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Construction of diverse C–S/C–Se bonds *via* nickel catalyzed reductive coupling employing thiosulfonates and a selenosulfonate under mild conditions†

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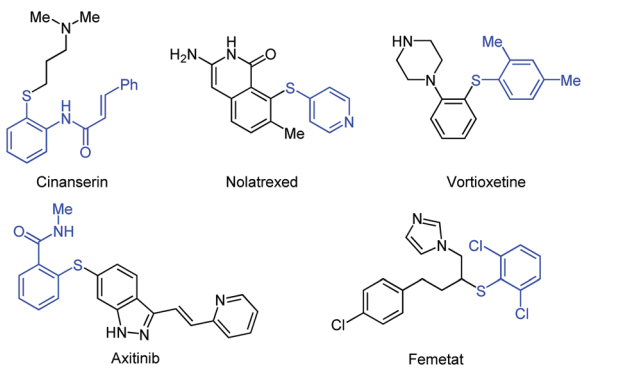
A nickel-catalyzed reductive cross coupling between organic iodides and thiosulfonates and a selenosulfonate under mild conditions is disclosed. This practical method provides a facile access to a series of unsymmetrical thioethers with low catalyst loading, good functional group tolerance, and excellent chemoselectivity. Notably, the synthetic applications of the approach feature scaling-up of reactions, late-stage modification of pharmaceuticals, and preparation of various useful targeted compounds, including sulfoximine, bipyridine, and vortioxetine. Primary mechanistic studies showed that a radical pathway was involved. Moreover, diverse C–S/C–Se bond formations were achieved under mild reaction conditions.

Introduction

The development of efficient methodologies for the construction of C–S bonds is of great significance and prime interest as these thioethers, especially unsymmetrical diaryl thioethers, are important core structural motifs that have been widely utilized in ligand chemistry,[1] medicinal chemistry,[2] and materials science[3] (Scheme 1). Furthermore, thioethers can be divergently transformed into a series of other related functionalized scaffolds, such as sulfones,[4] sulfoximines[5] and sulfur ylides,[6] which will greatly expand the molecule complexity and diversity.

Therefore, the development of efficient methods to achieve C–S bonds will be highly valuable.[7] Recently, transition-metal catalyzed cross coupling (Migita reaction) has become the focus of intense research in the formation of C–S bonds (Scheme 2A).[8] Generally, aromatic thiolates, generated from thiols under basic conditions, can serve as nucleophiles in the coupling reaction with haloarenes. However, this strategy is sharply limited by the requirement of specific ligands, strong bases, high catalyst loadings, and elevated reaction temperatures due to the strong coordination of thiolates to metals.[9] To overcome these shortcomings, photochemical[10] and electrochemical[11] reactions *via* generating free thiol radicals as new reaction intermediates offer an alternative strategy for the preparation of thioethers with limited scope (Scheme 2B). To replace highly toxic and odorous thiols, various electrophilic sulfur reagents have been successfully applied to the reactions with functional carbon nucleophiles under very mild reaction conditions although the step economy was sacrificed (Scheme 2C).[12]

Cross-electrophile coupling represents one of the most straightforward methods for the direct formation of C–C bonds, and typically employs two electrophilic partners as substrates.[13] The attractive points of this strategy are: (1) a highly step-economical transformation can be achieved by avoiding the preparation of air and moisture sensitive organometallic



Scheme 1 Drug molecules and chemicals containing thioethers.

