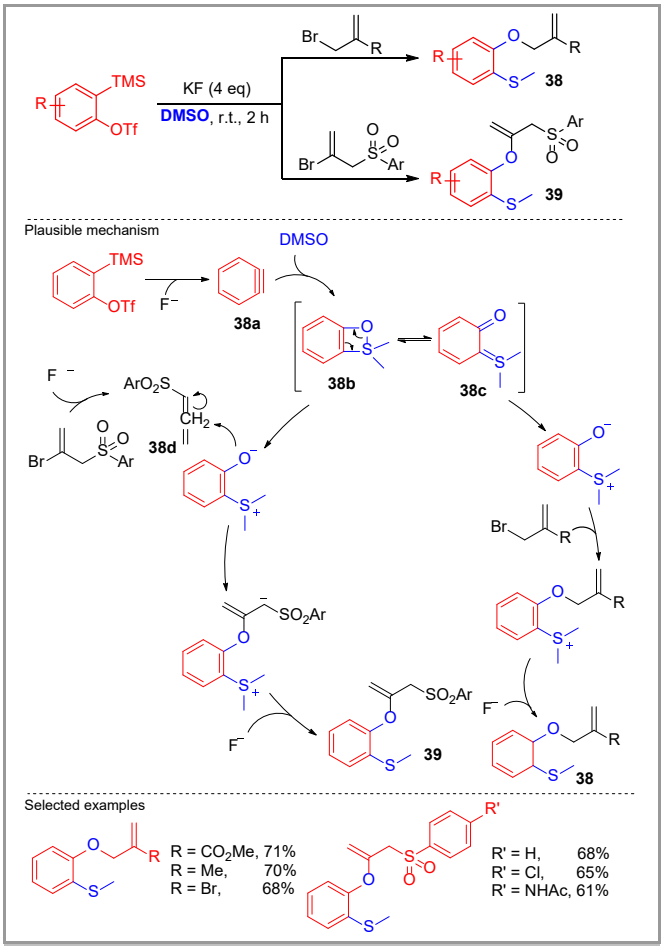
In 2021, Liu and co-workers disclosed a thioetherification reaction for activated C(sp^3)-H of carbonyl compounds, including β-dicarbonyl, β-ketophosphonate, and β-ketonitrile, using sulfoxide as the thiolating source (Scheme 42).[77] In this reaction, the sulfoxide is first activated by acetyl chloride to form a sulfonium salt (**37a**), which then undergoes electrophilic addition and deprotonation with the enol tautomer of the carbonyl compound to generate intermediate **37b** and HCl. The target product (**37**) is formed via the nucleophilic attack of excess sulfoxide on **37b**. However, the reaction exhibits low atom economy, as it requires at least 8.0 equivalents of sulfoxide and 4.0 equivalents of acetyl chloride to achieve good yields.



Scheme 42 Thioetherification of activated C(sp^3)-H with sulfoxides

4. Hydro/halo/oxy-thiolation of unsaturated hydrocarbons

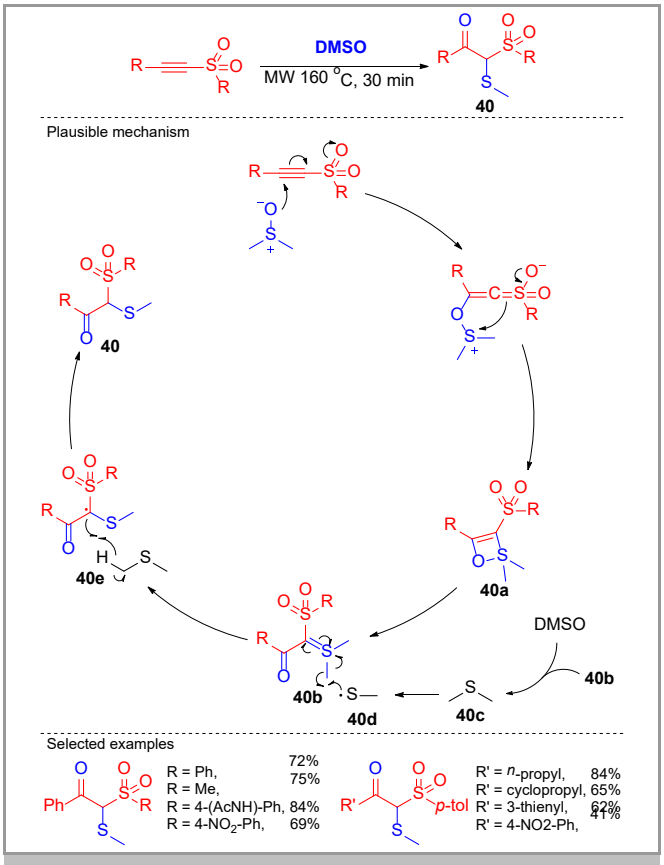
In 2020, Hazarika and Gogoi disclosed a three-component reaction involving aryne, activated alkene, and DMSO to synthesize *o*-methylthio allyl/vinyl arylethers (Scheme 43).[78] The reaction begins with the formation of aryne (**38a**) through KF-promoted 1,2-elimination of *o*-silyl aryl triflate. This aryne then inserts into DMSO, generating a four-membered intermediate **38b**, which undergoes ring opening to form a quinone intermediate (**38c**). The desired allyl ether (**38**) s obtained through sequential nucleophilic attack of **38c** on the activated alkene, followed by demethylation. Similarly, the vinyl ether (**39**) is formed by the nucleophilic attack of **38c** on an in-situ generated allene (**38d**), leading to a zwitterionic intermediate (**38e**), which then undergoes demethylation to yield the final product.



