How to cite: *Angew. Chem. Int. Ed.* **2023**, *62*, e202305510
doi.org/10.1002/anie.202305510

Cross-coupling

# Manganese-Catalyzed Redox-Neutral Thiolation of Alkyl Halides with Thioformates

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**Abstract:** Transition metal-catalyzed C–S cross-coupling has emerged as an important strategy to furnish thioethers; however, the dominant utilization of noble metal catalysts as well as the construction of challenging C($sp^3$)–S bonds by transition metal-catalysis remain highly problematic. Earth-abundant manganese has gathered increasing interest as an attractive catalyst for new reaction development; nevertheless, C($sp^3$)–S cross-coupling reaction by manganese catalysis has not been reported. Herein, we disclose a highly efficient manganese-catalyzed redox-neutral thiolation of a broad range of alkyl halides with thioformates as practical sulfuration agents. Strategically, employing easily synthesized thioformates as thiyl radical precursors allows access to various aryl and alkyl thioethers in good to excellent yields. Notably, this redox-neutral method avoids the utilization of strong bases, external ligands, forcing reaction conditions, and stoichiometric manganese, thus presenting apparent advantages, such as broad substrate scope, excellent functional group compatibility, and mild reaction conditions. Finally, the utilities of this method are also illustrated by downstream transformations and late-stage thiolation of structurally complex natural products and pharmaceuticals.

## Introduction

C–S bond is widely present in proteins, natural products, pharmaceuticals, and organic materials.[1] Besides, organosulfur compounds often function as versatile synthetic precursors for diverse useful transformations.[2] In light of its significant importance, transition metal-catalyzed cross-coupling reactions of aryl-based electrophiles with thiols as nucleophilic thiolates have emerged as an important tool for constructing C–S bonds (Figure 1a, type I).[3] However, strong binding of thiolates to metals often results in catalyst deactivation and low efficiency. Although different kinds of organosulfur reagents have been developed to avoid the direct utilization of thiols in cross-coupling, they are