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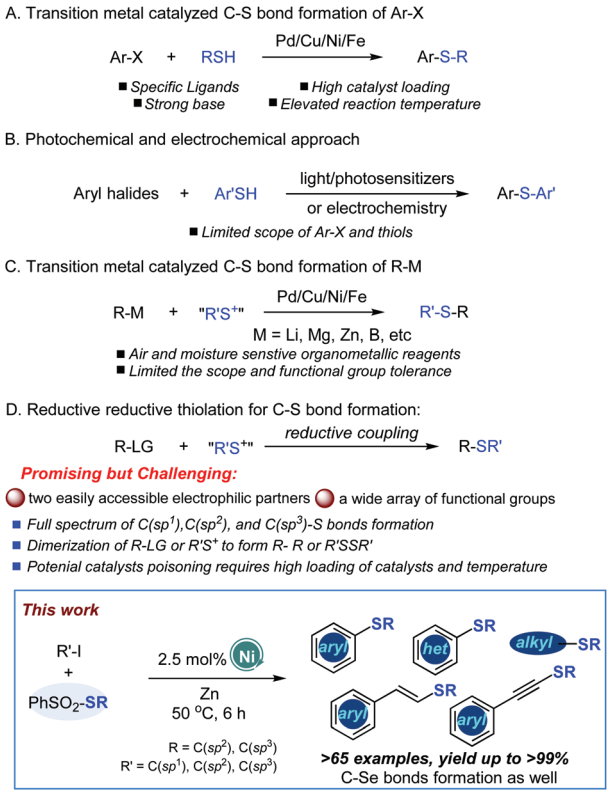


Scheme 2 Selective strategies for C–S bond formation.

reagents, and thus the substrate scope can be widely extended and (2) various haloarenes and related substrates commonly exist in the chemical industry and are easily accessible or commercially available. In contrast, catalytic reductive thiolation for C–S bond formation is less documented due to the scarcity of appropriate candidates of sulfur electrophiles,[14] potential deactivation of metal catalysts[9] and dimerization of organic halides[15] (Scheme 2D).

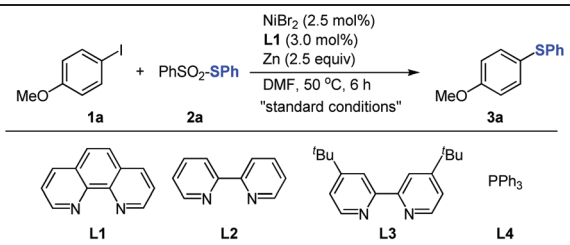
The Taniguchi[16] and Mao[17] groups accomplished the reductive thiolation of aryl iodides with disulfides or aryl ethanethioates catalyzed by nickel; however, the process required a very high temperature and long time to furnish the desired products. Very recently, Wang and co-workers developed an interesting benzimidazolium sulfonamide (IMDN-SO_2R) as a novel "S^+" source for nickel/Zn promoted reductive coupling.[18] An active "N–S^+" intermediate was generated in the reaction according to the mechanistic study. Despite the significant advances in this area, the development of cheap and efficient catalysts, along with new applications of sulfur surrogates which facilitate the synthesis of functionalized sulfides under milder reaction conditions, is still highly desirable.

Readily accessible and bench-stable thiosulfonates have been recognized as powerful reagents for preparing versatile organsulfur compounds *via* practical cleavage of weak S–S bonds.[19] However, in some cases they were used in the thiolation of air and moisture sensitive organometallic reagents, such as RLi and RMgX.[20] Moreover, C(sp^1)/C(sp^2)/C(sp^3)–S bond formation from the same sulfur electrophile as the donor of thiolated groups leading to unsymmetrical thioethers has been rarely reported.[21] In the light of recent achievements, we envisioned that metal catalyzed reductive thiolation of a suitable electrophile may proceed through thiosulfonates under mild reaction conditions (Scheme 2D).

Results and discussion

To test our hypothesis, we began our investigation on the reductive coupling of 4-iodoanisole **1a** as the model substrate with *S*-phenyl benzenethiosulfonate **2a** (Table 1). The optimal conditions employed 2.5 mol% $NiBr_2$ with 3 mol% ligand **L1** as the catalyst, 2.5 equivalents of Zn as the reductant and 50 °C as the reaction temperature (entry 1, for more details, see the ESI†). After 6 h, the desired diaryl thioether **3a** was isolated in 91% yield with complete conversion of **1a**. Encouraged by this result, we further explored the impact of various reaction conditions. Comparable yields of **3a** were achieved when $NiCl_2(PPh_3)_2$ or $Ni(OAc)_2$ (entries 2 and 3) was used as the catalyst in the reaction. However, attempts to use $FeCl_2$ and $CoBr_2$ as the catalysts were not successful, leading to less than 5%

