

## RESEARCH ARTICLE

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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 intermediates relevant to the synthesis of drug and bioactive molecule.

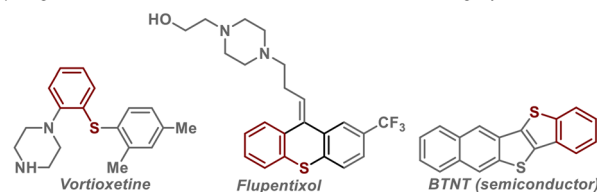
Aryl sulfides are important structural motifs that are ubiquitous in pharmaceutical drugs and bioactive molecules, exhibiting various bioactivities as therapeutic compounds.<sup>1</sup> Furthermore, aryl sulfides have significant applications in functional organic materials, as the introduction of sulfur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

In recent years, transition metal-catalyzed C–H functionalization has emerged as a robust tool for the construction of aryl C–S bonds.<sup>6</sup> 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.<sup>7</sup> 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<sup>3</sup>)-H functionalization,<sup>8</sup> the transient directing group (TDG) strategy has gained significant attention and made considerable advancements over the past few decades.<sup>9</sup> In this strategy, an

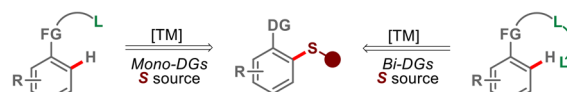
imine is typically formed *in situ* to act as the directing group that promotes C–H activation.<sup>10</sup> Despite this progress, C–H thiolation *via* the transient directing group strategy still remains underdeveloped. It is important to note that two major potential obstacles must be overcome to develop such reactions: (1) catalyst poisoning by strongly coordinating sulfur atoms<sup>4c,6d</sup> and (2) the tendency of sulfides to undergo oxidation.<sup>11</sup> 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

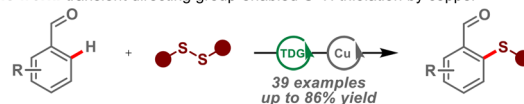
a) Drug and bioactive molecules and functional materials containing aryl sulfide moieties



b) Previous work: DG-assisted direct C–H thiolation



c) This work: transient directing group-enabled C–H thiolation by copper



- TDG-promoted C–H thiolation reaction
- Inexpensive green catalyst
- Broad substrate scope
- Facile transformation

**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,<sup>12</sup> 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.<sup>13</sup> 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,<sup>14</sup> copper-catalyzed/mediated oxidative C–H functionalization has gained significant attention and a number of reactions have been developed.<sup>7a,15</sup> 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.<sup>16</sup> 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<sub>1</sub>**) failed to facilitate the thiolation reaction, the desired thiolated product **3a** was obtained in a 22% yield using a  $\beta$ -amino acid (**TDG<sub>2</sub>**) in the presence of 50 mol% Cu(OAc)<sub>2</sub> and 2 equivalents of TMSOAc in DMSO. The yield improved to 37% with the use of 2-aminobenzoic acid (**TDG<sub>3</sub>**). 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<sub>4</sub>**), while an electron-withdrawing trifluoromethyl group resulted in a lower yield (**TDG<sub>5</sub>**). Notably, the yield dramatically increased to 69% with the use of 2-aminobenzoic acid containing a fluoro group (**TDG<sub>6</sub>**). However, the presence of two fluoro groups led to a decrease in yield (**TDG<sub>7</sub>**). 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<sub>8</sub>**).