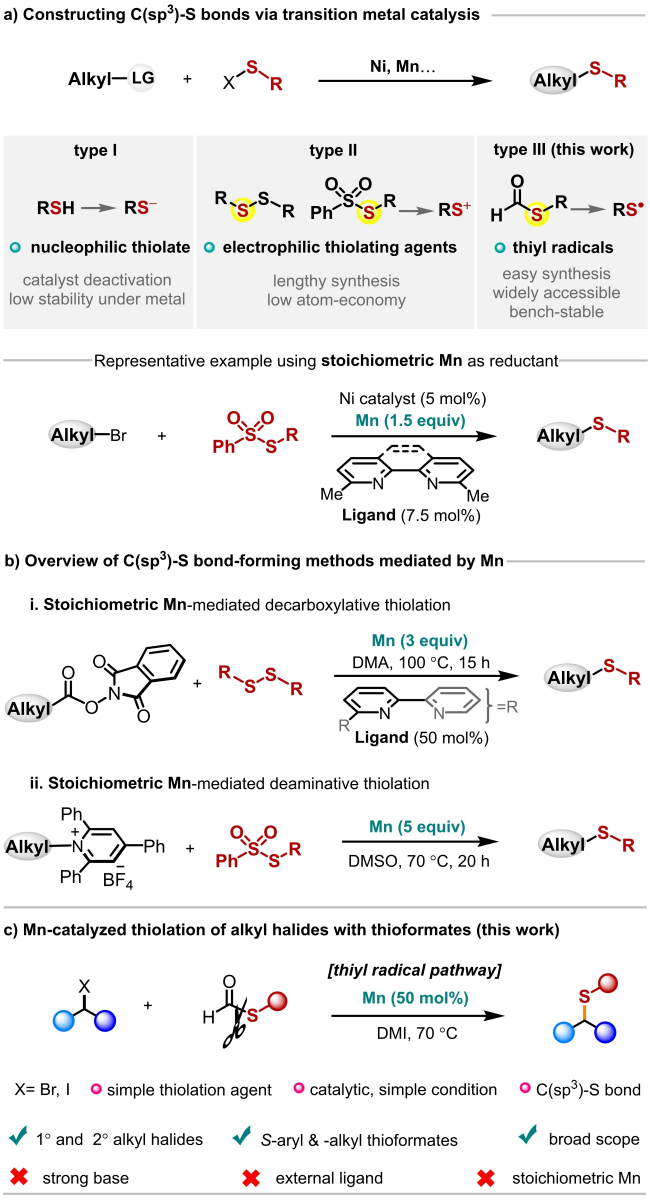


***Figure 1.*** The background of C($sp^3$)–S cross-coupling reactions by Mn.

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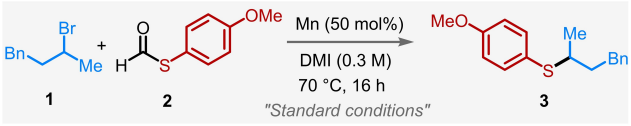
generally employed as electrophilic thiolating agents to form C($sp^2$)–S bond (Figure 1a, type II).[4] Moreover, most of these reagents require lengthy synthetic procedures from thiols and possess limited substrate scope, hampering further applications in synthetic chemistry. Recently, by means of photochemistry[5] and electrochemistry,[6] thiyl radicals have been introduced as an important class of coupling intermediates in the C($sp^2$)–S bond-forming reactions, which has gathered growing interest because of high reactivity and eschewing catalyst deactivation (Figure 1a, type III). Despite these advances, developing novel and efficient organosulfur reagents as thiyl radical precursors for diverse types of transformations (e.g., C($sp^3$)–S bonds) is highly desirable and meaningful.

Conventional methods for constructing C($sp^3$)–S bonds mainly rely on the nucleophilic substitution reactions between the structurally simple alkyl halides and thiols with the requirement of stoichiometric base and forcing reaction conditions, thus limiting substrate counterparts with narrow functional groups. Compared to the booming methods for furnishing C($sp^2$)–S bonds via transition metal catalysis, the delivery of the C($sp^3$)–S bond remains highly problematic, likely due to potential β-H elimination and inert reactivity of alkyl species towards metal.[7] Therefore, the development of efficient and general methods for the construction of the C($sp^3$)–S bond that delivers $sp^3$-enriched centers under mild conditions using inexpensive and readily available organosulfur reagents is of significant value in terms of biological interest.[1]

Compared to expensive noble metals,[8–12] earth-abundant metals,[13–17] from the standpoint of economic and environmental features, are more desirable in transition metal-catalyzed cross-coupling reactions for the construction of C–S bond. In particular, manganese is the third most abundant transition metal in the Earth's crust, possessing low cost, low toxicity, and environmentally benign features, holding the ability to generate complexes bearing coordination numbers up to 7.[18] The wide range of available oxidation states (−3 to +7) of manganese provides great potential redox activity in organometallic chemistry and catalysis. Therefore, manganese catalysts represent appealing and practical alternatives to new reaction development. In contrast with other earth-abundant metals, C–S bond-forming cross-coupling by Mn has been largely underdeveloped.[17] The sporadic examples remain highly limited, such as requiring external ligands, strong bases, high reaction temperatures, or stoichiometric Mn. Notably, Ji and Wang reported a nickel-catalyzed reductive thiolation of generally primary alkyl bromides with thiosulfonates as electrophilic thiolation reagents using stoichiometric Mn as a reductant (Figure 1a).[16j] Although recent efforts from Wang and Liu have been devoted to achieving Mn-mediated C($sp^3$)–S cross-coupling, all examples, unfortunately, suffered from the requirement of stoichiometric Mn (>3 equiv) (Figure 1b).[17c] To the best of our knowledge, the effort to build up C($sp^3$)–S bonds by Mn catalysis has not been documented. Therefore, exploring concise, mild, and highly efficient Mn-catalyzed C($sp^3$)–S cross-coupling reactions using inexpensive and readily accessible thiolation agents remains a worthwhile pursuit.

Thioformates are readily accessible from cheap formic acid and thiols in one simple synthetic step, enabling them

***Table 1:*** Optimization of reaction conditions.[a]




| Entry | Changes to standard conditions | NMR Yield (%)[b] |
|---|---|---|
| 1 | none | 94(90)[c,d] |
| 2 | no Mn | 0 |
| 3 | Mn (30 mol%) was used | 50 |
| 4 | $Ni(cod)_2$ (10 mol%), Mn (30 mol%) | 60 |
| 5 | $Ni(cod)_2$ (10 mol%), Mn (30 mol%), bpy (11 mol%) | 82 |
| 6 | $Ni(cod)_2$ (10 mol%) | <5 |
| 7 | Fe or Zn | 49 or 70 |
| 8 | Mg or Al | 0 or 0 |
| 9 | DMA | 89 |
| 10 | DMF | 82 |
| 11 | 1,4-dioxane | 0 |
| 12 | 50 or 80 °C | 40 or 95 |
| 13 | 4-OMePhSH | 65[c] |
| 14 | 4-OMePhSNa | 55[c] |
| 15 | $(4\text{-OMePhS})_2$ | <10[c] |

[a] Reaction conditions: **1** (0.30 mmol, 1.0 equiv), **2** (0.36 mmol, 1.2 equiv), Mn (50 mol%), solvent (0.9 mL), 70 °C, 16 h. [b] Yield based on $^1$H NMR. [c] Isolated yield. [d] 20% total yield of 4-OMePhSH and $(4\text{-OMePhS})_2$ was detected by GC.