Table 1 Variations of the reaction conditions for nickel-catalyzed reductive coupling of 4-iodoanisole **1a** with *S*-phenyl benzenethiosulfonate **2a**[a]



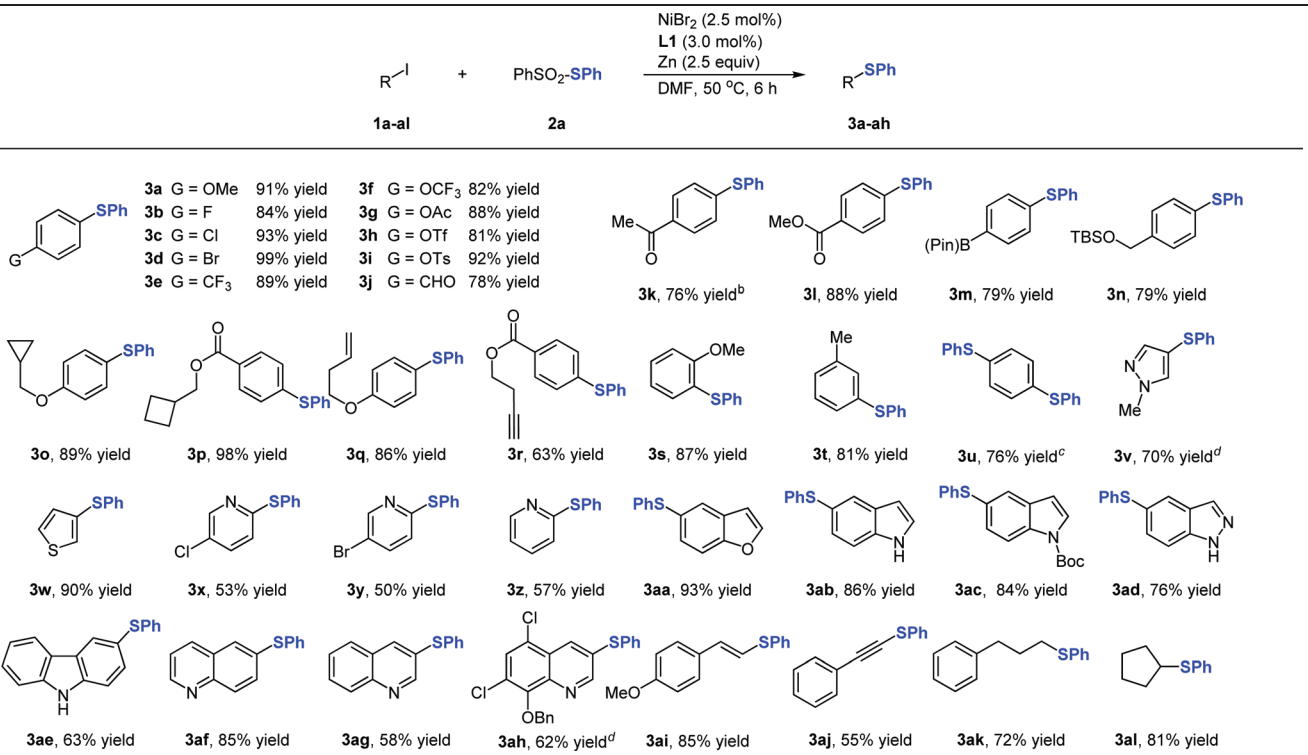
Entry	Variation from the "standard conditions"	Yield of **3a** (%)
1	None	99 (91)[b]
2	$NiCl_2(PPh_3)_2$ instead of NiB_2	97
3	$Ni(OAc)_2$ instead of $NiBr_2$	96
4	$FeCl_2$, $CoBr_2$ instead of $NiBr_2$	<5
5	**L2** instead of **L1**	96
6	**L3** instead of **L1**	95
7	**L4** instead of **L1**	43
8	Mn instead of Zn	98
9	B_2pin_2/K_3PO_4 instead of Zn	<5
10	1.0 equiv. Zn used	51
11	w/o Zn	<5
12	3 h	92
13	30 °C	31
14	Ch_2Cl_2	<5
15	MeCN	71
16	DMA	96
17	Under air	<10
18	1.5 mol% $NiBr_2$, 3.0 mol% **L1** used	35
19	4-MeO-C_6H_4-Br or OTf instead of **1a**	Trace