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 reac-

**Table 1** Optimization of reaction conditions for the thiolation of aldehydes<sup>a,b</sup>

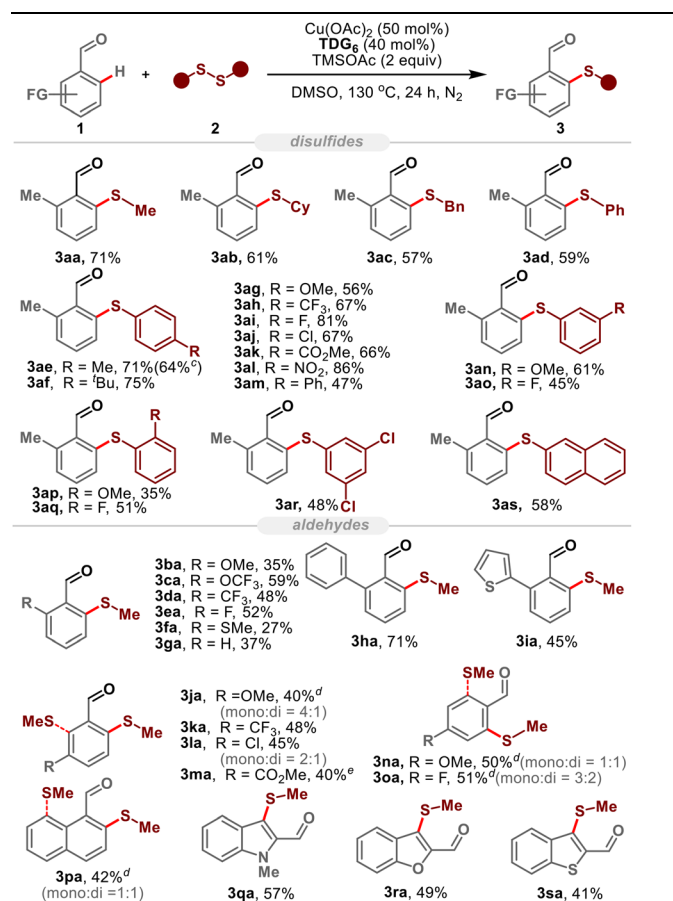
Entry	Variations	Yield <sup>b</sup> (%)
1	None	69
2	With AcOH (2 equiv.) instead of TMSOAc	NR
3	HFIP instead of DMSO	13
4	w/o Cu(OAc) <sub>2</sub>	NR
5	w/o TDG <sub>6</sub>	NR
6	Cu(OAc) <sub>2</sub> (25 mol%)	34
7	TDG <sub>6</sub> (20 mol%)	10
8	TMSOAc (1 equiv.)	41
9	18 h	63
10	120 °C	40
11	DMSO (3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

<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), Cu(OAc)<sub>2</sub> (50 mol%), TDG (40 mol%), TMSOAc (2 equiv.), DMSO (2 mL), 130 °C, 24 h, N<sub>2</sub>. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis using CH<sub>2</sub>Br<sub>2</sub> as an internal standard. <sup>c</sup> **1a** was recovered in a yield of 22%. <sup>d</sup> Isolated yields. <sup>e</sup> DMSO (4 mL). NR: no reaction.

tion 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)<sub>2</sub> or TDG<sub>6</sub> (entries 4 and 5). Decreasing the amounts of Cu catalyst, TDG<sub>6</sub>, 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<sub>2</sub> 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)<sub>2</sub> (50 mol%), TDG<sub>6</sub> (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<sup>2</sup>)-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 2** Substrate scope of the thiolation of aldehydes.<sup>a,b</sup>

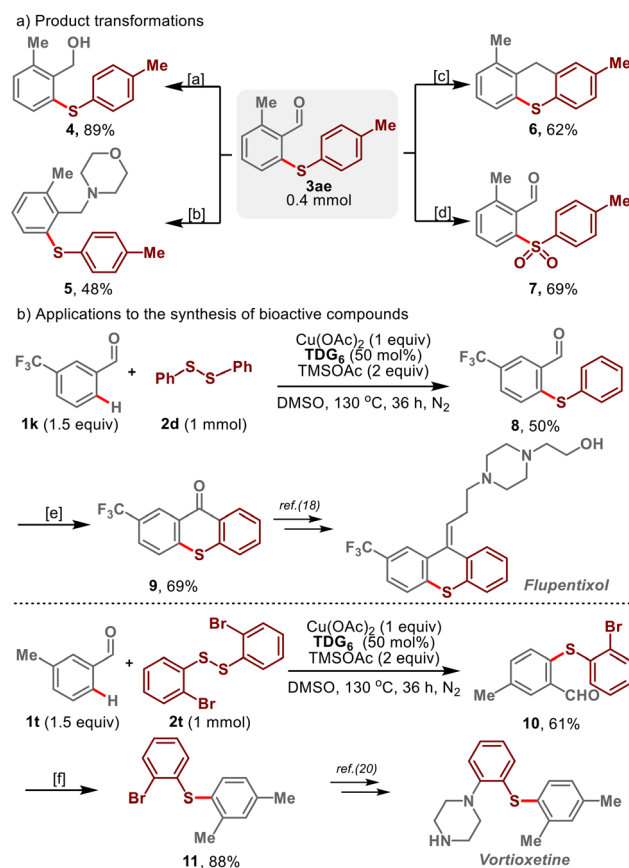
<sup>a</sup> Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), Cu(OAc)<sub>2</sub> (50 mol%), TDG<sub>6</sub> (40 mol%), TMSOAc (2 equiv.), DMSO (3 mL), 130 °C, 24 h, N<sub>2</sub>. <sup>b</sup> Isolated yield. <sup>c</sup> Gram scale reaction. <sup>d</sup> Overall yield of mono- and dithiolated products. <sup>e</sup> Cu(OAc)<sub>2</sub> (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<sub>3</sub> 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<sub>3</sub>, CF<sub>3</sub> and F. A methylthio, phenyl, and even thiophenyl group were also com-