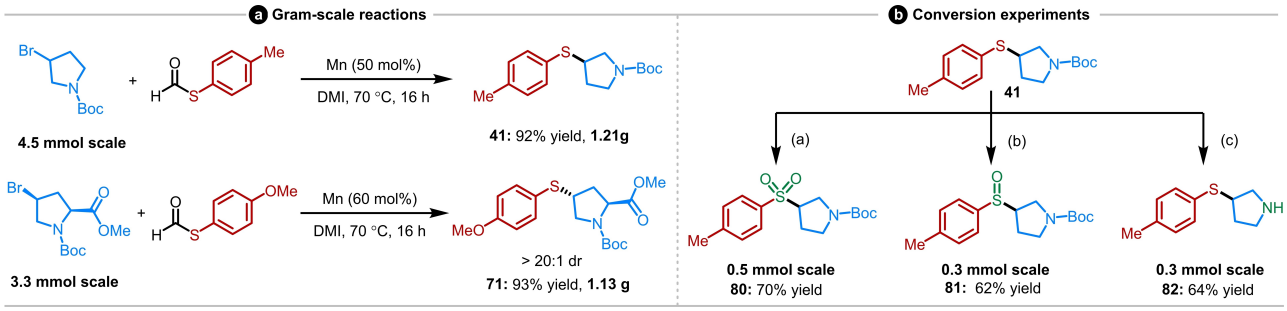
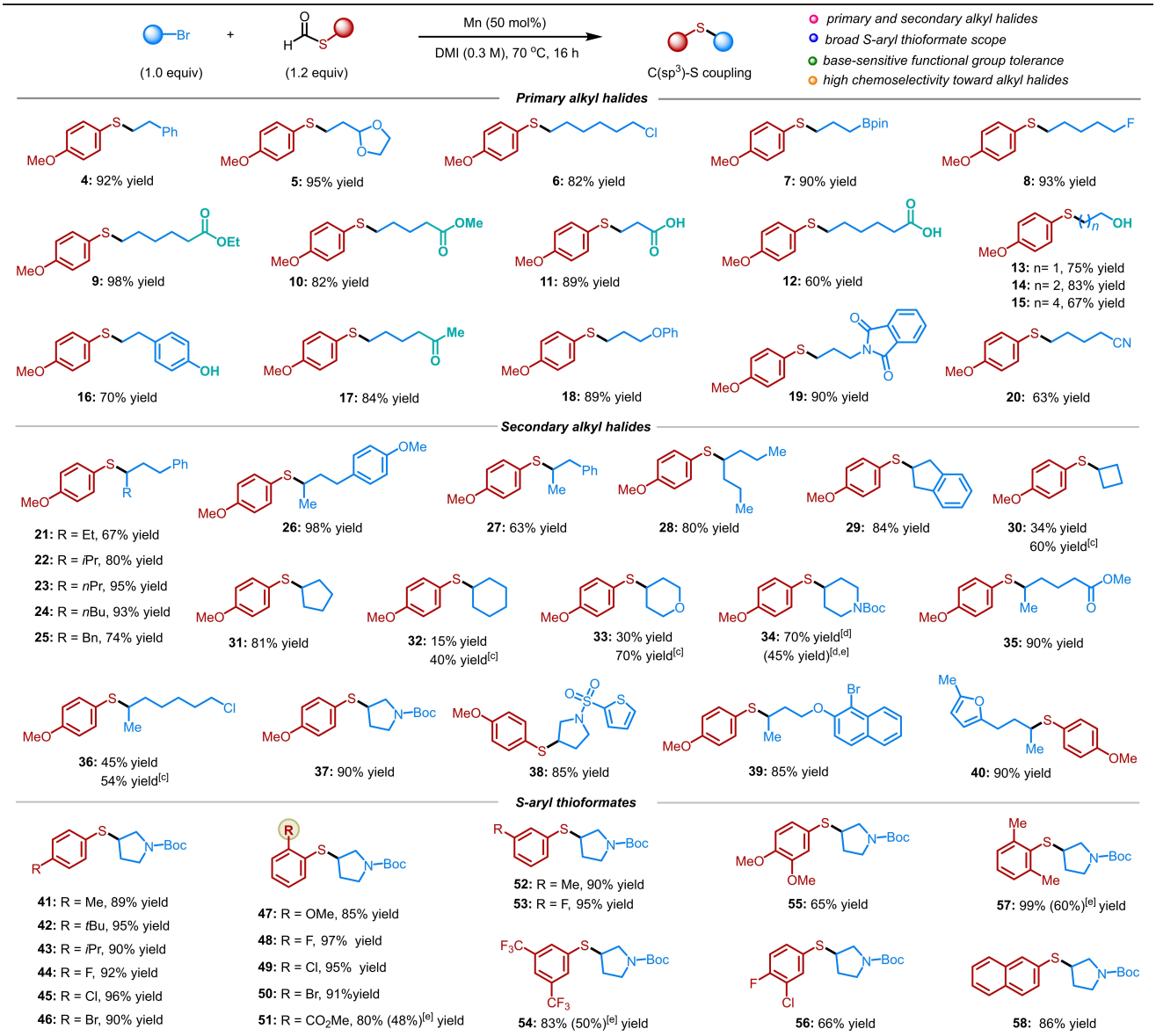