[a] Reaction conditions: **1a** (0.5 mmol), *S*-phenyl benzenethiosulfonate **2a** (1.0 mmol), $NiBr_2$ (2.5 mol%), ligand **L1** (3.0 mol%), Zn (2.5 equiv.), DMF (2.5 mL) at 50 °C for 6 h. Yield was determined by ^{1}H NMR spectroscopy in the presence of CH_2Br_2 as an internal standard. [b] Isolated yield.

yield (entry 4). The above results showed that a nickel catalyst could efficiently promote the transformation. Ligands **L2** and **L3** containing the skeleton of bipyridine (entries 5 and 6). Additionally, lower conversion of 4-iodoanisole **1a** was observed when triphenylphosphine **L4** was employed as the ligand (entry 7). The choice of the reductant was also critical for this transformation. Switching the reductant to Mn could furnish **3a** in a comparable yield (entry 8), while the reaction using combined B_2pin_2/K_3PO_4 failed to furnish any products with complete recovery of both starting materials **1a** and **2a** (entry 9). Reducing the amount of Zn to 1.0 equivalent afforded the desired product **3a** in 51% yield (entry 10), while the reaction did not occur in the absence of Zn or Mn (entry 11). The desired product **3a** could also be generated with slightly less efficiency when the reaction was conducted in a shorter reaction time (entry 12). A lower temperature was then examined, but it resulted in decreased conversion (entry 13). Carrying out the reaction in polar solvents such as MeCN and DMA could deliver the coupling product **3a** in 71–96% yields, while the use of CH_2Cl_2 led to a low yield (entries 14–16). No desired product was obtained when the reaction was conducted under air (entry 17). Performing the reaction by reducing the catalyst loading to 1.5 mol% with 3.0 mol% ligand led to a much lower yield (entry 18). It was found that a trace amount of the desired product **3a** was detected when the leaving group was replaced by Br or OTf (entry 19).

With the optimal reaction conditions established, we next sought to evaluate the scope of the reaction with respect to a variety of (hetero)aryl iodides, as presented in Table 2. To our delight, a wide range of functional groups (electron-withdrawing or electron-donating groups) including OMe, F, Cl, Br, CF_3, OCF_3, OAc, OTf, OTs, Bpin, and silyl substituted alcohol at the aryl *para* position were well tolerated, affording the corresponding products (**3a–i**, **3m and 3n**) in 79–99% yields. Catalytic reductive thiolation displayed excellent chemoselectivity when (pseudo)halides (**3g–i**) were employed as the substituents, which would enable straightforward downstream orthogonal transformations. Carbonyl compounds, such as aldehyde (**3j**), ketone (**3k**), and esters (**3l**, **3o**, **3p**, **3r**), could be coupled efficiently as well, and the coupled products were obtained in moderate to good yields. The standard process also worked well for cyclopropane and cyclobutane substituted aryl iodides, affording **3o** and **3p** in high yields after simple column chromatography purification. Unactivated alkene (**3q**) and alkyne (**3r**) were compatible with the reaction conditions, giving the corresponding products in 86% and 63% yields, respectively. It was found that steric factors did not affect the efficiency of the reaction. For *ortho*-methoxyl and *meta*-methyl-substituted aryl iodides, the transformation proceeded smoothly, providing the target products (**3s and 3t**) in 81–87% yields. Notably, when 4.0 equivalents of **2a** were treated with *para*-diiodobenzene bearing two reaction sites on the benzene

Table 2 Scope of the nickel-catalyzed reductive coupling of **1a–al** with **2a** [a]



[a] Reaction conditions: **1a–al** (0.5 mmol), *S*-phenyl benzenethiosulfonate **2a** (1.0 mmol), $NiBr_2$ (2.5 mol%), ligand **L1** (3.0 mol%), Zn (2.5 equiv.), DMF (2.5 mL) at 50 °C for 6 h. Isolated yields are reported. [b] $NiBr_2$ (5.0 mol%), ligand **L1** (10 mol%). [c] $NiBr_2$ (5.0 mol%), ligand **L1** (6.0 mol%), and Zn (5.0 equiv.) were used. [d] Reaction time was 12 h.