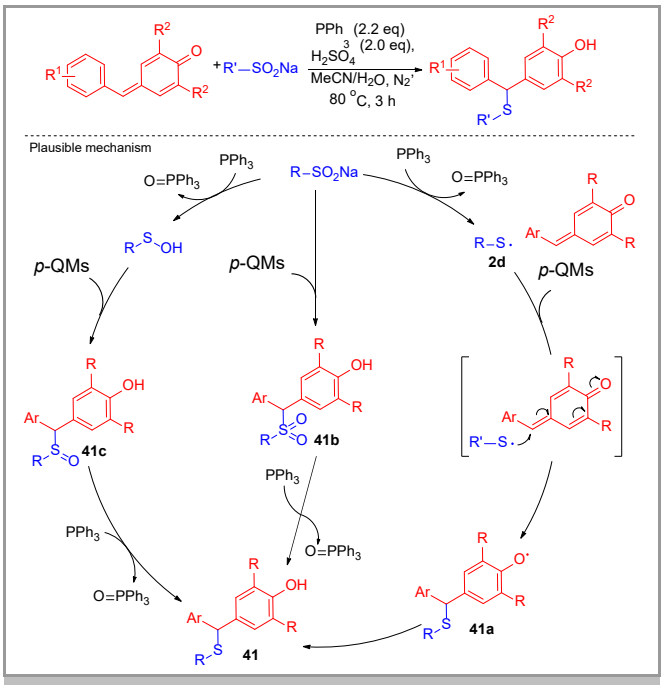
Scheme 43 Three-component reaction to access *o*-methylthio allyl/vinyl ethers

In 2021, Xu and co-workers developed a 1,2-oxothioetherification of acetylenic sulfone under microwave heating (Scheme 44).[79] The reaction proceeds through a cascade mechanism starting with the nucleophilic attack of DMSO on the alkyne, leading to the formation of a four-membered ring intermediate (**40a**). This intermediate undergoes ring-opening to form a sulfonium ylide intermediate (**40b**). Subsequently, dimethyl sulfide (**40c**) is generated from the decomposition of DMSO, which then dissociates into a methylthiyl radical (**40d**). The radical attack of **40d** on **40b** generates a C-centered radical intermediate (**40e**), which undergoes a HAT process with **40d** to afford the desired product (**40**).

In 2021, Wong and co-workers disclosed a H_2SO_4/PPh_3-induced thioetherification using sodium sulfinate and *p*-quinone methides (*p*-QMs) (Scheme 45).[80] Radical-trapping experiments with 2.0 equivalents of TEMPO showed that the formation of product **41** was completely hindered, and the thiyl radical (**2d**) was trapped and detected by GC-MS. The proposed mechanism suggests that the thiyl radical (**2d**) is generated from the cascade deoxygenation of sodium sulfinate in the presence of PPh_3 and acid. This radical then adds to *p*-QMs, forming a radical intermediate (**41a**), which undergoes a HAT process to yield the desired 1,6-conjugate addition product (**41**). Additionally, the desired product **41** can also be formed via a minor pathway involving the direct reaction with sulfinic acid or sulfanol to generate sulfonyl (**41b**) or sulfinyl intermediate **(41c)**, followed by deoxygenation.

