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Copper-catalyzed aryl *ortho*-C–H thiolation of aldehydes *via* a transient directing group strategy†

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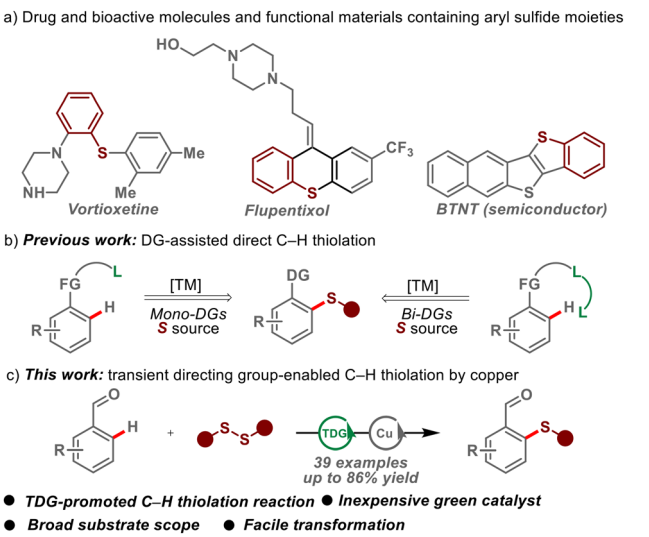
Transition metal-catalyzed C–H functionalization represents a robust method for the synthesis of aryl sulfides. The current reactions primarily rely on the use of preinstalled directing groups, which limits their practical applications. Herein, we report the first example of transient directing group-enabled C–H thiolation. Using an aminobenzoic acid as catalyst, aryl aldehydes form the transient imine directing groups and undergo copper-catalyzed aryl *ortho*-C–H thiolation. The reactions feature a broad substrate scope, facilitating easy access to a diverse range of aryl sulfides. Furthermore, the synthetic utilities of these reactions have been demonstrated by their applications to key intermdediates relevant to the synthesis of drug and bioactive molecule.

Aryl sulfides are important structural motifs that are ubiquitous in pharmaceutical drugs and bioactive molecules, exhibiting various bioactivities as therapeutic compounds.[1] Furthermore, aryl sulfides have significant applications in functional organic materials, as the introduction of sulfur into organic molecules profoundly affects their physical and electronic properties (Scheme 1a).[2] Consequently, the development of new methods for the synthesis of aryl sulfides has been the subject of extensive research.[3] Traditional methods for synthesizing aryl sulfides primarily rely on the direct cross-coupling of prefunctionalized arene substrates, such as aryl halides,[4] and on electrophilic modifications of electron-rich aromatic compounds.[5]

In recent years, transition metal-catalyzed C–H functionalization has emerged as a robust tool for the construction of aryl C–S bonds.[6] C–H functionalization eliminates the need for prefunctionalized substrates, offering significant advantages in terms of step- and atom-economy compared to traditional synthetic methods that rely on the transformation of functional groups. Currently, a variety of C–H thiolation reactions have been developed.[7] However, these reactions primarily depend on the use of directing groups that need additional steps for installation and removal (Scheme 1b). Since Jun and Yu developed reactions for aldehydic C–H and aliphatic C(sp^3)–H functionalization,[8] the transient directing group (TDG) strategy has gained significant attention and made considerable advancements over the past few decades.[9] In this strategy, an imine is typically formed *in situ* to act as the direcitng group that promotes C–H activation[10] Despite this progress, C–H thiolation *via* the transient directing group strategy still remains underdeveloped. It is important to note that two major potential obstacles must be overcome to develop such reactions: (1) catalyst poisoning by strongly coordinating sulfur atoms[4c,6d] and (2) the tendency of sulfides to undergo oxidation.[11] Furthermore, as strong nucleophiles, thiols could react with aldehydes and consequently hinder the formation of transient directing groups.

On the other hand, the majority of TDG-assisted C–H functional reactions involve noble metals such as Pd, Rh, Ru, and



Scheme 1 C–H thiolation of aldehydes *via* a transient directing group strategy.

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Ir, which limits their practical applicability. In contrast to noble metals, the abundant and cost-effective first-row transition metals offer significant advantages as catalysts. Recently, the development of C–H functionalization methodologies using first-row transition metals, such as Fe, Co, Ni, and Cu,[12] has become a major research focus. Most current first-row transition metal-enabled C–H activation reactions rely on strong-coordinating groups, particularly bidentate directing groups, while C–H activation reactions employing TDG strategies remain scarce.[13] Among the first-row transition metals, copper is particularly attractive as the catalyst due to its abundance, cost-effectiveness, and versatile reactivity. Pioneered by the work of Yu and Chatani,[14] copper-catalyzed/mediated oxidative C–H functionalization has gained significant attention and a number of reactions have been developed.[7a,15] Most of copper-mediated reactions are also enabled by strong-coordinating groups, and transient directing group-enabled reactions had not been achieved until the Bull group reported elegant examples very recently.[16] It is significant to develop new copper-catalyzed C–H activation reactions *via* a transient directing group strategy, particularly in the establishment of new protocols.

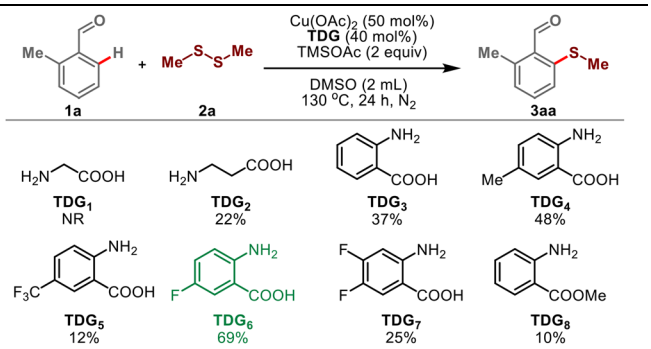
Herein, we present an *ortho*-C–H thiolation reaction of aldehydes utilizing a transient directing group strategy (Scheme 1c). The reaction represents the first example of C–H thiolation *via* a transient directing group strategy and are among the rare instances of transition directing group-enabled C–H functionalization using first-row transition metals. The practical applications of the C–H thiolation reaction have been demonstrated.