***Figure 2.*** Gram-scale reactions and diversification of products. (a) *m*-CPBA (2.2 equiv), DCM, rt. (b) *m*-CPBA (1.2 equiv), DCM, rt. (c) TFA, DCM, 0 °C to rt.

***Table 2:*** Scope of alkyl halides and *S*-aryl thioformates.[a,b]




[a] Reaction conditions: alkyl bromides (0.30 mmol, 1.0 equiv), *S*-aryl thioformates (0.36 mmol, 1.2 equiv), Mn (50 mol%), DMI (0.9 mL), 70 °C, 16 h. [b] Isolated yield. [c] $Ni(cod)_2$ (10 mol%), **L** (bpy) (11 mol%), Mn (30 mol%). [d] Alkyl iodide was used. [e] Corresponding thiophenol was used.

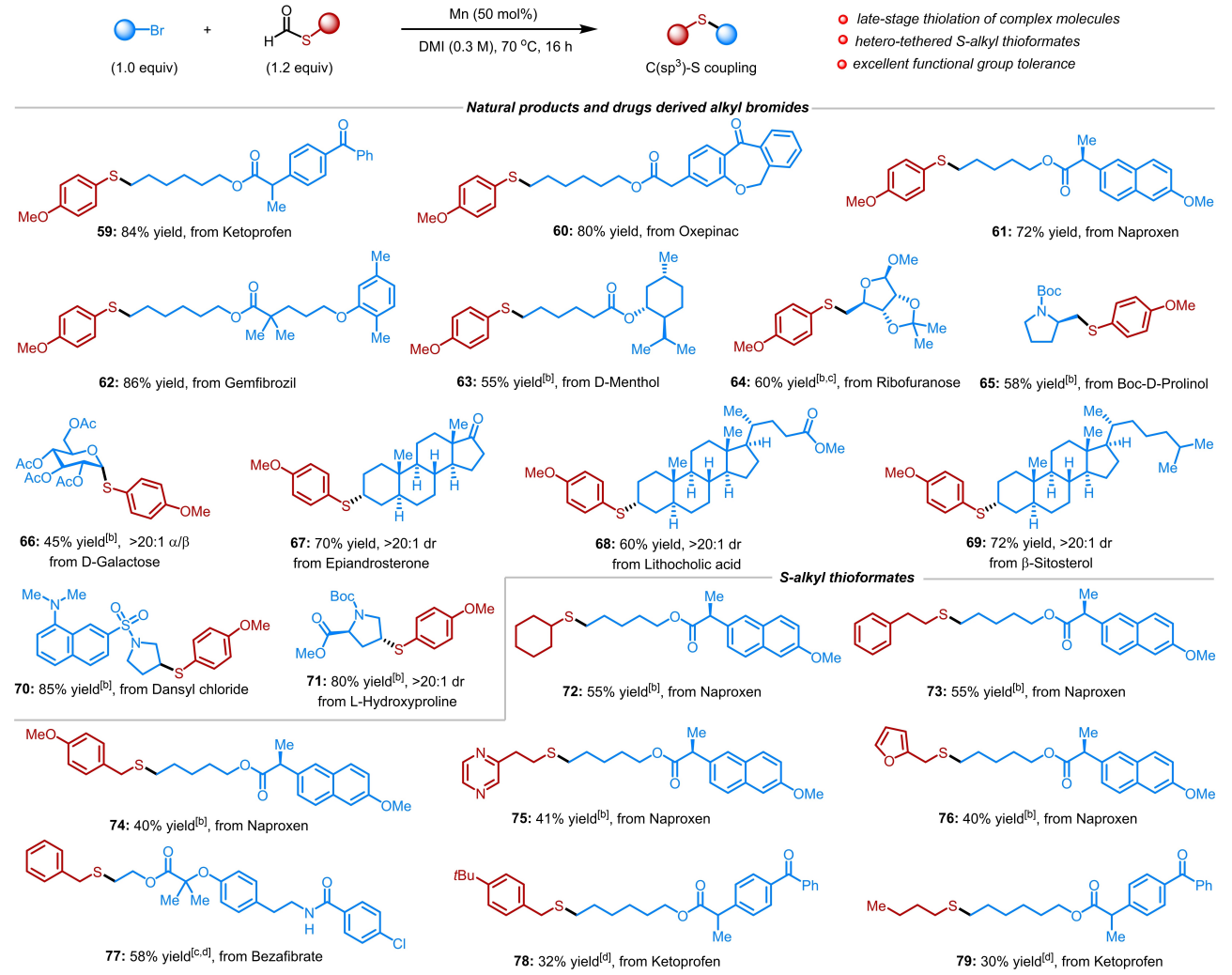
to be versatile formylating reagents[19] and CO-releasing molecules[20] in organic synthesis. However, the utilization of structurally simple thioformates as thiolation reagents for delivering C–S bonds is still unknown. Herein, we present a highly efficient Mn-catalyzed redox-neutral $C(sp^3)$–S cross-coupling reaction of alkyl halides with thioformates as ideal alternative thiolating agents under mild conditions (Figure 1c). Mechanistically, by using thioformates as thiyl radical precursors, diverse aryl and alkyl thioethers are synthesized in good to excellent yields, avoiding the employment of strong bases, extra ligands, high reaction temperatures, and stoichiometric Mn. We envisioned that the successful activation of this class of simple and readily accessible thioformates by Mn catalysis would not only offer a general and practical platform for making libraries of organosulfur frameworks but also open up a new frontier for the new reaction development by Mn catalysis.

