

Copper-Catalyzed C–F Bond Functionalization of Polyfluoroarenes for C–S Bond Formation: Mechanistic Insights, Synthetic Strategies, Regioselectivity and Future Perspectives

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ABSTRACT

Carbon–fluorine (C–F) bonds are among the strongest and most chemically inert single bonds in organic chemistry. However, their selective cleavage has emerged as a powerful strategy for the late-stage functionalization of fluoroarenes, which serve as critical structural motifs in pharmaceuticals, agrochemicals, and advanced materials. Among transition-metal catalysts, copper provides a highly attractive, low-cost, and sustainable platform for constructing carbon–sulfur (C–S) bonds through the activation and substitution of C–F bonds in electron-deficient fluoroarenes. This review comprehensively summarizes the development of copper(I)-mediated and -catalyzed defluorinative functionalizations leading to C–S bond formation. We highlight the utility of diverse sulfur sources—including thiols, thiolates, disulfides, and thioacetates—and evaluate the critical roles of ligands, bases, solvents, and oxidants in modulating reactivity. Special attention is dedicated to the factors governing regioselectivity and the underlying mechanistic pathways, specifically distinguishing between conventional nucleophilic aromatic substitution (S_NAr) and transition-metal-assisted pathways such as oxidative addition/reductive elimination, copper–thiolate intermediates, and single-electron transfer (SET). Finally, we discuss current limitations and outline future opportunities in the field, including the catalytic activation of mono- and difluoroarenes, ligand-controlled selectivity, photocatalytic and electrochemical copper chemistry, heterogeneous catalysis, and applications in materials science.

Keywords: Copper catalysis; C–F bond activation; C–S bond formation; Polyfluoroarenes; Thiolation; Regioselectivity; Defluorinative functionalization; Reaction mechanisms.

INTRODUCTION

The construction of carbon–sulfur (C–S) bonds constitutes a cornerstone of modern synthetic organic chemistry. Organosulfur motifs such as diaryl, aryl alkyl, and heteroaryl sulfides—are ubiquitous features in biologically active compounds, functional materials, coordination ligands, and clinical pharmaceuticals. Consequently, developing efficient, sustainable, and highly selective methodologies to access these architectures remains a priority. Traditional protocols for synthesizing aryl sulfides typically rely on the nucleophilic aromatic substitution (S_NAr) of activated aryl halides or transition-metal-catalyzed cross-couplings utilizing precious metals like palladium. Over the past few decades, copper catalysis has emerged as a premier alternative to noble metals due to its low cost, abundance, low toxicity, and versatile redox chemistry Cu(I)/Cu(II)/Cu(III), which enables a wide array of radical and ionic pathways. While cross-couplings with aryl iodides, bromides, and activated chlorides are well-established, utilizing aryl fluorides as electrophilic coupling partners presents distinct challenges and opportunities. The C–F bond is characterized by exceptionally high bond dissociation energy and significant polarization. While the strong affinity of fluorine for electropositive metal centers can facilitate metal-assisted activation, the inertness of the C–F bond generally precludes traditional cross-coupling pathways. However, polyfluoroarenes occupy a unique niche: the cumulative electron-withdrawing effect of multiple fluorine substituents strongly depletes the electron density of the aromatic ring, rendering specific positions highly susceptible to nucleophilic attack.

This electronic landscape turns an otherwise inert C–F bond into a versatile, programmable handle for regioselective functionalization.

Early milestones demonstrated the viability of leveraging copper to drive C–S bond formation via C–F bond cleavage in highly fluorinated systems. In 2012, Zhou and co-workers reported a regioselective C–S bond-forming protocol that coupled electron-deficient perfluoroarenes with aryl or benzyl thioacetates using a CuBr/L-proline catalytic system, delivering polyfluoroaryl thioethers under mild conditions with excellent functional group tolerance.¹⁵ Concurrently, Yu, Zhang, and Shi demonstrated the direct thiolation of pentafluorobenzene using diaryl disulfides or aryl thiols via a tandem C–H and C–F bond activation strategy.¹⁶ Controlled by a CuBr alkoxide system in DMSO under an oxygen atmosphere, this approach yielded bisarylthiolation products, while the addition of 1,10-phenanthroline and DDQ successfully shifted the pathway toward monoarylthiolation.¹⁶

These pioneering studies validated the concept that C–F bonds in polyfluoroarenes can be strategically exploited for targeted C–S bond construction. This review details the synthetic evolution, diverse sulfur reagent scopes, regioselective nuances, and competing mechanical pathways of copper-catalyzed defluorinative thiolation, concluding with a forward-looking analysis of next-generation catalytic paradigms.

Why C–F Bond Activation is Challenging

Bond Strength and Polarization

The C–F bond is strongly polarized toward fluorine and has high bond dissociation strength. In aromatic systems, activation is further influenced by the electronic structure of the ring. Direct oxidative addition of an isolated aryl C–F bond is substantially more difficult than activation of many C–Cl, C–Br, or C–I bonds. The challenge becomes especially severe as the number of fluorine substituents decreases. Reviews of transition-metal C–F activation consistently emphasize the importance of both thermodynamics and kinetics, as well as competition between C–F and C–H activation.

Why Poly fluoroarenes are Different

Polyfluoroarenes are activated substrates rather than simply highly fluorinated versions of ordinary fluoroarenes. Several fluorine atoms lower the electron density of the ring and stabilize the anionic character that develops during nucleophilic aromatic substitution. Consequently, nucleophilic attack can occur at selected carbon atoms followed by fluoride elimination. This is the mechanistic basis for many successful thiolation reactions. By contrast, mono- and difluoroarenes frequently lack sufficient activation for ordinary S_NAr and may require fundamentally different catalytic or radical strategies.