We first studied copper-catalyzed C–H thiolation of benzaldehydes, and the study commenced with an extensive screening of transient directing groups using 2-methylbenzaldehyde (**1a**) and dimethyl disulfide (**2a**) as model substrates (Table 1). While glycine (**TDG$_1$**) failed to facilitate the thiolation reaction, the desired thiolated product **3a** was obtained in a 22% yield using a β-amino acid (**TDG$_2$**) in the presence of 50 mol% Cu(OAc)$_2$ and 2 equivalents of TMSOAc in DMSO. The yield improved to 37% with the use of 2-aminobenzoic acid (**TDG$_3$**). Considering that the electronic properties of the amino group may influence the formation of the imine and its coordination with the copper catalyst, we investigated 2-aminobenzoic acids bearing various substituents. An electron-donating methyl group enhanced the yield (**TDG$_4$**), while an electron-withdrawing trifluoromethyl group resulted in a lower yield (**TDG$_5$**). Notably, the yield dramatically increased to 69% with the use of 2-aminobenzoic acid containing a fluoro group (**TDG$_6$**). However, the presence of two fluoro groups led to a decrease in yield (**TDG$_7$**). These results suggest that the electronic properties of 2-aminobenzoic acids significantly impact the thiolation reaction. Additionally, 2-aminobenzoate proved to be an effective catalyst, albeit in a lower yield (**TDG$_8$**).

Control experiments were conducted to clarify the role of each reagent and further improve the yield. The reaction did not yield the thiolated product when AcOH was used instead of TMSOAc (entry 2). A low yield was observed when the reaction was performed in HFIP (entry 3), which is often employed as a solvent in transient imine-directed C–H activation. As anticipated, the reaction did not proceed in the absence of either Cu(OAc)$_2$ or **TDG$_6$** (entries 4 and 5). Decreasing the amounts of Cu catalyst, **TDG$_6$**, or TMSOAc led to diminished yields to varying degrees (entries 6–8). Additionally, a lower yield was obtained when the reaction time was reduced or when the reaction was conducted at 120 °C (entries 9 and 10). Interestingly, the concentration of the reaction mixture significantly influenced the catalytic activity of copper. Reducing the concentration increased the yield to 75%, but further dilution resulted in a decreased yield (entry 11). Finally, although the addition of CuF_2 slightly improved the yield (entry 12), we opted not to pursue this option due to economic and practical considerations. Thus, the optimized reaction conditions were established as follows: Cu(OAc)$_2$ (50 mol%), **TDG$_6$** (40 mol%), TMSOAc (2 equivalents) in DMSO at 130 °C. It is worth noting that compound **1a** was recovered in 22% yield under the optimal conditions (entry 11), indicating that the conversion of **1a** is essentially equivalent to the yield.

With the optimal reaction conditions established, the substrate scope of the C(sp^2)–H thiolation reaction was explored. The performance of disulfides was investigated first. As shown in Table 2, alkyl disulfides containing a bulky cyclohexyl group or an easily removable benzyl group yielded thiolated products

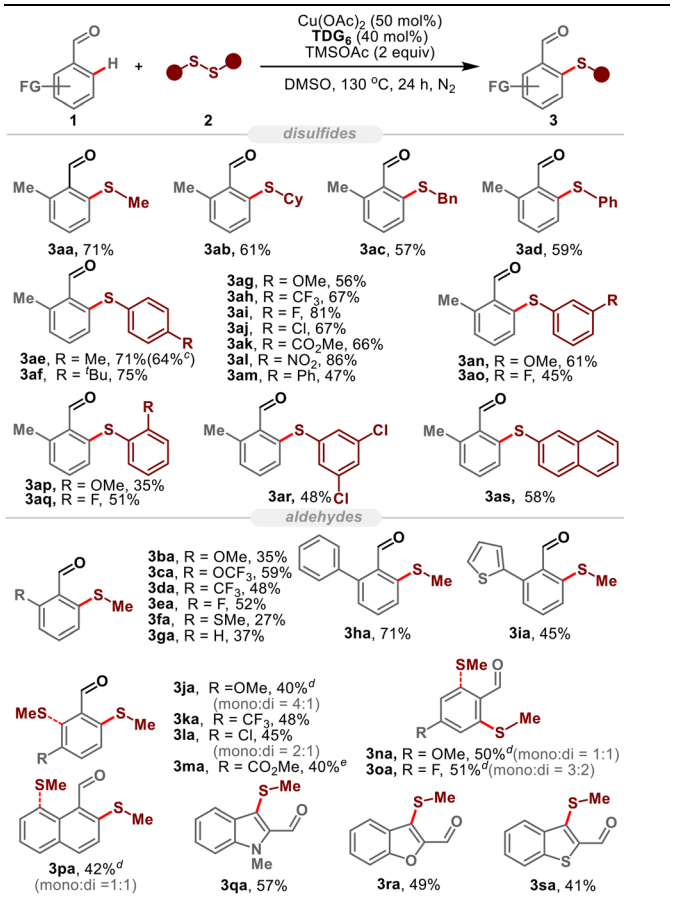
Table 1 Optimization of reaction conditions for the thiolation of aldehydes[a,b]



Entry	Variations	Yield[b] (%)
1	None	69
2	With AcOH (2 equiv.) instead of TMSOAc	NR
3	HFIP instead of DMSO	13
4	w/o Cu(OAc)$_2$	NR
5	w/o TDG$_6$	NR
6	Cu(OAc)$_2$ (25 mol%)	34
7	TDG$_6$ (20 mol%)	10
8	TMSOAc (1 equiv.)	41
9	18 h	63
10	120 °C	40
11	DMSO (3 mL)	75[c](71[d]), 49[e]
12	With CuF_2 (2 equiv.)	78

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), Cu(OAc)$_2$ (50 mol%), TDG (40 mol%), TMSOAc (2 equiv.), DMSO (2 mL), 130 °C, 24 h, N_2. [b] Determined by ^{1}H NMR analysis using CH_2Br_2 as an internal standard. [c] **1a** was recovered in a yield of 22%. [d] Isolated yields. [e] DMSO (4 mL). NR: no reaction.