## Results and Discussion

### Reaction Optimization

We commenced our studies by exploring Mn-catalyzed thiolation of alkyl bromide **1** with thioformate **2** (Table 1). In the presence of Mn (50 mol%) in 1,3-dimethyl-2-imidazolidinone (DMI) at 70 °C for 16 h, the desired product **3** was obtained in 94% yield, together with a combined 20%

***Table 3:*** Late-stage thiolation of complex molecules and *S*-alkyl thioformate scope.[a]




[a] Reaction conditions: alkyl bromides (0.30 mmol, 1.0 equiv), thioformates (0.36 mmol, 1.2 equiv), Mn (50 mol%), DMI (0.9 mL), 70 °C, 16 h. [b] Mn (60 mol%). [c] Alkyl iodide was used. [d] Mn (80 mol%).

yield of 4-OMePhSH and $(4\text{-OMePhS})_2$ (entry 1). Without adding Mn, no product **3** was detected, while considerable disulfide was formed (entry 2). These results indicated that the thiyl radical is likely formed from thioformate. Ultrapure Mn powders from different purities and different suppliers gave similar yields, excluding the potential of reactivity arising from trace metal contaminants (see Supporting Information). When the catalyst loading was reduced to 30 mol%, the yields decreased dramatically (entry 3). Other manganese species (10 mol%) used individually or in combination with various ligands (11 mol%) produced worse results (see Supporting Information). The combination of Mn (30 mol%) and $Ni(cod)_2$ (10 mol%) afforded a 60% yield (entry 4), additional bipyridine (bpy) ligand (11 mol%) could increase the yield to 82% (entry 5). However, $Ni(cod)_2$ (10 mol%) gave a much worse result (entry 6). Other earth-abundant metals were also examined; iron and zinc gave 49% and 70% yield, respectively, while magnesium and aluminum could not afford any product (entries 7 and 8). Various solvents were investigated, such as dimethylacetamide (DMA), dimethylformamide (DMF), and 1,4-dioxane, but no improvements were detected (entries 9–11). Decreasing the reaction temperature to 50 °C delivered a lower yield, and increasing the temperature to 80 °C only slightly improved the yield (entry 12). When 4-OMePhSH or 4-OMePhSNa was employed instead of thioformate **2**, a much lower yield was observed (entries 13 and 14). Notably, thiol showed a much lower reaction rate (see Supporting Information). $(4\text{-OMePhS})_2$ only delivered $<10$% yield (entry 15). Various stir rates (400, 800, and 1200 rpm) were examined to generate similar yields, suggesting that stir rate does not significantly affect the yield (see Supporting Information).