Thermodynamic Versus Kinetic Control

The fundamental obstacle to activating the carbon–fluorine bond resides in its thermodynamic stability. The bond dissociation energy (BDE) of an aryl C–F bond is exceptionally high (~130 kcal/mol), vastly exceeding that of aryl C–I (~65 kcal/mol), aryl C–Br (~80 kcal/mol), and aryl C–Cl (~96 kcal/mol). Additionally, the extreme electronegativity of fluorine induces a highly polarized (C^{δ+}–F^{δ-}) bond, resulting in a short bond length (~1.35 Å) and a high electrostatic barrier that resists conventional transition-metal oxidative addition.

In highly fluorinated aromatic systems, the cumulative inductive effect of multiple fluorine atoms fundamentally alters the electronic landscape. The sum of Hammett substituent constants (sum of σ_m) and (σ_p) for polyfluorinated rings induces a severe lowering of the lowest unoccupied molecular orbital (LUMO), making the ring highly susceptible to nucleophilic attack. As a result, C–F functionalization in these platforms can proceed via multiple competing pathways: classical or transition-metal-assisted nucleophilic aromatic substitution (S_NAr), single-electron transfer (SET), or true organometallic oxidative addition.

Therefore, the term "C–F activation" must be used with strict mechanistic precision within copper catalysis. Productive defluorinative thiolation does not inherently imply direct insertion of the copper center into the C–F bond; rather, it often represents a cooperative process where the transition metal modulates the nucleophilicity of the sulfur partner or stabilizes transient highly reactive states.

Scope And Classification of the Chemistry

The literature can be organized into four operational categories: (i) direct S_NAr of polyfluoroarenes by sulfur nucleophiles; (ii) copper-assisted nucleophilic substitution in which copper activates or organizes the sulfur reagent and/or substrate; (iii) copper catalytic cycles involving organocopper intermediates and possible higher oxidation states; and (iv) radical or photochemical processes in which copper participates in single-electron transfer or radical capture. These categories overlap, but they should not be presented as interchangeable.

A practical criterion is catalytic turnover. If a stoichiometric amount of copper merely generates thiolate and the same product forms efficiently without copper, the transformation is better described as S_NAr with copper assistance rather than definitive Cu-catalyzed C–F activation. If removal of copper strongly suppresses reaction, ligand identity changes activity or selectivity, and copper-containing intermediates are supported by spectroscopy or computation, a catalytic copper role becomes more convincing.

Sulfur Sources for C–F-To-C–S Functionalization

Thiols and Thiolates

Thiols are chemically direct sulfur nucleophiles. Under basic conditions they can be converted into thiolates, which are substantially more nucleophilic toward electron-deficient fluoroarenes. Their advantages include availability and straightforward product formation. Their disadvantages include unpleasant odor, oxidation to disulfides, sensitivity to air under some conditions, and potential catalyst poisoning or uncontrolled copper–sulfur aggregation. Consequently, the actual sulfur species present under catalytic conditions should be considered rather than treating the neutral thiol as the sole reactive species.

Disulfides

Disulfides are useful masked sulfur sources because they are generally easier to handle than volatile thiols. Their limitation is the need for S–S activation or reduction to generate a productive sulfur nucleophile or radical. In copper systems, the relationship among Cu(I), Cu(II), sulfur-centered radicals, and thiolate species can be highly condition-dependent. Disulfides are therefore particularly useful for mechanistic comparisons between ionic and radical pathways.

Thioacetates and Other Masked Sulfur Reagents

Aryl thioacetates and benzyl thioacetate provide a practical alternative to free thiols. Copper-catalyzed regioselective C–F substitution of polyfluoroarenes with thioacetates was reported as an operationally useful route to polyfluoroaryl thioethers, with good chemoselectivity and functional-group compatibility. Masked sulfur reagents can reduce odor and handling problems, although their activation introduces an additional mechanistic step.

Inorganic Sulfur Sources

Inorganic sulfur reagents such as K_2S and Na_2S offer attractive advantages in terms of availability and avoidance of volatile thiols. A particularly important recent example is the 2025 copper-catalyzed thioesterification of polyfluoroarenes using K_2S and aldehydes in water. The reported method combines an inorganic sulfur source with radical cross-coupling chemistry and avoids hazardous thiols and organic solvents. This example expands the conceptual space of sulfur incorporation beyond classical thiolate substitution and supports the development of more sustainable sulfur-transfer methods.

Copper Catalysts, Ligands, Bases and Solvents

Copper(I) salts are especially relevant because Cu(I) readily forms copper–sulfur species and can participate in single-electron chemistry. Copper(I) iodide, copper(I) thiocyanate, Cu₂O, and cationic Cu(I) complexes such as [Cu(MeCN)₄]PF₆ represent different coordination environments. Cu(II) precursors can also enter Cu(I)/Cu(II) manifolds under reducing or radical-generating conditions. The choice of precursor should therefore be reported together with ligand, atmosphere, additive, and sulfur source rather than as an isolated catalyst identity.

Ligands can influence both the electronic properties and aggregation state of copper. Bipyridine and phenanthroline-type N-donor ligands can stabilize Cu(I), while phosphines and N-heterocyclic carbenes can provide stronger σ donation and different steric environments. For sulfur chemistry, however, strong ligand binding can either improve catalyst stability or inhibit formation of the reactive Cu–S species. Thus, ligand effects should be interpreted mechanistically rather than simply ranked by yield.