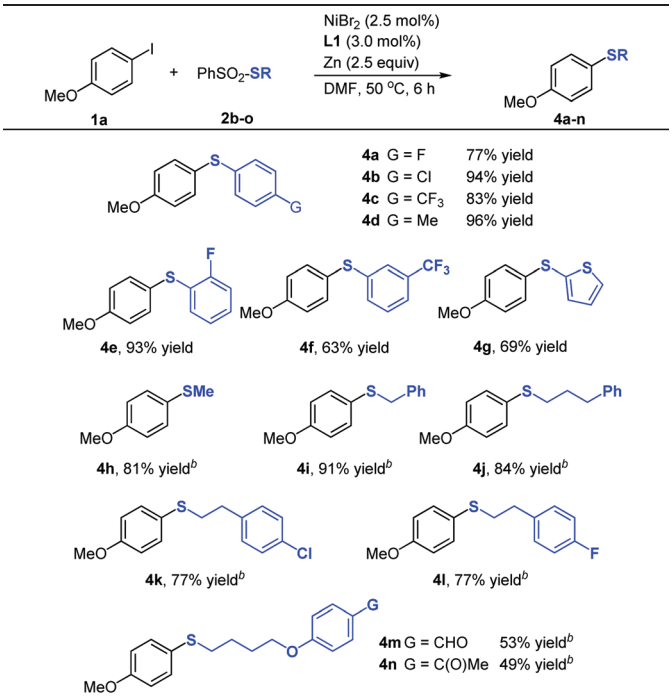
ring, the dual thiolation product (**3u**) was successfully obtained in 76% yield. Likewise, numerous heteroaryl iodides would participate in the reductive thiolation as well to deliver a variety of desired thioethers in moderate to good yields. Diverse structurally varied hetero-aromatic rings including pyrrole (**3v**), thiophene (**3w**), pyridine (**3x–z**), benzofuran (**3aa**), indoles (**3ab** and **3ac**), indazole (**3ad**), carbazole (**3ae**), isoquinoline (**3af**), and quinoline (**3ag and 3ah**) were well tolerated in the established reductive thiolation with **2a**. In the cases of pyrrole and quinoline derivates (**3v** and **3ah**), the reaction required a longer reaction time (12 h) to achieve complete conversion.[22] Interestingly, when the Boc-protected indazole was tested under standard reaction conditions, the final product (**3ad**) was obtained in 76% yield with the deprotection of the Boc group.[23] Our developed methodology could be further applied to more challenging aliphatic and cyclic alkyl iodides (**3ak and 3al**), as well as alkenyl iodide (**3ai**) and alkynyl iodide (**3aj**), delivering the thioether products in moderate to good yields.

Encouraged by the successful applications of (hetero)aryl iodides with high efficiency, we proceeded to investigate other thiosulfonates to synthesize various thioethers under these practical reaction conditions (Table 3). Excellent tolerance of functional groups such as F, Cl, Me, and CF_3 was obtained, and the desired products were afforded in 63–96% yields. *S*-(thiophen-2-yl) benzenesulfonothioate (**2h**) reacted facilely with **1a**, generating unsymmetrical thioether (**4g**) in 69% yield. Likewise, more sterically bulky functional groups were suitable for the transformation. For instance, *ortho*-fluoro and *meta*-trifluoromethyl-substituted thiosulfonates could well couple with **1a**, affording the corresponding products in 93% and 63% yields, respectively. Moreover, the construction of unsymmetrical alkyl-aryl sulfides was achieved from several alkyl thiosulfonates with a good substrate scope (**4h–n**) although slightly harsher reaction conditions were required.