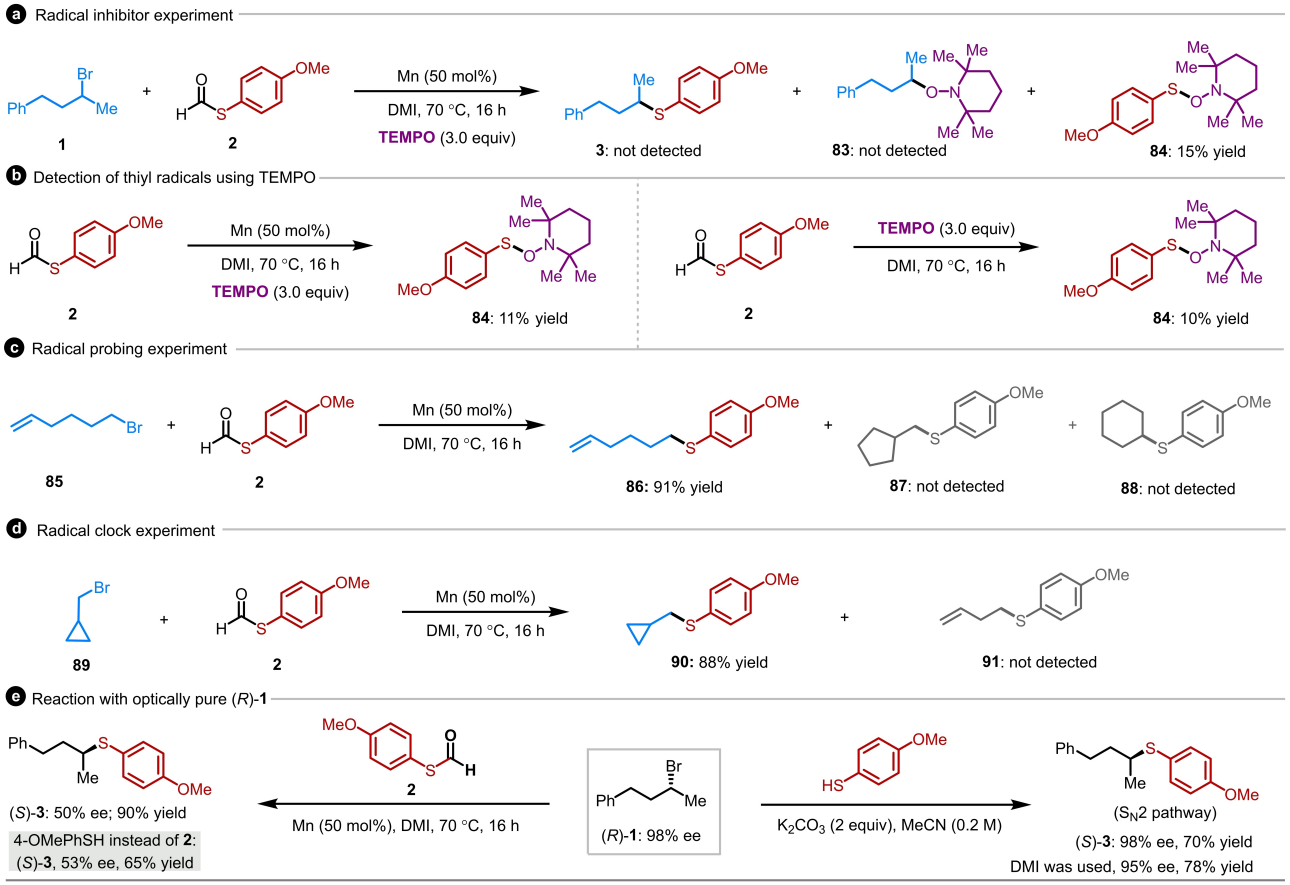



***Figure 3.*** Mechanistic studies.

### *Evaluation of Substrate Scope*

With the optimal reaction conditions in hand, we next evaluated the scope of alkyl halides and thioformates (Table 2). Diverse primary alkyl halides were examined, giving the corresponding thioethers **4**–**20** in 60–98 % yields. Dihaloalkanes (for **6** and **8**) exhibited excellent chemoselectivities. Bpin-substituted halide proceeded well, delivering the corresponding thioether **7** in 90 % yield, which showed strong potential for further transformations. Intriguingly, one of the notable advantages of this method was that the alkyl halides (products **9**–**17**) containing highly reactive functional groups, such as ester, carboxylic acid, alcohol, phenol, and ketone, which are not generally compatible with traditional strong alkaline reaction conditions, reacted smoothly under standard conditions. Different kinds of secondary alkyl halides, including linear and cyclic halides, were also tolerated, affording the corresponding thioethers **21**–**40** in 15–98 % yields. For alkyl halides (for **30**, **32**, **33**, and **36**), standard conditions produced much lower yields, while the integration of Mn with $Ni(cod)_2$ could improve the yields. Unfortunately, tertiary alkyl halides were not tolerated under current reaction conditions, likely due to the slow oxidative addition of Mn catalyst to sterically hindered alkyl halides (see Supporting Information). Various *S*-aryl thioformates were compatible with standard conditions, resulting in the corresponding thioethers **41**–**58** in 65–99 % yields. Diverse electron-donating or electron-withdrawing groups at the *para*, *meta*, or *ortho* position of the aryl moiety of thioformates did not display apparent influences on the yields. It was worth stressing that the highly sterically demanding *S*-aryl thioformates were well eligible for this Mn-catalyzed C–S coupling reaction, delivering the products in up to 99 % yields (**47**–**51**, **57**). *S*-naphthalenyl thioformate was an acceptable substrate, leading to the corresponding thioether **58** in 86 % yield. To showcase the power and advantage of this method, some comparative reactions using thiols as sulfenylating agents were carried out. In stark contrast, all thiols, uniformly, led to much worse results than the corresponding thioformates (see products **34**, **51**, **54**, and **57**).