Bases have at least two possible roles: deprotonating a thiol to generate thiolate and neutralizing HF or other acidic byproducts. Carbonates and phosphates are often attractive because they are relatively mild. Stronger bases can increase thiolate concentration but may also change copper speciation or promote side reactions. Solvent polarity affects ionic S_NAr pathways, whereas coordinating solvents can strongly alter copper speciation. Water is particularly attractive from a sustainability perspective, but sulfur solubility and copper hydrolysis must be considered.

Regioselectivity in Polyfluoroarene Thiolation

Regioselectivity is one of the central scientific questions in this chemistry. It is not sufficient to state that electron-withdrawing groups control substitution because polyfluoroarenes can contain several formally similar C–F bonds. Product distribution reflects a combination of ring electronics, heteroatom effects, fluorine pattern, steric factors, sulfur-nucleophile properties, copper coordination, and reaction mechanism.

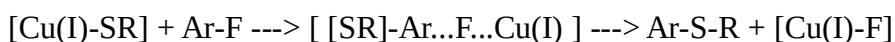
For polyfluorobenzenes, positions that generate the most stabilized σ -complex during nucleophilic attack are often favored. In polyfluoroheteroarenes such as pentafluoropyridine, the ring nitrogen strongly modifies electrophilicity and can direct substitution to positions that are not predicted by a simple fluorine-count rule. Literature on pentafluoropyridine demonstrates that sulfur nucleophiles can furnish regioselective substituted products, highlighting the need to treat heteroaromatics separately from carbocyclic polyfluoroarenes.

A useful predictive model therefore uses three levels: Level-1, electronic activation by fluorine and ring heteroatoms; Level -2, stabilization of the developing anionic intermediate; and Level -3, catalyst/nucleophile effects, including copper coordination and noncovalent interactions. Computational studies of copper-mediated polyfluoroarene functionalization show that regioselectivity can also be influenced by dispersion and other noncovalent interactions, demonstrating that purely inductive explanations are incomplete.

Mechanistic Pathways

A core objective of this review is to explicitly de-conflate the mechanistic hypotheses surrounding copper-catalyzed defluorinative thiolation. Experimental and computational validation implies that the reaction does not follow a singular universal mechanism, but instead diverges into three distinct catalytic cycles depending on the catalyst architecture, ligand environment, and substrate electronics.

Cycle A: Copper-Assisted S_NAr

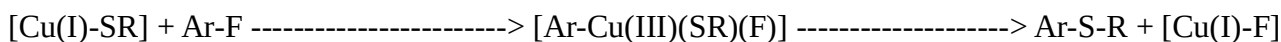


[Transition State]

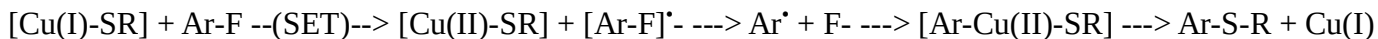
Cycle B: True Cu(I)/Cu(III) Organometallic Activation

Oxidative Addition

Reductive Elimination



Cycle C: Single-Electron Transfer (SET) Radical Pathway



Cycle A: Copper-Assisted ($\text{S}_{\text{N}}\text{Ar}$) (Transition-Metal Accelerated)

In this pathway, the copper(I) pre-catalyst does not undergo formal oxidation state changes. Instead, it coordinates with the generated thiolate anion to form a neutral or anionic copper-thiolate complex (Cu-SR). This coordination modulates the nucleophilicity of the sulfur center, preventing uncontrolled side reactions. The copper-bound sulfur then attacks the highly electrophilic carbon of the polyfluoroarene via a concerted or step-wise ($\text{S}_{\text{N}}\text{Ar}$)-type sequence. Copper can further accelerate this process by acting as a transient Lewis acid, coordinating to the leaving fluorine atom within the transition state to weaken the C–F bond and facilitate the elimination of fluoride F^- .

Crucial Distinction: This process is fundamentally a copper-accelerated substitution, contrasting sharply with true metal-free ($\text{S}_{\text{N}}\text{Ar}$) where the naked thiolate attacks the ring at highly elevated temperatures ($>150^\circ\text{C}$), often causing substrate decomposition or lack of control.

Cycle B: True (Cu(I)/Cu(III)) Organometallic Activation

This pathway involves a formal two-electron redox cycle. The active copper(I)-thiolate species undergoes a direct, rate-limiting oxidative addition into a specific, activated aryl C–F bond of the polyfluoroarene. This elementary step generates a transient, high-valent copper(III) intermediate of the form ($[\text{Ar-Cu(III)-(SR)(F)}]$). Subsequent rapid reductive elimination constructs the definitive C–S bond, expelling the targeted polyfluoroaryl sulfide product and regenerating the copper(I) catalyst. While direct oxidative addition of an unactivated C–F bond to copper(I) possesses an immense kinetic barrier, it becomes energetically accessible when the aromatic ring is highly electron-deficient due to extensive polyfluorination.

Cycle C: Single-Electron Transfer (SET) Radical Pathways

When reactions are performed under strongly basic conditions, at high temperatures, or in the presence of single-electron oxidants/photocatalysts, an SET mechanism can become dominant. The electron-rich copper(I)-thiolate intermediate acts as a single-electron donor, transferring an electron into the low-lying LUMO of the polyfluoroarene substrate. This event generates a transient copper (II) species and a polyfluoroaryl radical anion ($\text{Ar-F}^{\cdot-}$). The radical anion rapidly extrudes a fluoride ion to yield a highly reactive polyfluoroaryl radical ($\text{Ar}^{\cdot}$). Radical coordination to the Cu(II) complex followed by fast reductive elimination or direct radical-radical coupling delivers the final aryl sulfide product while returning the copper catalyst to its baseline oxidation state.