In terms of *Se*-phenyl benzenesulfonoselenoate **2p**, the reaction proceeded smoothly with several organic iodides to furnish the final products in good to excellent yields (Table 4). Methoxyl (**5a**), chloride (**5b**), aldehyde (**5c**), and ester (**5d**) were suitable for the selenylation, delivering the corresponding products in 76–95% yields. For *ortho*-methoxyl and *meta*-methyl-substituted aryl iodides, the reaction occurred smoothly with high efficiency (**5e and 5f**). However, no desired product was observed with complete conversion of the starting material when alkynyl iodide (**1aj**) was employed as the substrate. To our surprise, alkenyl iodide (**3ai**) and the more challenging aliphatic iodide (**1ak**) could participate in the reductive coupling reaction and gave the products **5h** and **5i** in 82% and 75% yields, respectively.

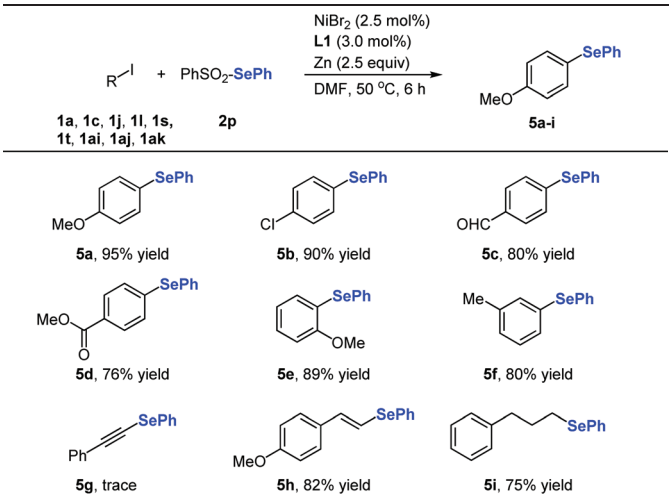
To illustrate the potential synthetic utility of the above reductive thiolation catalyzed by nickel, we next explored the late-stage modification of structurally complicated molecules derived from several potential bioactive compounds or drug-like scaffolds (Table 5). For instance, the reaction of indomethacin derivatives was successfully conducted under the same reaction conditions, delivering **7g** in 79% yield with good chemo-selectivity. Moreover, clofibrate (**7a**), menthol (**7c**), fenofibrate (**7d**), diacetonefructose (**7e**), cloquintocet-mexyl (**7f**), and vitamin E (**7h**) derivatives could readily undergo the cross-coupling, affording the thiolated analogues in moderate to excellent yields. Moreover, this approach could be applied in the late-stage selenylation of clofibrate (**7b**).

Table 3 Scope of the nickel-catalyzed reductive coupling of **1a** with **2b–o** [a]



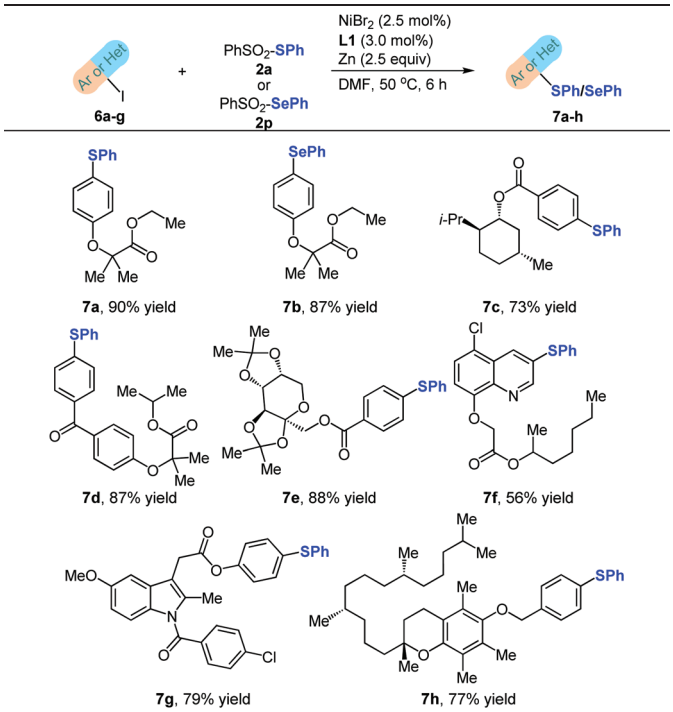
[a] Reaction conditions: **1a** (0.5 mmol), thiosulfonates **2b–h** (1.0 mmol), $NiBr_2$ (2.5 mol%), ligand **L1** (3.0 mol%), Zn (2.5 equiv.), DMF (2.5 mL) at 50 °C for 6 h. Isolated yields are reported. [b] **1a** (0.5 mmol), **2i–o** (1.0 mmol), $NiBr_2$ (5.0 mol%), ligand **L1** (10 mol%), Zn (3.0 equiv.), DMF (2.5 mL) at 120 °C for 12 h. Isolated yields are reported.