After proving the success of this Mn-catalyzed thiolation, we were encouraged further to explore the late-stage thiolation of natural products and pharmaceuticals (Table 3). Alkyl halides derived from drugs ketoprofen, oxepinac, naproxen, and gemfibrozil, as well as natural products epiandrosterone, lithocholic acid, and β-sitosterol were compatible with *S*-aryl thioformate **2** under standard conditions, leading to the corresponding thioethers in 60–86 % yields. Additionally, alkyl halides derived from complex molecules D-menthol, ribofuranose, Boc-D-prolinol, D-galactose, dansyl chloride, and L-hydroxyproline reacted

well by employing 60 mol % Mn, giving the corresponding thioethers in 45–85 % yields. Notably, this method imparts high levels of stereoselectivity, e.g., the alkyl bromides (products **66–69** and **71**) furnished the corresponding products with >20:1 dr. Besides *S*-aryl thioformates, diverse *S*-alkyl thioformates were also tolerated under more catalyst loading. Alkyl halides derived from the commercially available drugs naproxen, bezafibrate, and ketoprofen performed well, delivering the corresponding thioethers in 30–58 % yields.

### *Synthetic Applications*

To showcase the scalability and practical applicability of this method, two gram-scale reactions were performed to give thioethers **41** (92 %) and **71** (93 %) (Figure 2a). Various transformations of thioether **41** were also investigated (Figure 2b). For example, under different amounts of 3-chlorobenzoic acid (*m*-CPBA) in dichloromethane (DCM), thioether **41** underwent divergent oxidations, affording sulfone **80** (70 %) and sulfoxide **81** (62 %). After the removal of the Boc group under trifluoroacetic acid (TFA), thioether **82** was obtained in 64 % yield.

### *Mechanistic Studies*

To gain more mechanistic insight of this protocol, a series of control experiments were conducted. When 2,2,6,6-tetramethylpiperidinooxy (TEMPO), a well-known radical scavenger, was added to the reaction between alkyl bromide **1** with thioformate **2** under standard conditions, thioether **3** and compound **83** were not detected, while compound **84** was obtained in 15 % yield (Figure 3a). When only **2** and TEMPO were used under standard conditions, **84** could also be obtained in 11 % yield (Figure 3b). Without adding Mn, **84** was still obtained in 10 % yield from **2** and TEMPO under DMI. These results indicated that the reaction mechanism likely involves thiyl radical from thioformate, and the formation of thiyl radical does not need the participation of Mn. Furthermore, the thiyl radical species were also demonstrated by the considerable formation of disulfide (Table 1, entry 2).[20] However, heated in DMI in the absence of Mn, the thioformate decomposed to generate CO very slowly. By adding a catalytic amount of Mn, the generation of CO from the decomposition of thioformate was significantly accelerated, which was detected by GC (see Supporting Information). These results demonstrated that the catalyst Mn could largely facilitate the generation of CO. Meanwhile, it could promote the formation of thiyl radicals with the aid of gas CO release concomitantly.

When alkyl bromide **85** was employed under standard conditions, thioformate **86** was isolated in 91 % yield, while cyclic products **87** and **88** were not formed (Figure 3c). Additionally, no corresponding thiol-ene products were observed. Furthermore, (bromomethyl)cyclopropane **89** was also tolerated, giving thioformate **90** in 88 % yield, while ring-open product **91** was not detected (Figure 3d). These results suggested that no alkyl radical is formed from alkyl halides in the catalytic cycle. Furthermore, when optically pure (*R*)-**1** (98 % ee) was employed in the reaction with