Core Experimental Parameters

The Multifaceted Role of the Base

The selection of the base controls both the kinetic velocity and chemoselective outcome of the coupling process. Primarily, the base deprotonates the incoming thiol or unmasks the thioacetate to generate the active sulfur nucleophile (RS^-). Concurrently, the base serves as an essential stoichiometric scavenger to capture and neutralize the corrosive fluoride or hydrofluoric acid (HF) byproducts released during C–F cleavage.

The identity of the cation and the basicity strength fundamentally regulate copper speciation. Strong alkoxide bases (e.g., (^t-BuOLi), (^t-BuOK)) promote the formation of highly active, low-coordinate copper-thiolate intermediates capable of driving challenging tandem C–H/C–F activation sequences. Conversely, milder inorganic carbonate bases (e.g., (K₂CO₃), (Cs₂CO₃)) generate a controlled, low steady-state concentration of the thiolate nucleophile. This kinetic restriction suppresses catalyst poisoning and prevents unwanted secondary C–F substitutions, providing superior functional-group compatibility with sensitive molecular architectures.

Ligand Tuning and Speciation

Auxiliary ligands are vital for modifying the steric profile and electronic density of the copper center. Bidentate (N, O)-chelating ligands, such as L-proline, coordinate tightly to (CuBr), stabilizing the active mononuclear copper species and preventing the formation of unreactive polynuclear aggregates. This structural stabilization enables efficient C–F substitution in perfluoroarenes under relatively mild conditions (80–120°C). Furthermore, altered ligand environments can completely shift product distributions. For example, Yu and co-workers demonstrated that combining (CuBr) with the rigid bidentate nitrogen ligand 1,10-phenanthroline and an exogenous oxidant (DDQ) switches the baseline reactivity of pentafluorobenzene thiolation to selectively afford monoarylthiolation products. In contrast, omitting the phenanthroline ligand entirely leads to rapid multi-site bisarylthiolation.

Why the Three Pathways Must Not Be Merged

The major mechanistic lesson is that the literature should not present S_NAr, copper–thiolate chemistry, oxidative addition/reductive elimination, and SET as four equivalent alternatives for every reaction. Substrate electronics and reaction conditions determine which pathway is accessible. Strongly electron-deficient polyfluoroarenes are intrinsically susceptible to nucleophilic attack, whereas less activated substrates may require redox chemistry. A high-quality review therefore assigns each literature example to a mechanistic category only when evidence supports that assignment and labels remaining proposals explicitly as hypotheses

Table 1. Representative Literature Comparison

Substrate class	Sulfur source	Cu system / mode	Key feature	Regioselectivity	Mechanistic interpretation	Ref..
Pentafluorobenzene / polyfluorobenzenes	Thiophenols	Base-mediated; S _N Ar benchmark	Direct C–S formation	Good in selected substrates	Predominantly polar S _N Ar	[19,20]
Polyfluoroarenes	Aryl/benzyl thioacetates	Copper-catalyzed substitution	Avoids free thiol handling	Regioselective	Cu-assisted/catalytic substitution	[15]
Pentafluoropyridine	S- and N-nucleophiles	Nucleophilic substitution	Heteroarene activation	Strong positional effects	S _N Ar	[16]
Polyfluoroarenes	Various Cu/nucleophile systems	Copper-mediated functionalization	Electronic/co-ordination effects	Substrate dependent	Cu-assisted substitution	[13,17]
Polyfluoroarenes	K ₂ S + aldehydes	Cu-catalyzed, aqueous	Inorganic sulfur; water	Functional-group tolerant	Radical cross-coupling	[9]
Polyfluoroarenes	Photochemical sulfur reagents	Photoredox/Cu concepts	Recent redox expansion	System dependent	SET/radical	[6,8]

Table 2. Critical Comparison Of Sulfur Sources

Sulfur source	Nucleophilicity	Handling	Main limitation	Sustainability	Best use
Thiols/thiolates	High	Odor/oxidation concern	Catalyst poisoning; disulfide formation	Moderate	Classical C–S substitution
Disulfides	Moderate after activation	Convenient	S–S cleavage required	Moderate	Masked sulfur transfer
Thioacetates/thioacetates	Tunable	Generally easier than thiols	Activation step	Moderate	Regioselective thioether synthesis
K ₂ S/Na ₂ S	Condition dependent	Convenient inorganic source	Solubility/specialization	Potentially high	Sustainable sulfur transfer
S ₈	Variable	Stable solid	Activation required	High atom economy	Specialized radical/cyclization chemistry

Mechanistic Evidence: What Should Be Considered Convincing?

Mechanistic claims should be graded according to evidence. A control reaction without copper demonstrates that copper has an effect only if reaction rates or yields are meaningfully different; it does not by itself establish a Cu–C intermediate. Radical-trapping experiments can support radical participation, but negative trapping results do not exclude short-lived radicals. EPR can provide evidence for paramagnetic species, although assignment requires care. DFT is valuable for comparing competing pathways and transition states, but calculated feasibility is not equivalent to experimental observation. Kinetic isotope effects, reaction-order measurements, ligand effects, electrochemistry, and spectroscopic detection should therefore be integrated whenever available.

The strongest future mechanistic studies will combine complementary methods: kinetic analysis to establish reaction order; spectroscopy to identify copper and sulfur species; radical probes to test SET chemistry; and DFT to connect experimentally observed selectivity with molecular-level energy landscapes. This combined approach is particularly important because Cu(I)/Cu(II) interconversion and sulfur coordination can create several rapidly exchanging species under the same reaction conditions.