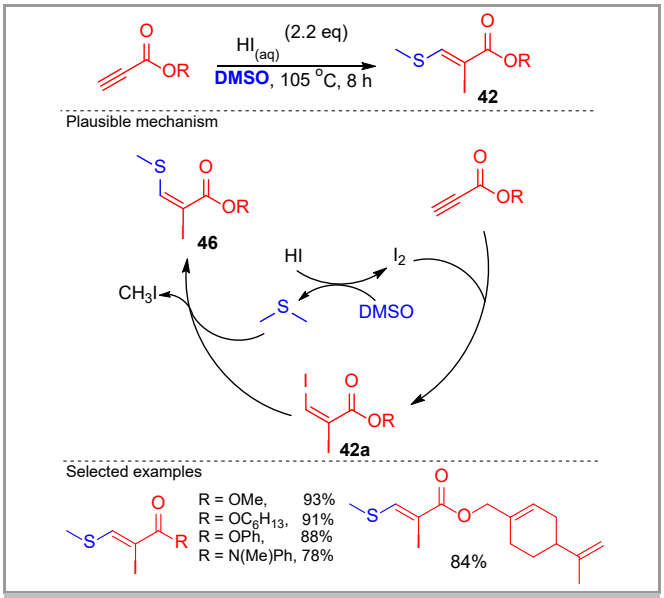


Scheme 44 Microwave-assisted 1,2-oxosulfenylation of acetylenic sulfones



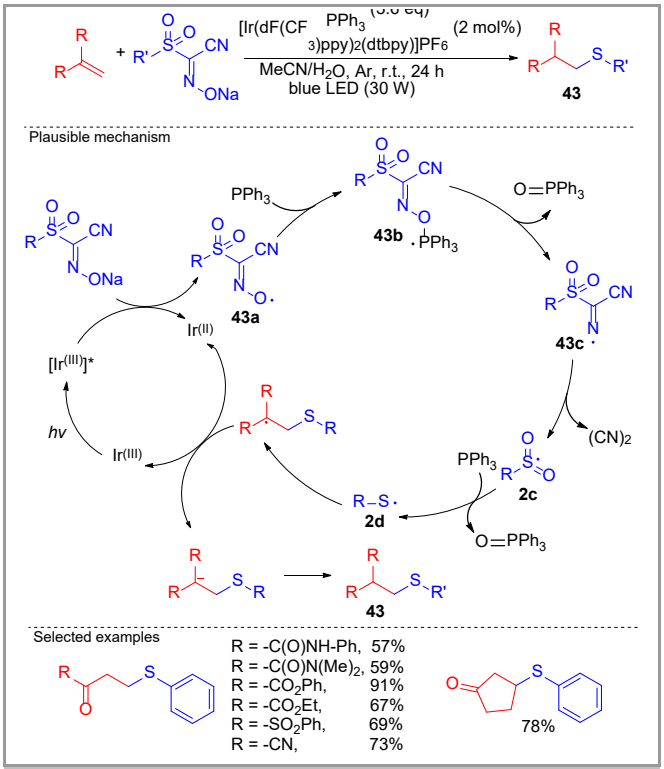
Scheme 45 PPh_3/H_2SO_4-induced thioetherification of *p*-QMs with sodium sulfinates

In 2021, Wu and co-workers reported an iodo-methylthiolation protocol for electron-deficient alkynes to synthesize *(E)*-2-iodo-3-(methylthio)acrylates using DMSO and HI (Scheme 46).[81] Under the reaction conditions, a variety of natural products were well tolerated, achieving good to excellent yields and demonstrating high functional group tolerance. According to the proposed mechanism, the reaction involves HI-promoted deoxygenation of DMSO to generate dimethyl thioether as the active thiolating species and I_2. The I_2 then adds to ethyl propiolate to form a diiodoacrylate intermediate (**42a**), which subsequently reacts with the generated dimethyl sulfide to yield the desired product (**42**). This transformation has demonstrated good scalability up to 30 mmol and allowed the late-stage modification of complicated alkyne.



Scheme 46 Iodo-methylthiolation of electron-deficient alkynes

Sulfonyl oxime has been widely used as a synthetic synthon in radical chemistry due to the good leaving group propensity of the sulfonyl group, allowing for the preparation of diverse oxime derivatives via radical addition processes.[82] In 2024, Yang and co-workers described the first photocatalytic anti-Markovnikov hydrothiolation of electron-deficient alkenes using sulfonyl oxime as a thiolating source under phosphine mediation (Scheme 47).[83] In this transformation, a SET process occurs between the sulfonyl oxime anion and the excited $[Ir^{III}]^*$ complex, generating reduced $[Ir^{II}]$ and a sulfonyl oxime radical (**43a**), which is then trapped by PPh_3 to form a phosphoranyl radical (**43b**). This is followed by β-scission of the N-O bond and fragmentation to release cyanogen, generating a sulfonyl radical (**2c**). This radical is converted to a thiyl radical (**2d**) via cascade deoxygenation with excess PPh_3. Upon radical addition of **2d** to the alkene, a radical intermediate (**43c**) is formed. This intermediate is then reduced by $[Ir^{II}]$ and undergoes subsequent protonation to yield the desired product (**43**). This protocol is the first to employ sulfonyl oxime as a thiyl radical precursor, thereby broadening the synthetic utility of sulfonyl oxime.



Scheme 47 Photocatalytic hydrothiolation of alkenes with sulfonyl oximes

5. Conclusion

In conclusion, oxygenated sulfur compounds, such as sulfinates, sulfonyl derivatives, sulfur oxyacid derivatives, and sulfoxides, serve as ideal thiol surrogates due to their cost-effectiveness, commercial availability, and stability. This review has focused on recent advancements in thioether synthesis using these oxygenated sulfur surrogates, categorized by reaction type, including coupling, C-H activation, and thiolation of unsaturated hydrocarbons. We have also highlighted the reaction mechanisms of various protocols. Given the widespread importance of thioether motifs across diverse research fields,

we anticipate the development of more efficient, and environmentally friendly thioetherification protocols. We hope this review will contribute to the continued growth and innovation in sulfur chemistry.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

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Biosketches

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