Table 2 Substrate scope of the thiolation of aldehydes.[a,b]

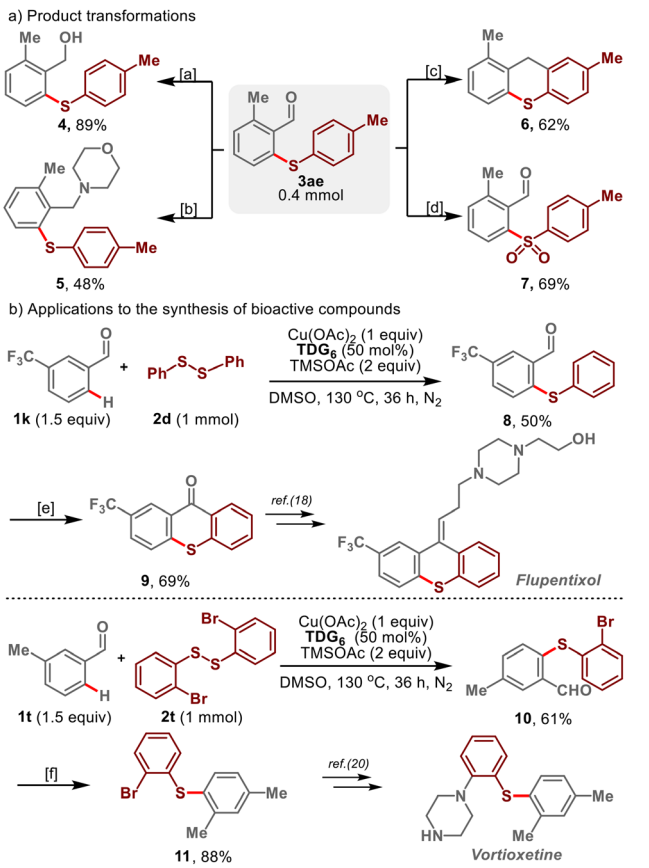


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), $Cu(OAc)_2$ (50 mol%), TDG (40 mol%), TMSOAc (2 equiv.), DMSO (3 mL), 130 °C, 24 h, N_2. [b] Isolated yield. [c] Gram scale reaction. [d] Overall yield of mono- and dithiolated products. [e] $Cu(OAc)_2$ (1.5 equiv.).

in moderate yields (**3ab–3ac**). A diverse range of diaryl disulfides, featuring various functionalities at the *para* positions of the benzene rings, including electron-donating (Me, *tert*-Bu, and OMe) and electron-withdrawing (CF_3 and F) groups, underwent the thiolation reaction effectively (**3ae–3ai**). Functionalities such as chloro, ester, nitro, and phenyl groups were well-tolerated, resulting in the desired products being obtained in moderate to high yields (**3aj–3am**). Notably, the method enabled the gram-scale synthesis of compound **3ae**, achieving a yield of 64%. Both electron-donating methoxy group and electron-withdrawing fluoro group at the *meta* or *ortho* positions were compatible (**3an–3aq**). Additionally, disulfides containing disubstituted phenyl or naphthyl groups were also suitable substrates (**3ar** and **3as**)

The performance of aryl aldehydes was also investigated using **2a** as the thiolating reagent. A range of electronically and sterically diverse aldehydes were effectively compatible (**3ba–3ia**), including electron-donating groups such as OMe and electron-withdrawing groups like OCF_3, CF_3 and F. A methylthio, phenyl, and even thiophenyl group were also compatible. However, for benzaldehyde, which lacks an *ortho* substituent, the yield was low (**3ga**). The reactions of *meta*- and *para*-substituted benzaldehydes were also examined, with a range of functionalities being well-tolerated (**3ja–3oa**). It is noteworthy that dithiolated products were formed for some *meta*-substituted aldehydes (**3ja** and **3la**) and for *para*-substituted benzaldehydes (**3na** and **3oa**). In the case of 1-naphthaldehyde, thiolation occurred not only at the *ortho* position but also at the 8 position, yielding mono- and dithiolated products in a 1 : 1 ratio (**3pa**). Importantly, heterocyclic aldehydes, including indole-, benzofuran-, and benzothiophene-2-carbaldehydes, also successfully underwent the thiolation reaction (**3qa–3sa**). It should be mentioned that *meta*- or *para*-functionalized benzaldehyde products were not observed in all reactions.

To demonstrate the synthetic utility of the C–H thiolation reactions, we investigated the transformation of the thiolated products. As exhibited in Scheme 2a, the aldehyde group in **3ae** can be reduced or undergo reductive amination to yield products **4** and **5**, respectively. Additionally, **3ae** can undergo $TiCl_4$-mediated cyclization followed by reduction,[17] resulting