patible. 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<sub>4</sub>-mediated cyclization followed by reduction,<sup>17</sup> resulting



**Scheme 2** Product transformations. [a] NaBH<sub>4</sub> (2 equiv.), MeOH, 0 °C–r.t., 2 h. [b] NaBH<sub>3</sub>CN (2.0 equiv.), morpholine (2 equiv.), MeOH, 0 °C–r.t., 2 h. [c] TiCl<sub>4</sub> (4 equiv.), DCM, r.t. 24 h, then Et<sub>3</sub>SiH (4 equiv.), 12 h, r.t.. [d] Oxone (3 equiv.), THF/H<sub>2</sub>O (1:1), r.t., 3 h. [e] 1, TiCl<sub>4</sub> (4 equiv.), DCM, r.t. 24 h, then H<sub>5</sub>O<sub>6</sub> (1.75 equiv.), CrO<sub>3</sub> (2.5 mol%), 30 min, r.t.. [f] N<sub>2</sub>H<sub>4</sub>·H<sub>2</sub>O (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.<sup>4d</sup>

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,<sup>18</sup> 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.<sup>19</sup> Additionally, the C–H thiolation reaction facilitates easy access to compound **11**, which can be transformed into Vortioxetine, a serotonin modulator and antidepressant.<sup>20</sup>

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<sub>2</sub>O, 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.<sup>7g</sup>

## 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

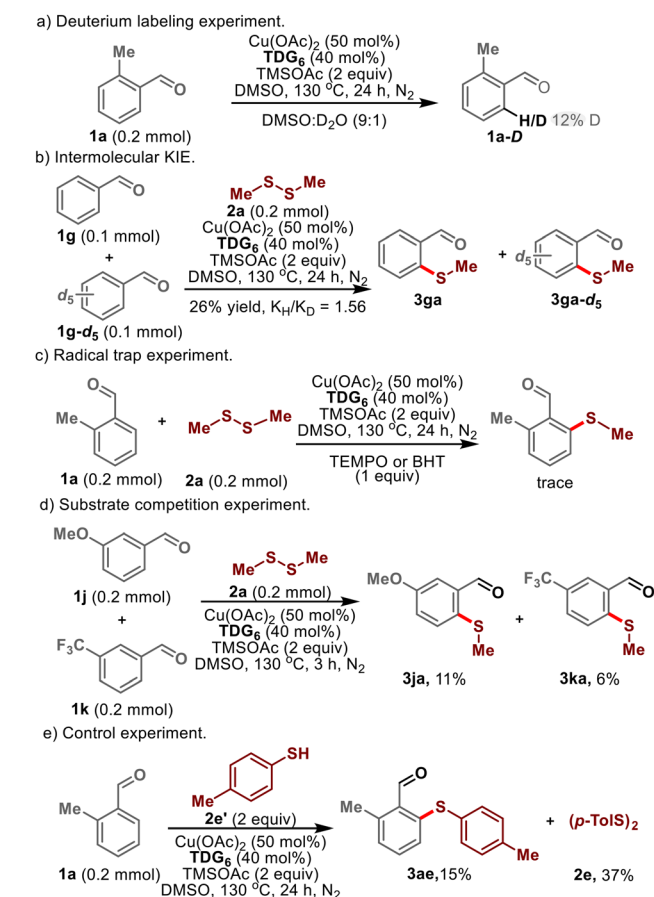
M. Mei, D. Yi, F. Meng and J. Tang performed the experiments and analysed the data. Y. Zhang conceived the project and analysed experimental data. The manuscript was written by Y. Zhang and M. Mei.

## 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.



Scheme 3 Mechanistic studies.



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