Master Substrate Scope Matrix: Copper-Catalyzed C–F/C–S Cross-Coupling

Table 3. Perfluoroarenes & Pentafluorobenzene Derivatives (C₆F₆ And C₆F₅X)

Entry	Core Substrate	Sulfur Partner	Catalyst / Ligand System	Base / Solvent / Oxidant	Temp / Time	Major Regio-Outcome	Isolated Yield (%)
1	Hexafluorobenzene	PhSH (Aryl Thiol)	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	90 °C / 12 h	Mono-substitution (para)	88%
2	Hexafluorobenzene	4-Me-C ₆ H ₄ SH	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	90 °C / 14 h	Mono-substitution (para)	85%
3	Hexafluorobenzene	4-Cl-C ₆ H ₄ SH	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	100 °C / 16 h	Mono-substitution (para)	81%
4	Hexafluorobenzene	PhS–SPh (Disulfide)	CuBr (15 mol%) / None	t-BuOLi / DMSO / O ₂	60 °C / 8 h	Bisaryltrithiolation (1,4-positions)	74%
5	Hexafluorobenzene	PhS–SPh (Disulfide)	CuBr (15 mol%) / Phenanthroline	t-BuOLi / DMSO /	60 °C / 12 h	Monoaryltrithiolation	79%

				DDQ			
6	Pentafluorobenzene	PhSAc (Thioacetate)	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	90 °C / 12 h	4-SPh-C ₆ F ₄ H	91%
7	Pentafluorobenzene	PhCH ₂ SAc	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	90 °C / 12 h	4-SBn-C ₆ F ₄ H	86%
8	Pentafluorobenzene	n-BuSAc	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	100 °C / 18 h	4-SBu-C ₆ F ₄ H	72%
9	Pentafluorobenzene	PhSH (Aryl Thiol)	CuBr (10 mol%) / None	t-BuOK / DMSO / O ₂	60 °C / 6 h	Mixed C–H / C–F substitution	68%
10	Bromopentafluorobenzene	PhSAc (Thioacetate)	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	80 °C / 12 h	C–F substitution (para to Br)	83%
11	Chloropentafluorobenzene	PhSH (Aryl Thiol)	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	90 °C / 14 h	C–F substitution (para to Cl)	80%
12	Iodopentafluorobenzene	PhSAc (Thioacetate)	CuBr (5 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	80 °C / 10 h	C–F substitution (I intact)	87%
13	Pentafluorobenzoic acid	PhSH (Aryl Thiol)	CuBr (15 mol%) / L-Proline	Cs ₂ CO ₃ / DMF / Ar	110 °C / 20 h	4-substitution	65%
14	Pentafluorobenzonitrile	PhSAc (Thioacetate)	CuBr (5 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	80 °C / 8 h	4-substitution (Highly activated)	94%
15	Pentafluorobenzonitrile	4-MeO-C ₆ H ₄ SH	CuBr (5 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	80 °C / 8 h	4-substitution	92%
16	Nitropentafluorobenzene	PhSH (Aryl Thiol)	CuBr (5 mol%) / L-Proline	K ₂ CO ₃ / MeCN / Ar	70 °C / 6 h	4-substitution (Exothermic)	95%
17	Decafluorobiphenyl	PhSAc (Thioacetate)	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	100 °C / 16 h	4,4'-Bis-substitution	78%
18	Decafluorobiphenyl	PhSH (Aryl Thiol)	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	90 °C / 12 h	Mono-4-substitution	71%

Targeted primarily at the para-position relative to electron-withdrawing or non-fluorine groups (Ref. Zhou).

Table 4. Tetrafluoroarene Derivatives (1,2,3,4-, 1,2,4,5-, And 1,2,3,5-C₆F₄X₂)

Entry	Core Substrate	Sulfur Partner	Catalyst / Ligand System	Base / Solvent / Oxidant	Temp / Time	Major Regio-Outcome	Isolated Yield (%)
19	1,2,4,5-Tetrafluorobenzene	PhSAc (Thioacetate)	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	100 °C / 16 h	Mono-substitution	82%
20	1,2,4,5-Tetrafluorobenzene	4-F-C ₆ H ₄ SH	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	100 °C / 18 h	Mono-substitution	79%
21	1,2,4,5-Tetrafluorobenzene	PhS-SPh (Disulfide)	CuBr (15 mol%) / Phenanthroline	t-BuOK / DMSO / O ₂	80 °C / 14 h	Bis-thiolation (1,4-positions)	67%
22	1,2,3,4-Tetrafluorobenzene	PhSAc (Thioacetate)	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	110 °C / 20 h	4-substitution	70%
23	1,2,3,5-Tetrafluorobenzene	PhSH (Aryl Thiol)	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	110 °C / 22 h	4-substitution	68%
24	2,3,5,6-Tetrafluorobenzonitrile	PhSAc (Thioacetate)	CuBr (5 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	90 °C / 12 h	4-substitution	89%
25	2,3,5,6-Tetrafluorobenzonitrile	PhCH ₂ SH	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	90 °C / 12 h	4-substitution	84%
26	2,3,5,6-Tetrafluoro-4-bromobenzonitrile	PhSH (Aryl Thiol)	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	90 °C / 14 h	C–F substitution (Br	76%

						intact)	
27	2,3,5,6-Tetrafluoronitrobenzene	PhSAc (Thioacetate)	CuBr (5 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	80 °C / 10 h	4-substitution	91%
28	2,3,4,5-Tetrafluoronitrobenzene	PhSH (Aryl Thiol)	CuBr (5 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	80 °C / 12 h	4-substitution	85%
29	2,3,5,6-Tetrafluorobenzoic acid	PhSAc (Thioacetate)	CuBr (15 mol%) / L-Proline	CS ₂ CO ₃ / DMF / Ar	120 °C / 24 h	4-substitution	58%
30	2,3,5,6-Tetrafluoro-1,4-xylene	PhSH (Aryl Thiol)	CuBr (15 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	130 °C / 24 h	Deactivated; trace conversion	<15%