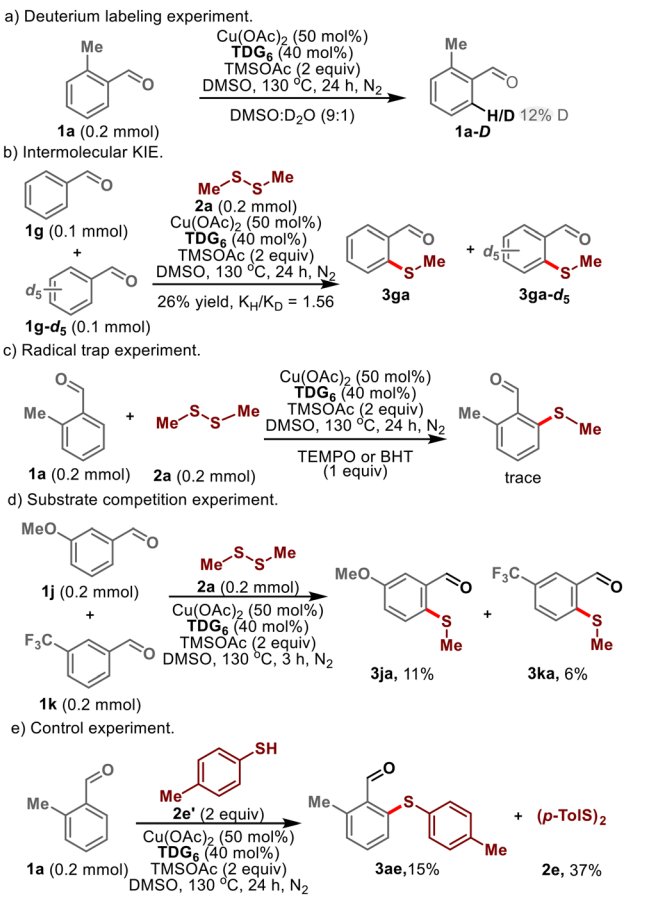


Scheme 2 Product transformations. [a] $NaBH_4$ (2 equiv.), MeOH, 0 °C–r.t., 2 h. [b] $NaBH_3CN$ (2.0 equiv.), morpholine (2 equiv.), MeOH, 0 °C–r.t., 2 h. [c] $TiCl_4$ (4 equiv.), DCM, r.t. 24 h, then Et_3SiH (4 equiv.), 12 h, r.t.. [d] Oxone (3 equiv.), THF/H_2O (1 : 1), r.t., 3 h. [e] 1, $TiCl_4$ (4 equiv.), DCM, r.t. 24 h, then H_5IO_6 (1.75 equiv.), CrO_3 (2.5 mol%), 30 min, r.t.. [f] $N_2H_4{\cdot}H_2O$ (8 equiv.), KOH (6 equiv.), DME,140 °C.

in the formation of compound **6** as the final product. This reaction provides a straightforward strategy for the synthesis of 9*H*-thioxanthene. Furthermore, the sulfide group can be oxidized to a sulfone group (**7**). These products may find applications in agrochemicals and pharmaceuticals.[4d]

We also explored the practical applications of the C–H thiolation reactions in the synthesis of drug and bioactive molecules (Scheme 2b). Notably, compound **9**, a key intermediate in the synthesis of flupentixol,[18] can be readily synthesized through the thiolation of benzaldehyde **8** followed by subsequent cyclization. Flupentixol is a clinically approved thioxanthene-based neuroleptic used in the treatment of schizophrenia and depression.[19] Additionally, the C–H thiolation reaction facilitates easy access to compound **11**, which can be transformed into Vortioxetine, a serotonin modulator and antidepressant.[20]

To gain insights into the mechanism of the C–H thiolation reactions, we conducted mechanistic studies. As illustrated in Scheme 3, isotope-labeling experiments were first carried out. In the presence of D_2O, when substrate **1a** was subjected to the otherwise standard conditions, D/H exchange occurred at the *ortho* positions of the recovered aldehyde, resulting in 12% D incorporation (Scheme 3a). Additionally, kinetic isotope effect (KIE) experiments indicate that C–H bond cleavage may be not the rate-determining step in the C–H thiolation reaction of aldehydes, with a KIE value of 1.56 (Scheme 3b). The presence of radical traps such as TEMPO or BHT completely suppressed the thiolation reaction (Scheme 3c), suggesting that radical species may be involved. Furthermore, a competition experiment involving an equimolar mixture of **1j** and **1k** was conducted to assess the electronic preferences of the reaction. The resulting 2 : 1 ratio of products **3ja** and **3ka** indicated that the electron-rich benzaldehyde (**1j**) exhibited higher reactivity (Scheme 3d). Additionally, substituting the thiolating agent with 4-methylbenzenethiol (**2e′**) also produced the corresponding thiolated products, as well as disulfide **2e** (Scheme 3e). This outcome suggests that interconversion between thiols and disulfides may occur during the reaction and could be involved in the catalytic cycle.[7g]



Scheme 3 Mechanistic studies.

Conclusions

In conclusion, we have successfully developed transient directing group-promoted C–H thiolation reactions for the first time. In the presence of 2-amino-5-fluorobenzoic acid as catalysts, aryl aldehydes form the corresponding imines, which act as transient directing groups, and undergo copper-catalyzed aryl *ortho*-C–H thiolation. The reactions are compatible with a wide range of disulfides and aldehydes, allowing for easy access to various aryl sulfides. The thiolated products can be directly utilized in subsequent reactions without the need for additional steps to remove the directing group, demonstrating the practical utility of these reactions. The practical applications have been validated through product transformations relevant to the synthesis of drug and bioactive molecules. We anticipate that these findings will not only provide a new strategy for C–H thiolation but also contribute to a deeper understanding of the transient directing group strategy in C–H functionalization.

Author contributions

M. Mei, D. Yi, F. Meng and J. Tang performed the experiments and analysed the data. Y. Zhang conceived the project and analysed experimental data. The manuscript was written by Y. Zhang and M. Mei.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

The authors declare no conflict of interest.

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References

1 (*a*) E. Moreno, D. Plano, I. Lamberto, M. Font, I. Encío, J. A. Palop and C. Sanmartín, Sulfur and Selenium Derivatives of Quinazoline and Pyrido[2,3-D]Pyrimidine: Synthesis and Study of Their Potential Cytotoxic Activity in Vitro, *Eur. J. Med. Chem.*, 2012, **47**, 283–298; (*b*) E. D. A. dos Santos, E. Hamel, R. Bai, J. C. Burnett, C. S. S. Tozatti, D. Bogo, R. T. Perdomo, A. M. M. Antunes, M. M. Marques, M. D. F. C. Matos and D. P. de Lima, Synthesis and Evaluation of Diaryl Sulfides and Diaryl Selenide Compounds for Antitubulin and Cytotoxic Activity, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 4669–4673; (*c*) M. Feng, B. Tang, S. H. Liang and X. Jiang, Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistry, *Curr. Top. Med. Chem.*, 2016, **16**, 1200–1216; (*d*) M. Wang and X. Jiang, Prospects and Challenges in Organosulfur Chemistry, *ACS Sustainable Chem. Eng.*, 2022, **10**, 671–677.

2 (*a*) D. A. Boyd, Sulfur and Its Role in Modern Materials Science, *Angew. Chem., Int. Ed.*, 2016, **55**, 15486–15502; (*b*) G. Wang, Q. Guo, D. Chen, Z. Liu, X. Zheng, A. Xu, S. Yang and G. Ding, Facile and Highly Effective Synthesis of Controllable Lattice Sulfur-Doped Graphene Quantum Dots via Hydrothermal Treatment of Durian, *ACS Appl. Mater. Interfaces*, 2018, **10**, 5750–5759.