Table 4 Scope of the nickel-catalyzed reductive coupling of organic iodides with **2p** [a]

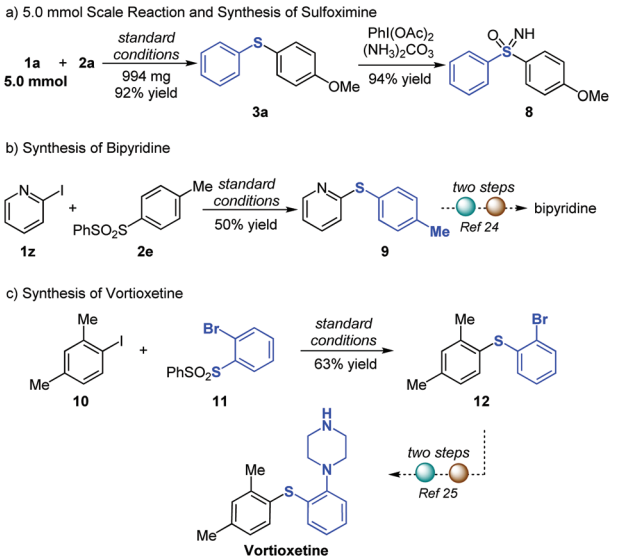


[a] Reaction conditions: organic iodides (0.5 mmol), selenosulfonate **2p** (1.0 mmol), $NiBr_2$ (2.5 mol%), ligand **L1** (3.0 mol%), Zn (2.5 equiv.), DMF (2.5 mL) at 50 °C for 6 h. Isolated yields are reported.

Table 5 Late-stage modification of complex molecules[a]



[a] Reaction conditions: **6a–g** (0.5 mmol), thiosulfonate **2a** or selenosulfonate **2p** (1.0 mmol), $NiBr_2$ (2.5 mol%), ligand **L1** (3.0 mol%), Zn (2.5 equiv.), DMF (2.5 mL) at 50 °C for 6 h. Isolated yields are reported.