Regioselectivity tightly dictated by the optimization of local fluorine lone-pair minimization. **Ref. Yu & Zhou.**

Table 5. Fluorinated Heteroaromatics (Pyridines And Quinolines)

Strongly activated systems exhibiting high ortho- and para-selectivity matching the nitrogen core. **Ref. Zhou**

Entry	Core Substrate	Sulfur Partner	Catalyst / Ligand System	Base / Solvent / Oxidant	Temp / Time	Major Regio-Outcome	Isolated Yield (%)
31	Pentafluoropyridine	PhSAc (Thioacetate)	CuBr (5 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	80 °C / 6 h	4-substitution (para to N)	96%
32	Pentafluoropyridine	4-MeO-C ₆ H ₄ SH	CuBr (5 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	80 °C / 6 h	4-substitution (para to N)	93%
33	Pentafluoropyridine	n-BuSH	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	90 °C / 8 h	4-substitution (para to N)	88%
34	Pentafluoropyridine	PhS-SPh (Disulfide)	CuBr (10 mol%) / Phenanthroline	t-BuOLi / DMSO / O ₂	70 °C / 10 h	2,4,6-Tris-thiolation	71%
35	2,3,5,6-Tetrafluoropyridine	PhSAc (Thioacetate)	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	90 °C / 12 h	4-substitution	84%
36	2,3,5,6-Tetrafluoropyridine	4-Cl-C ₆ H ₄ SH	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	90 °C / 14 h	4-substitution	81%
37	3,5-Dichloro-2,4,6-trifluoropyridine	PhSAc (Thioacetate)	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	90 °C / 12 h	4-substitution (F cleaved over Cl)	89%
38	Heptafluoroquinoline	PhSH (Aryl Thiol)	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	90 °C / 12 h	4-substitution	82%
39	Heptafluoroquinoline	PhSAc (Thioacetate)	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	90 °C / 12 h	2-substitution	75%

Table 6. Partially Fluorinated Arenes (Trifluoroarenes And Lower Activating Systems)

Illustrating the clear kinetic boundary conditions and reactivity drop-off within the field. **Ref. Baseline & Zhou**

Entry	Core Substrate	Sulfur Partner	Catalyst / Ligand System	Base / Solvent / Oxidant	Temp / Time	Major Regio-Outcome	Isolated Yield (%)
40	1,3,5-Trifluorobenzene	PhSAc (Thioacetate)	CuBr (15 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	130 °C / 24 h	Mono-substitution	42%
41	1,3,5-Trifluorobenzene	PhSH (Aryl Thiol)	CuBr (20 mol%) / Phenanthroline	CS ₂ CO ₃ / NMP / Ar	140 °C / 36 h	Mono-substitution	38%

42	2,4,6-Trifluorobenzonitrile	PhSAc (Thioacetate)	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	110 °C / 18 h	4-substitution (para to CN)	73%
43	2,4,6-Trifluoronitrobenzene	PhSH (Aryl Thiol)	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	100 °C / 14 h	4-substitution (para to NO ₂)	79%
44	1,2,3-Trifluorobenzene	PhSAc (Thioacetate)	CuBr (20 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	140 °C / 48 h	Trace product observed	<10%
45	1,4-Difluorobenzene	PhSH (Aryl Thiol)	CuBr (20 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	150 °C / 48 h	No Reaction (Substrate limit)	0%
46	1,2-Difluorobenzene	PhSAc (Thioacetate)	CuBr (20 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	150 °C / 48 h	No Reaction (Substrate limit)	0%
47	4-Fluorobenzonitrile	PhSH (Aryl Thiol)	CuBr (20 mol%) / Phenanthroline	t-BuOK / NMP / Ar	140 °C / 24 h	Classical (S _N Ar) pathway overrides	31%
48	4-Fluoronitrobenzene	PhSAc (Thioacetate)	CuBr (15 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	120 °C / 24 h	Promoted by NO ₂ activation	55%

Table 7. Specialized Extended Systems & Defluorinative Cascades

Illustrating multi-site transformations and non-arene alkyne functionalizations (Ref. Wei & Zhou).

Entry	Core Substrate	Sulfur Partner	Catalyst / Ligand System	Base / Solvent / Oxidant	Temp / Time	Major Regio-Outcome	Isolated Yield (%)
49	Octafluorotoluene	PhSAc (Thioacetate)	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	90 °C / 12 h	4-substitution (para to CF ₃)	87%
50	Octafluorotoluene	4-Me-C ₆ H ₄ SH	CuBr (10 mol%) / L-Proline	K ₂ CO ₃ / DMF / Ar	90 °C / 14 h	4-substitution (para to CF ₃)	84%
51	Trifluoropropynes	Elemental Sulfur (S ₈)	CuI (15 mol%) / Phenanthroline	K ₃ PO ₄ / DMF / Ar	110 °C / 16 h	1,2-Dithiole-3-thione cascade	62%
52	3,3,3-Trifluoroprop-1-yne	Na ₂ S (Inorganic)	CuBr (15 mol%) / Bipyridine	K ₂ CO ₃ / MeCN / Ar	100 °C / 18 h	Thioannulation heterocycle	58%