3 (*a*) H. Liu and X. Jiang, Transfer of Sulfur: From Simple to Diverse, *Chem. – Asian J.*, 2013, **8**, 2546–2563; (*b*) A. Hosseinian, S. Ahmadi, F. A. H. Nasab, R. Mohammadi and E. Vessally, Cross-Dehydrogenative C–H/S–H Coupling Reactions, *Top. Curr. Chem.*, 2018, **376**, 39–71; (*c*) Y.-F. Wei, W.-C. Gao, H.-H. Chang and X. Jiang, Recent Advances in Thiolation via Sulfur Electrophiles, *Org. Chem. Front.*, 2022, **9**, 6684–6707.

4 (*a*) T. Kondo and T.-a. Mitsudo, Metal-Catalyzed Carbon–Sulfur Bond Formation, *Chem. Rev.*, 2000, **100**, 3205–3220; (*b*) C. F. Lee, Y. C. Liu and S. S. Badsara, Transition–Metal–Catalyzed C-S Bond Coupling Reaction, *Chem. – Asian J.*, 2014, **9**, 706–722; (*c*) I. P. Beletskaya and V. P. Ananikov, Transition-Metal-Catalyzed C–S, C–Se, and C–Te Bond Formations via Cross-Coupling and Atom-Economic Addition Reactions. Achievements and Challenges, *Chem. Rev.*, 2022, **122**, 16110–16293; (*d*) S. Huang, M. Wang and X. Jiang, Ni-catalyzed C–S bond Construction and Cleavage, *Chem. Soc. Rev.*, 2022, **51**, 8351–8377.

5 C.-F. Lee, R. S. Basha and S. S. Badsara, Engineered C–S Bond Construction, *Top. Curr. Chem.*, 2018, **376**, 153–157.

6 (*a*) C. Shen, P. Zhang, Q. Sun, S. Bai, T. S. A. Hor and X. Liu, Recent Advances in C–S Bond Formation via C–H Bond Functionalization and Decarboxylation, *Chem. Soc. Rev.*, 2015, **44**, 291–314; (*b*) S. Chen, M. Wang and X. Jiang, C–H Functionalization Strategies for the Construction of Thioethers, *Acta Phys.-Chim. Sin.*, 2019, **35**, 954–967; (*c*) W. Ma, N. Kaplaneris, X. Fang, L. Gu, R. Mei and L. Ackermann, Chelation-assisted Transition Metal-catalysed C–H Chalcogenylations, *Org. Chem. Front.*, 2020, **7**, 1022–1060; (*d*) C.-S. Wang, Y. Xu, S.-P. Wang, C.-L. Zheng, G. Wang and Q. Sun, Recent Advances in Selective Mono-/dichalcogenation and Exclusive Dichalcogenation of C(sp^2)–H and C(sp^3)–H Bonds, *Org. Biomol. Chem.*, 2024, **22**, 645–681.

7 (*a*) L. D. Tran, I. Popov and O. Daugulis, Copper-Promoted Sulfenylation of sp^2 C–H Bonds, *J. Am. Chem. Soc.*, 2012, **134**, 18237–18240; (*b*) F.-J. Chen, G. Liao, X. Li, J. Wu and B.-F. Shi, Cu(II)-Mediated C–S/N–S Bond Formation via C–H Activation: Access to Benzoisothiazolones Using Elemental Sulfur, *Org. Lett.*, 2014, **16**, 5644–5647; (*c*) P. Gandeepan, J. Koeller and L. Ackermann, Expedient C–H Chalcogenation of Indolines and Indoles by Positional-Selective Copper Catalysis, *ACS Catal.*, 2017, **7**, 1030–1034; (*d*) Y. Li, Y. J. Liu and B. F. Shi, Copper–Mediated Thiolation of Unactivated Heteroaryl C–H Bonds with Disulfides under Ligand– and Metal–Oxidant–Free Conditions, *Adv. Synth. Catal.*, 2017, **359**, 4117–4121; (*e*) X. Wang, X. Yi, H. Xu and H.-X. Dai, Cu-Mediated C–H Thioetherification of Arenes at Room Temperature, *Org. Lett.*, 2019, **21**, 5981–5985; (*f*) R. Kajiwara, K. Takamatsu, K. Hirano and M. Miura, Copper-Mediated Regioselective C–H Sulfenylation and Selenation of Phenols with Phenanthroline Bidentate Auxiliary, *Org. Lett.*, 2020, **22**, 5915–5919; (*g*) P. Wu, T.-J. Cheng, H.-X. Lin, H. Xu and H.-X. Dai, Copper-mediated C H Thiolation of (Hetero) arenes Using Weakly Coordinating Directing Group, *Tetrahedron Lett.*, 2020, **61**, 152062; (*h*) Y.-S. Xiong, Y. Yu, J. Weng and G. Lu, Copper-catalyzed Peri-selective Direct Sulfenylation of 1-Naphthylamines with Disulfides, *Org. Chem. Front.*, 2018, **5**, 982–989; (*i*) T. Gensch, F. J. R. Klauck and F. Glorius, Cobalt-Catalyzed C–H Thiolation through Dehydrogenative Cross-Coupling, *Angew. Chem., Int. Ed.*, 2016, **55**, 11287–11291; (*j*) T. Müller and L. Ackermann, Nickel–Catalyzed C–H Chalcogenation of Anilines, *Chem. – Eur. J.*, 2016, **22**, 14151–14154; (*k*) M. Iwasaki, M. Iyanaga, Y. Tsuchiya, Y. Nishimura, W. Li, Z. Li and Y. Nishihara, Palladium–Catalyzed Direct Thiolation of Aryl C-H Bonds with Disulfides, *Chem. – Eur. J.*, 2014, **20**, 2459–2462; (*l*) C. Xu and Q. Shen, Palladium-Catalyzed Trifluoromethylthiolation of Aryl C–H Bonds, *Org. Lett.*, 2014, **16**, 2046–2049; (*m*) S. Guin, A. Deb, P. Dolui, S. Chakraborty, V. K. Singh and D. Maiti, Promoting Highly Diastereoselective γ-C–H Chalcogenation of α-Amino Acids and Aliphatic Carboxylic Acids, *ACS Catal.*, 2018, **8**, 2664–2669; (*n*) Y. Yang, W. Hou, L. Qin, J. Du, H. Feng, B. Zhou and Y. Li, Rhodium–Catalyzed Directed Sulfenylation of Arene C-H Bonds, *Chem. – Eur. J.*, 2013, **20**, 416–420; (*o*) Y. S. Kang, P. Zhang, M. Y. Li, Y. K. Chen, H. J. Xu, J. Zhao, W. Y. Sun, J. Q. Yu and Y. Lu, Ligand–Promoted

RhIII–Catalyzed Thiolation of Benzamides with a Broad Disulfide Scope, *Angew. Chem., Int. Ed.*, 2019, **58**, 9099–9103.