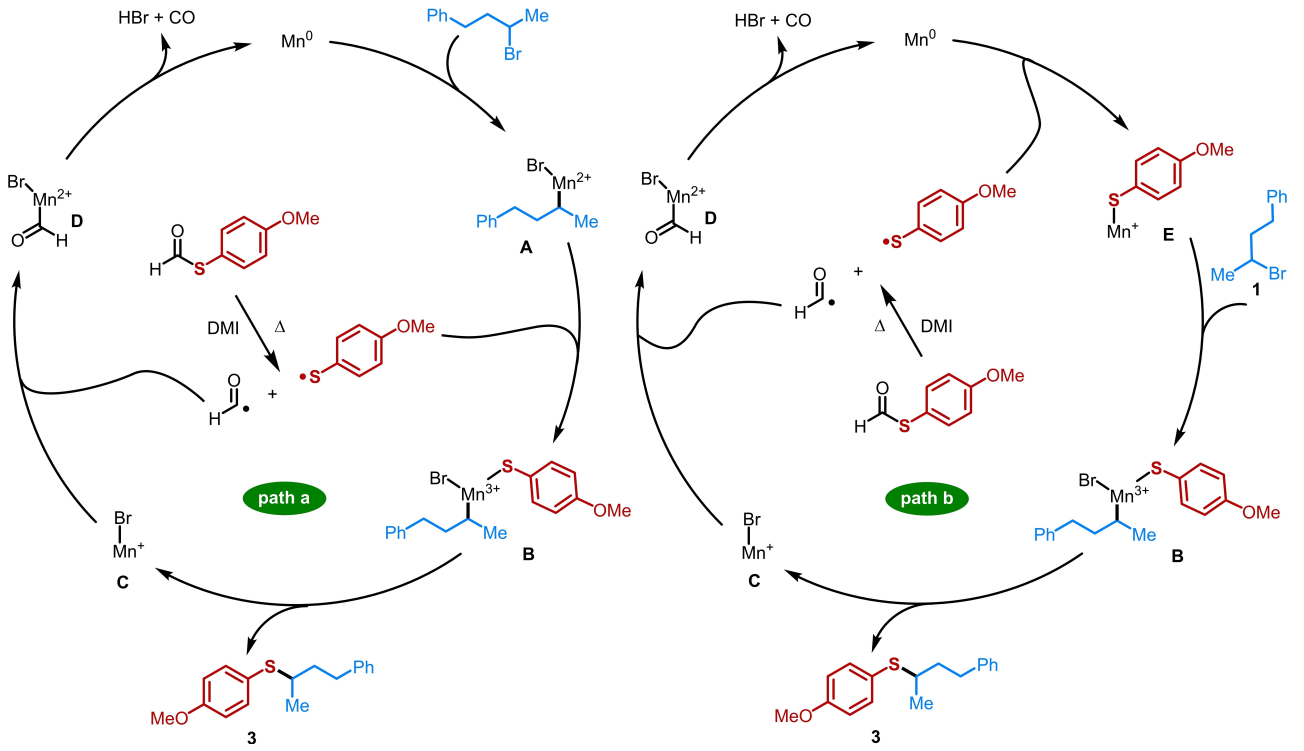



***Figure 4.*** Plausible catalytic cycles.

thioformate or thiol (Figure 3e), part stereo-inversion of the product (*S*)-**3** (50–53 % ee) was observed under standard conditions, while traditional $S_N2$ conditions gave total stereo-inversion of the product (*S*)-**3** (98 % ee), not only further demonstrating the alkyl halides does not generate alkyl radical species, but also strongly indicating the reaction mechanism involving Mn catalysis is different from the traditional $S_N2$ pathway (Figure 4). Furthermore, these results indicated that the stereo-inversion in the $Csp^3$–S cross-coupling reaction was caused by the $S_N2$ oxidative addition pathway from classical backside attack.

Based on our experimental results and literature reports,[16g,j,21] we proposed two possible mechanisms (Figure 4). For path a, $Mn^0$ firstly undergoes oxidative addition into alkyl bromide **1** to produce intermediate **A**. Meanwhile, formyl radical and thiyl radical is generated from thioformate **2** in DMI under heating. The subsequent reaction between intermediate **A** and thiyl radical gives intermediate **B**. Reductive elimination delivers the desired product **3** and intermediate **C**, which interacts with formyl radical to give intermediate **D**. Sequential release of CO regenerates $Mn^0$ for the next catalytic cycle. Alternatively (path b), $Mn^0$ could also firstly reacts with thiyl radical to generate intermediate **E**, which undergoes oxidative addition into alkyl bromide **1** to form intermediate **B**.

## Conclusion

In conclusion, we have developed an Mn-catalyzed redox-neutral $C(sp^3)$–S cross-coupling between alkyl halides and thioformates. In contrast with reported methods using thioformates as formylating reagents and CO-releasing molecules, we herein employ easily prepared thioformates as masked sulfuration reagents, affording different kinds of thioethers in good to excellent yields. This strategy features mild reaction conditions, broad substrate scope, and late-stage thiolation of structurally complex natural products and pharmaceuticals, avoiding the employment of strong bases, extra ligands, high reaction temperatures, and stoichiometric Mn. Preliminary mechanistic investigations indicate that thiyl radical from thioformate is involved in the reaction mechanism.

## Acknowledgements

We gratefully acknowledge funding from National Natural Science Foundation of China (No. 22071111), Jiangsu Specially Appointed Professor Plan, and Natural Science Foundation of Jiangsu Province of China (No. BK20201368 and BK20220409).

## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** $C(Sp^3)$–S Coupling · Manganese · Thioformate · Thiolation · Thiyl Radical

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Manuscript received: April 19, 2023
Accepted manuscript online: June 17, 2023
Version of record online: July 10, 2023