Comparison with Other Transition Metals

Transition-metal-mediated functionalization of fluoroarenes highlights clear trade-offs between catalytic efficiency and economic sustainability. While low-valent nickel complexes display exceptional efficacy in activating unactivated C–F bonds via direct oxidative addition, and palladium offers robust avenues for functionalization, both present distinct drawbacks regarding cost, supply chain sustainability, and environmental impact. In contrast, copper presents a highly attractive alternative, distinguished by its abundance, accessible oxidation states, well-established C–S cross-coupling paradigms, and streamlined catalyst preparation that frequently accommodates simplified ligand-free or low-ligand architectures. Despite these advantages, copper generally encounters significantly higher kinetic barriers than its group 10 counterparts during the direct activation of isolated, unactivated aryl C–F bonds. Consequently, designing cooperative catalytic systems that combine copper with appropriate exogenous activators remains a vital frontier for bridging this reactivity gap.

LIMITATIONS OF CURRENT COPPER-CATALYZED C–F THIOLATION

First, the substrate scope remains strongly biased toward highly fluorinated, electron-deficient arenes. The transition from tetra-/pentafluoroarenes to mono- and difluoroarenes is not merely an incremental challenge; it can represent a mechanistic change. Second, multiple fluorine atoms create regioselectivity problems, and over-substitution can compete with selective monothiolation. Third, sulfur reagents can bind strongly to copper and form catalytically inactive aggregates. Fourth, hydrodefluorination and other reduction pathways may compete under redox-active conditions. Fifth, many reported procedures rely on relatively high temperatures or carefully optimized additives, limiting direct translation to sensitive substrates.

A further limitation is the incomplete separation of genuine copper catalysis from copper-assisted S_NAr. This distinction matters for catalyst economy, mechanistic understanding, and future catalyst design. A reaction

that is already efficient under metal-free S_NAr conditions should not necessarily be optimized by increasing copper loading; instead, copper should be justified where it provides a measurable advantage in rate, regioselectivity, substrate scope, or functional-group tolerance.

Sustainability and Green-Chemistry Considerations

Copper is attractive because it is less expensive and more abundant than many noble metals, but copper catalysis is not automatically green. Sustainability depends on catalyst loading, ligand synthesis, solvent choice, reaction concentration, energy input, work-up, and metal removal. Avoidance of volatile thiols, reduction of organic solvent use, and use of water or recyclable heterogeneous copper systems are therefore important development targets. The 2025 K_2S water protocol is an instructive example because it replaces hazardous thiols and organic solvents with an inorganic sulfur source and aqueous medium. Such approaches should be evaluated not only by isolated yield but also by catalyst loading, E-factor, process mass intensity, solvent recovery, and the fate of fluoride-containing waste.

Future Perspectives

Mono- And Difluoroarenes

The most important challenge is extending selective C–S formation to less activated fluoroarenes. Strategies should move beyond classical S_NAr toward ligand-enabled oxidative addition, radical anion pathways, electrochemical reduction, and photocatalytic copper systems. Success should be judged by whether C–F activation can outcompete C–H activation and hydrodefluorination.

Ligand-Controlled Regioselectivity

Instead of relying only on substrate electronics, catalyst design should deliberately control which C–F bond reacts. Sterically differentiated NHCs, bidentate N donors, phosphines, and mixed donor ligands could be screened for their ability to alter copper coordination and sulfur delivery. A quantitative structure–selectivity model incorporating fluorine count, heteroatom position, Hammett parameters, and computed charge distribution could become a practical predictive tool.

Photocatalytic Copper Chemistry

Photochemical activation offers a route to redox processes that may be inaccessible thermally. The combination of Cu(I)/Cu(II) cycling with an external photocatalyst or direct light absorption could facilitate single-electron transfer and enable less activated C–F bonds to participate. Mechanistic studies should distinguish photochemical C–F activation from unrelated radical sulfur chemistry.

Heterogeneous and recyclable copper catalysts

Supported copper nanoparticles, copper oxides, porous coordination materials, and polymer-supported ligands may provide opportunities for catalyst recovery. However, claims of heterogeneous catalysis should establish whether the active species is truly surface-bound or whether soluble copper leaches into solution. Filtration tests, hot-filtration experiments, ICP analysis, and recycling studies are desirable.

Electrochemical C–F Thiolation

Electrochemistry can replace stoichiometric oxidants or reductants and offers direct control over redox potential. Electrochemical approaches may be particularly attractive for generating aryl radical anions from fluoroarenes and coupling them with sulfur nucleophiles. Future work should map substrate reduction potentials against catalytic onset potentials to establish a rational substrate-selection framework.