8 (*a*) C.-H. Jun, D.-Y. Lee and J.-B. Hong, Hydroacylation of 1-Alkene with Heteroaromatic Aldehyde by Rh(I) and Additives, *Tetrahedron Lett.*, 1997, **38**, 6673–6676; (*b*) C.-H. Jun, H. Lee and J.-B. Hong, Chelation-Assisted Intermolecular Hydroacylation: Direct Synthesis of Ketone from Aldehyde and 1-Alkene, *J. Org. Chem.*, 1997, **62**, 1200–1201; (*c*) F.-L. Zhang, K. Hong, T.-J. Li, H. Park and J.-Q. Yu, Functionalization of C(sp3)–H Bonds Using a Transient Directing Group, *Science*, 2016, **351**, 252–256; (*d*) X.-Y. Chen, S. Ozturk and E. J. Sorensen, Pd-Catalyzed *Ortho* C–H Hydroxylation of Benzaldehydes Using a Transient Directing Group, *Org. Lett.*, 2017, **19**, 6280–6283; (*e*) X.-H. Liu, H. Park, J.-H. Hu, Y. Hu, Q.-L. Zhang, B.-L. Wang, B. Sun, K.-S. Yeung, F.-L. Zhang and J.-Q. Yu, Diverse ortho-C(sp^2)–H Functionalization of Benzaldehydes Using Transient Directing Groups, *J. Am. Chem. Soc.*, 2017, **139**, 888–896; (*f*) X.-Y. Chen and E. J. Sorensen, Pd-Catalyzed, ortho C–H Methylation and Fluorination of Benzaldehydes Using Orthanilic Acids as Transient Directing Groups, *J. Am. Chem. Soc.*, 2018, **140**, 2789–2792; (*g*) M.-S. Mei and Y. Zhang, Synthesis of Naphthalimides through Tandem Pd(II)-Catalyzed C(sp^3)–H Oxidation and Diels–Alder Reaction Using a Transient Directing Group Strategy, *Org. Lett.*, 2023, **25**, 4985–4989.

9 (*a*) S. St John-Campbell and J. A. Bull, Transient Imines as 'Next Generation' Directing Groups for the Catalytic Functionalisation of C–H Bonds in a Single Operation, *Org. Biomol. Chem.*, 2018, **16**, 4582–4595; (*b*) B. Niu, K. Yang, B. Lawrence and H. Ge, Transient Ligand-Enabled Transition Metal-Catalyzed C–H Functionalization, *ChemSusChem*, 2019, **12**, 2955–2969; (*c*) G. Liao, T. Zhang, Z.-K. Lin and B.-F. Shi, Transition Metal-Catalyzed Enantioselective C-H Functionalization via Chiral Transient Directing Group Strategies, *Angew. Chem., Int. Ed.*, 2020, **59**, 19773–19786; (*d*) M. I. Lapuh, S. Mazeh and T. Besset, Chiral Transient Directing Groups in Transition-Metal-Catalyzed Enantioselective C–H Bond Functionalization, *ACS Catal.*, 2020, **10**, 12898–12919; (*e*) J. I. Higham and J. A. Bull, Transient Imine Directing Groups for the C–H Functionalisation of Aldehydes, Ketones and Amines: an Update 2018–2020, *Org. Biomol. Chem.*, 2020, **18**, 7291–7315; (*f*) N. Goswami, T. Bhattacharya and D. Maiti, Transient Directing Ligands for Selective Metal-catalysed C–H Activation, *Nat. Rev. Chem.*, 2021, **5**, 646–659; (*g*) J. I. Higham, T.-K. Ma and J. A. Bull, When is an Imine Directing Group a Transient Imine Directing Group in C–H Functionalization?, *Chem. – Eur. J.*, 2024, **30**, e202400345.

10 (*a*) R. Bisht and B. Chattopadhyay, *J. Am. Chem. Soc.*, 2016, **138**, 84–87; (*b*) B. Chattopadhyay and R. Bisht, *Synlett*, 2016, 2043–2050; (*c*) S. Guria, M. M. M. Hassan, S. Dey, K. N. Singh and B. Chattopadhyay, *Angew. Chem., Int. Ed.*, 2024, **63**, e202409010.

11 (*a*) M. Kirihara, S. Naito, Y. Nishimura, Y. Ishizuka, T. Iwai, H. Takeuchi, T. Ogata, H. Hanai, Y. Kinoshita, M. Kishida, K. Yamazaki, T. Noguchi and S. Yamashoji, Oxidation of Disulfides with Electrophilic Halogenating Reagents: Concise Methods for Preparation of Thiosulfonates and Sulfonyl Halides, *Tetrahedron*, 2014, **70**, 2464–2471; (*b*) M.-Z. Zhang, P.-Y. Ji, Y.-F. Liu, J.-W. Xu and C.-C. Guo, Disulfides as Sulfonylating Precursors for the Synthesis of Sulfone-Containing Oxindoles, *Adv. Synth. Catal.*, 2016, **358**, 2976–2983.

12 (*a*) A. A. Kulkarni and O. Daugulis, Direct Conversion of Carbon-Hydrogen into Carbon-Carbon Bonds by First-Row Transition-Metal Catalysis, *Synthesis*, 2009, 4087–4109; (*b*) J. Miao and H. Ge, Recent Advances in First-Row-Transition-Metal-Catalyzed Dehydrogenative Coupling of C(sp^3)–H Bonds, *Eur. J. Org. Chem.*, 2015, 7859–7868; (*c*) P. Gandeepan, T. Muller, D. Zell, G. Cera, S. Warratz and L. Ackermann, 3d Transition Metals for C-H Activation, *Chem. Rev.*, 2019, **119**, 2192–2452 For selected reviews on Fe-catalyzed reactions: (*d*) C.-L. Sun, B.-J. Li and Z.-J. Shi, Direct C–H Transformation via Iron Catalysis, *Chem. Rev.*, 2011, **111**, 1293–1314; (*e*) F. Jia and Z. Li, Iron-catalyzed/mediated Oxidative Transformation of C–H Bonds, *Org. Chem. Front.*, 2014, **1**, 194–214; (*f*) R. Shang, L. Ilies and E. Nakamura, Iron-Catalyzed C–H Bond Activation, *Chem. Rev.*, 2017, **117**, 9086–9139. Co-catalyzed: (*g*) L.-P. Xu, E. E. L. N. Liu, J. Bacsa, C. E. MacBeth and D. G. Musaev, Mechanistic Details of the Cobalt-mediated Dehydrogenative Dimerization of Aminoquinoline-directed Benzamides, *Chem. Sci.*, 2020, **11**, 6085–6096; (*h*) R. Mei, U. Dhawa, R. C. Samanta, W. Ma, J. Wencel-Delord and L. Ackermann, Cobalt-Catalyzed Oxidative C–H Activation: Strategies and Concepts, *ChemSusChem*, 2020, **13**, 3306–3356; (*i*) Y. Zheng, C. Zheng, Q. Gu and S.-L. You, Enantioselective C-H functionalization Reactions Enabled by Cobalt Catalysis, *Chem Catal.*, 2022, **2**, 2965–2985; (*j*) Q.-J. Yao and B.-F. Shi, Cobalt(III)-Catalyzed Enantioselective C– H Functionalization: Ligand Innovation and Reaction Development, *Acc. Chem. Res.*, 2025, **58**, 971–990 Ni-catalyzed: (*k*) S. M. Khake and N. Chatani, Nickel-Catalyzed C–H Functionalization Using A Non-directed Strategy, *Chem*, 2020, **6**, 1056; (*l*) R. A. Jagtap and B. Punji, Nickel-Catalyzed C–H Bond Functionalization of Azoles and Indoles, *Chem. Rec.*, 2021, **21**, 3573–3588. Cu-catalyzed: (*m*) X.-X. Guo, D.-W. Gu, Z. Wu and W. Zhang, Copper-Catalyzed C–H Functionalization Reactions: Efficient Synthesis of Heterocycles, *Chem. Rev.*, 2015, **115**, 1622–1651; (*n*) W.-H. Rao and B.-F. Shi, Recent Advances in Copper-mediated Chelation-assisted Functionalization of Unactivated C–H Bonds, *Org. Chem. Front.*, 2016, **3**, 1028–1047; (*o*) B. E. Haines, T. Kawakami, K. Kuwata, K. Murakami, K. Itami and D. G. Musaev, Cu-Catalyzed Aromatic C–H Imidation with N-fluorobenzenesulfonimide: Mechanistic Details and Predictive Models, *Chem. Sci.*, 2017, **8**, 988–1001; (*p*) Z. Zhang, P. Chen and G. Liu, Copper-catalyzed Radical Relay in C(sp^3)–H Functionalization, *Chem. Soc. Rev.*, 2022,

51, 1640–1658; (*q*) O. Daugulis, H.-Q. Do and D. Shabashov, Palladium- and Copper-Catalyzed Arylation of Carbon–Hydrogen Bonds, *Acc. Chem. Res.*, 2009, **42**, 1074–1086; (*r*) S. Rej, Y. Ano and N. Chatani, Bidentate Directing Groups: An Efficient Tool in C–H Bond Functionalization Chemistry for the Expedient Construction of C–C Bonds, *Chem. Rev.*, 2020, **120**, 1788–1887; (*s*) L.-P. Xu, B. E. Haines, M. J. Ajitha, J.-Q. Yu and D. G. Musaev, Unified Mechanistic Concept of the Copper-Catalyzed and Amide-Oxazoline-Directed C-H Bond Functionalization, *ACS Catal.*, 2021, **11**, 12620–12631.

13 (*a*) J. Huang, J. Ding, T.-M. Ding, S. Zhang, Y. Wang, F. Sha, S.-Y. Zhang, X.-Y. Wu and Q. Li, Cobalt-Catalyzed Ortho-C(sp^2)–H Amidation of Benzaldehydes with Dioxazolones Using Transient Directing Groups, *Org. Lett.*, 2019, **21**, 7342–7345; (*b*) B. Khan, V. Dwivedi and B. Sundararaju, Cp*Co(III)-Catalyzed o-Amidation of Benzaldehydes with Dioxazolones Using Transient Directing Group Strategy, *Adv. Synth. Catal.*, 2020, **362**, 1195–1200; (*c*) S. Kopf, H. Neumann and M. Beller, Manganese-catalyzed Selective C–H Activation and Deuteration by Means of A Catalytic Transient Directing Group Strategy, *Chem. Commun.*, 2021, **57**, 1137–1140; (*d*) X. Cai, C. Ma, Y. Kang, Y. Ren, X. Meng, W. Lu, S. Fan and S. Liu, Nickel-catalyzed C(sp^2)–H Alkynylation of Free α-Substituted Benzylamines Using A Transient Directing Group, *Chin. Chem. Lett.*, 2025, DOI: **10.1016/j.cclet.2025.110901**.

14 (*a*) X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, Cu(II)-Catalyzed Functionalizations of Aryl C–H Bonds Using O_2 as an Oxidant, *J. Am. Chem. Soc.*, 2006, **128**, 6790–6791; (*b*) T. Uemura, S. Imoto and N. Chatani, Amination of the ortho C—H Bonds by the $Cu(OAc)_2$-M ediated Reaction of 2-Phenylpyridines with Anilines, *Chem. Lett.*, 2007, **35**, 842–843.