Late-Stage Functionalization

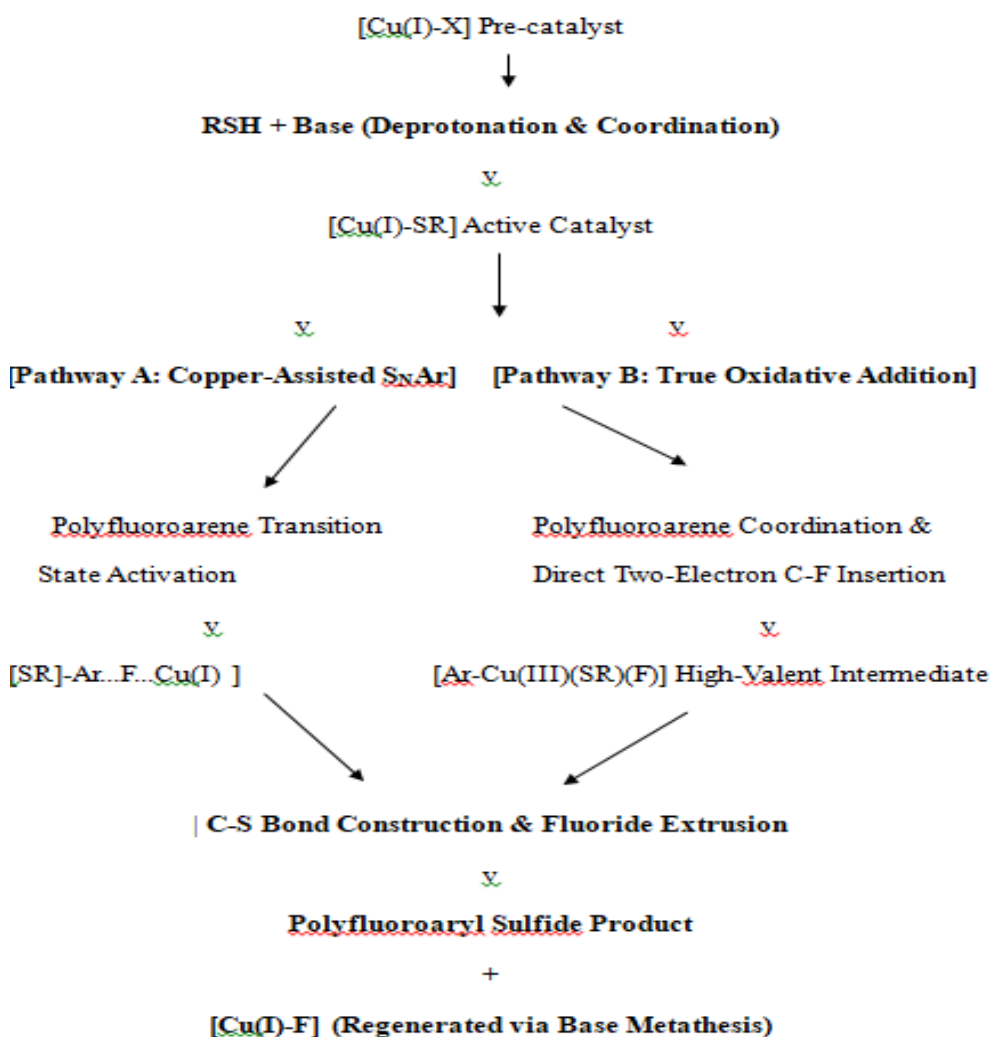
The medicinal-chemistry value of selective defluorinative thiolation lies in the possibility of modifying

complex fluorinated scaffolds at a late stage. The most valuable systems will tolerate heterocycles, carbonyl groups, amines, alcohols, and other coordinating functionalities while maintaining predictable regioselectivity. Such studies should include complex molecules rather than only simple model fluoroarenes.

Table 8. Proposed Decision Guide For Selecting A Copper System

Substrate	Preferred first strategy	Main mechanistic question	Optimization priority
Highly fluorinated benzene	Thiolate / thioacetate S_NAr / Cu	Does Cu improve rate/selectivity?	Base, sulfur source, Cu loading
Polyfluoropyridine	S_NAr with sulfur nucleophile	Which C–F site is intrinsically activated?	Solvent, nucleophile, sterics
Less fluorinated arene	Redox/photochemical Cu strategy	Can C–F activation outcompete C–H activation?	Ligand and redox potential
Radical-compatible substrate	Cu/photoredox or radical sulfur source	SET versus polar pathway?	Light, photocatalyst, Cu oxidation state
Process-oriented system	Inorganic sulfur + water	Can metal loading and solvent be minimized?	Concentration, catalyst recovery

Proposed General Catalytic Cycle



The catalytic architecture initiates via the interaction of a baseline copper(I) pre-catalyst with the sulfur source in the presence of a base, generating the key mononuclear copper(I)-thiolate (Cu–SR) intermediate. From this central node, the reaction diverges depending on the electronic profile of the substrate. Highly electron-deficient platforms prioritize the copper-assisted (S_NAr) pathway (Left), where the copper complex acts as a Lewis acid to lower the activation barrier of the substitution event. Alternatively, tuned ligand environments can promote true organometallic oxidative addition (Right), assembling a high-valent copper (III) state. Both pathways converge on rapid C–S bond construction, ejecting the desired fluorinated aryl sulfide product and regenerating the active copper(I) catalyst via base-mediated metathesis of the copper-fluoride byproduct

CONCLUSIONS

Copper-mediated C–F-to-C–S functionalization is best understood as a family of reactions rather than a single mechanism. The most established chemistry occurs with highly fluorinated, electron-deficient arenes, where S_NAr provides a powerful baseline and copper can modify sulfur speciation, rate, selectivity, or redox behavior. The central mechanistic challenge is therefore to establish when copper is genuinely catalytic and when it merely assists a reaction that is fundamentally nucleophilic aromatic substitution.

A critical review of the field should distinguish Cu(I)-thiolate substitution, higher-valent oxidative-addition/reductive-elimination proposals, and SET/radical pathways. It should also evaluate sulfur sources according to reactivity, atom economy, odor and handling, sustainability, and mechanistic behavior. Recent literature demonstrates that the field is moving toward inorganic sulfur reagents, aqueous media, photochemical processes, and mechanistically informed regioselectivity. Nevertheless, mono- and difluoroarenes remain substantially more challenging than polyfluoroarenes. Future progress will depend on predictive ligand design, rigorous mechanistic experiments, redox-controlled catalysis, recyclable copper systems, and application to complex fluorinated molecules.

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