15 (*a*) M. Nishino, K. Hirano, T. Satoh and M. Miura, Copper-Mediated C-H/C-H Biaryl Coupling of Benzoic Acid Derivatives and 1,3-Azoles, *Angew. Chem., Int. Ed.*, 2013, **52**, 4457–4461; (*b*) X. Wu, Y. Zhao, G. Zhang and H. Ge, Copper-Catalyzed Site-Selective Intramolecular Amidation of Unactivated C(sp^3)-H Bonds, *Angew. Chem., Int. Ed.*, 2014, **53**, 3706–3710; (*c*) Z. Wang, J. Ni, Y. Kuninobu and M. Kanai, Copper-Catalyzed Intramolecular C(sp^3)-H and C(sp^2)-H Amidation by Oxidative Cyclization, *Angew. Chem., Int. Ed.*, 2014, **53**, 3496–3499; (*d*) H. Kim, J. Heo, J. Kim, M.-H. Baik and S. Chang, Copper-Mediated Amination of Aryl C–H Bonds with the Direct Use of Aqueous Ammonia via a Disproportionation Pathway, *J. Am. Chem. Soc.*, 2018, **140**, 14350–14356; (*e*) Q. Zhang, T. Wang, X. Zhang, S. Tong, Y.-D. Wu and M.-X. Wang, Radical Reactivity, Catalysis, and Reaction Mechanism of Arylcopper(II) Compounds: The Missing Link in Organocopper Chemistry, *J. Am. Chem. Soc.*, 2019, **141**, 18341–18348; (*f*) J.-F. Yu, J.-J. Li, P. Wang and J.-Q. Yu, Cu-Mediated Amination of (Hetero)Aryl C–H Bonds with NH Azaheterocycles, *Angew. Chem., Int. Ed.*, 2019, **58**, 18141–18145; (*g*) G. Tan, I. Maisuls, F. Strieth-Kalthoff, X. Zhang, C. Daniliuc, C. A. Strassert and F. Glorius, AIE-Active Difluoroboron Complexes with N,O-Bidentate Ligands: Rapid Construction by Copper-Catalyzed C-H Activation, *Adv. Sci.*, 2021, **8**, 2101814; (*h*) H. M. Begam, S. Nandi and R. Jana, A Directing Group Switch in Copper-catalyzed Electrophilic C-H Amination/Migratory Annulation Cascade: Divergent Access to Benzimidazolone/Benzimidazole, *Chem. Sci.*, 2022, **13**, 5726–5733; (*i*) S.-B. Yan, R. Wang, Z.-G. Li, A.-N. Li, C. Wang and W.-L. Duan, Copper-catalyzed Asymmetric C(sp^2)–H Arylation for the Synthesis of P- and Axially Chiral Phosphorus Compounds, *Nat. Commun.*, 2023, **14**, 2264–2273; (*j*) X. Kuang, J.-J. Li, T. Liu, C.-H. Ding, K. Wu, P. Wang and J.-Q. Yu, Cu-mediated Enantioselective C–H Alkynylation of Ferrocenes with Chiral BINOL ligands, *Nat. Commun.*, 2023, **14**, 7698–7708; (*k*) A. Manna, K. Khamaru, V. B. Pathi, S. Sett, P. Ghosh and B. Banerji, Copper(II)-Mediated Dual Reactivity of 2-(5-Phenylisoxazol-3-yl) aniline: Directed Amination and Oxidative C(=O)–C Cleavage of Amides Enabling Direct Access to Urea Derivatives, *Org. Lett.*, 2024, **26**, 8774–8779; (*l*) A. M. Nair, R. Rahaman, J. Patra and C. M. R. Volla, Dual Copper Photoredox C–H Alkynylation with Arylacetylenes, *Org. Lett.*, 2024, **26**, 7822–7827; (*m*) M. Kumar, A. K. Sharma, K. Ishu and K. N. Singh, A Copper-Catalyzed Synthesis of Pyridoquinazolinones via C(sp^2)–H Functionalization and Annulation of Benzoic Acids with 2-Aminopyridines, *Org. Lett.*, 2024, **26**, 10517–10522; (*n*) Z.-Z. Zhang, G. Zhou, Q. Yue, Q.-J. Yao and B.-F. Shi, Copper/BINOL-Catalyzed Enantioselective C–H Functionalization toward Planar Chiral Ferrocenes Under Mild Conditions, *ACS Catal.*, 2024, **14**, 4030–4039; (*o*) J.-Y. Ma, Q.-J. Yao, L.-C. Jiang, F.-R. Huang, Q. Yue and B.-F. Shi, Copper-Mediated Enantioselective C–H Thiolation of Ferrocenes Enabled by the BINOL Ligand, *J. Am. Chem. Soc.*, 2025, **147**, 7061–7069.

16 (*a*) J. I. Higham and J. A. Bull, Amine–Catalyzed Copper–Mediated C–H Sulfonylation of Benzaldehydes via a Transient Imine Directing Group, *Angew. Chem., Int. Ed.*, 2022, **61**, e202202933; (*b*) J. Zhu, Y. Ye, Y. Yan, J. Sun and Y. Huang, Dual Copper- and Aldehyde-Catalyzed Transient C-H Sulfonylation of Benzylamines, *Org. Lett.*, 2023, **25**, 5324–5328.

17 Z. Shi, S. Chen, Q. Xiao and D. Yin, Formation and Disproportionation of Xanthenols to Xanthenes and Xanthones and Their Use in Synthesis, *J. Org. Chem.*, 2021, **86**, 3334–3343.

18 (*a*) C. Kaiser, A. M. Pavloff, E. Garvey, P. J. Fowler, D. H. Tedeschi, C. L. Zirkle, E. A. Nodiff and A. J. Saggiomo, Analogs of Phenothiazines. 4. Effect of Structure Upon Neuropharmacological Activity of Some Chlorpromazine Analogs of the Diphenylmethane Type, *J. Med. Chem.*, 1972, **15**, 665–673; (*b*) F. Villani, A. Nardi, A. Salvi and S. Maiorana, CN1867558(A), 2006.

19 J. Mahapatra, S. N. Quraishi, A. David, S. Sampson and C. E. Adams, Flupenthixol decanoate (depot) for schizophrenia or other similar psychotic disorders, *Cochrane*

Database Syst. Rev., 2014, DOI: 10.1002/14651858.CD001470.pub2.

20 (*a*) B. Bang-Andersen, T. Ruhland, M. Jørgensen, G. Smith, K. Frederiksen, K. G. Jensen, H. Zhong, S. M. Nielsen, S. Hogg, A. Mørk and T. B. Stensbøl, Discovery of 1-[2-(2,4-Dimethylphenylsulfanyl)phenyl] piperazine (Lu AA21004): A Novel Multimodal Compound for the Treatment of Major Depressive Disorder, *J. Med. Chem.*, 2011, **54**, 3206–3221; (*b*) X. F. Duan, CN104098530 (A), 2014.