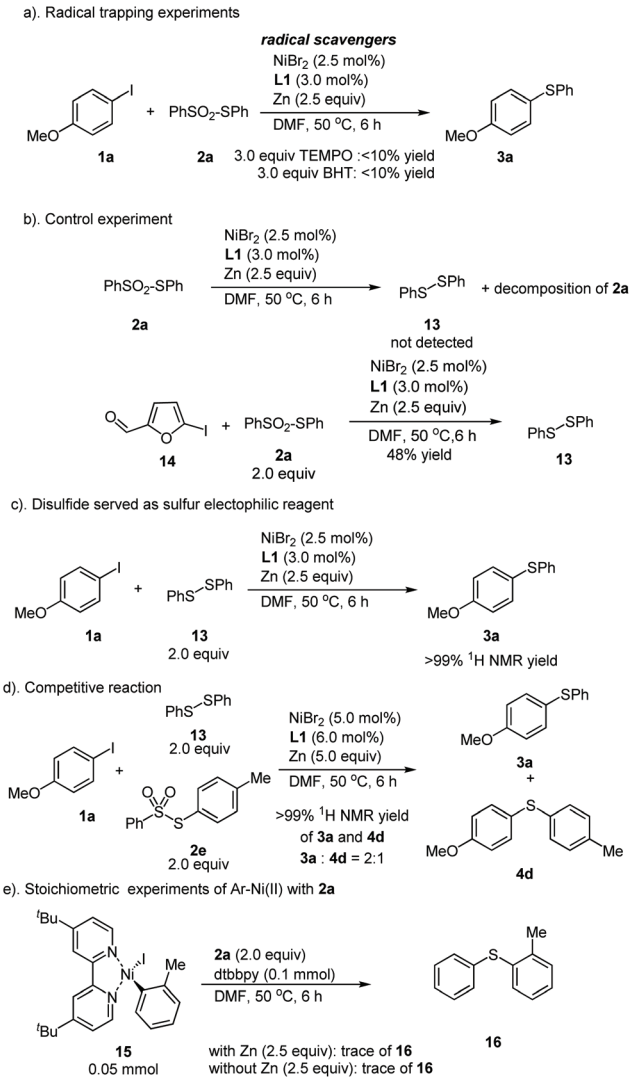


Scheme 3 The scale up reaction and synthetic applications.

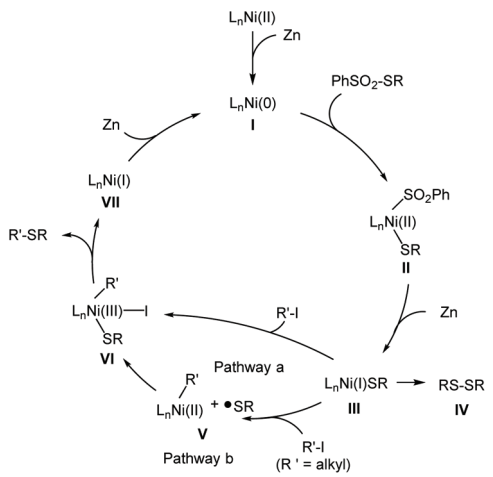
The potential applications of the current protocol were also studied. We firstly performed the standard reaction on a 5.0 mmol scale, and the product **3a** was formed in 92% yield with a minimal effect on the efficiency (Scheme 3). In the presence of $PhI(OAc)_2$ and $(NH_3)_2CO_3$, **3a** could transform into the corresponding sulfoximine **8** in 94% isolated yield. In addition, thioether **9**, the coupling product generated in the reaction between 2-iodopyridine **1z** and *S*-p-tolyl benzenesulfonothioate **2e**, could be further used for the synthesis of bipyridine according to Stockman's report.[24] Bipyridine-type ligands could act as useful ligands and could also promote our reductive thiolation as efficiently as the optimal ligand **L1** (Table 1, entries 5 and 6).[25] We then applied this method in the reaction between *S*-arylthiosulfonate **11** bearing bromide as the *ortho*-substituent and sterically hindered aryl iodide **10**. As a result, the coupled product thioether **12** was formed in 63% yield after purification, and it could be further transformed into vortioxetine through Buchwald–Hartwig cross coupling and the following deprotection of the Boc group.[26]

To gain more insights into the reaction mechanism, several reactions were conducted. No desired product **3a** was detected, 4-iodoanisole **1a** was completely recovered and *S*-phenyl benzenesulfonothioate **2a** was decomposed totally when radical scavengers such as TEMPO and BHT were added to the reaction, indicating that a radical pathway was involved (Scheme 4a). The control experiment showed that *S*-phenyl benzenesulfonothioate **2a** did not convert into the related disulfide **13** and it was decomposed totally into an unknown compound in the absence of 4-iodoanisole **1a** under standard reaction conditions (Scheme 4b). Moreover, in some failed cases such as 5-iodofuran-2-carbaldehyde **14**, complete consumption of *S*-phenyl benzenethiosulfonate **2a** was observed and disulfide **13** was isolated in 48% yield as the major product with almost complete recovery of heteroaryl iodide. These results suggested that the S–S bond of **2a** was relatively weak in the presence of the nickel catalyst and reductant. Surprisingly, the reductive thiolation using disulfide **13** could occur under our mild reaction conditions with very high efficiency compared to Taniguchi's method (10 mol% loading of the nickel catalyst and 110 °C) (Scheme 4c). To identify the difference in the reactivity of disulfide and thiosulfonate, competitive reactions were carried out when both disulfide **13** and thiosulfonate **2e** were added as reagents. Complete conversion of **1a** was observed, and the crude ^{1}H NMR yield of the corresponding products **3a** and **4d** was determined to be 67% and 33%, respectively (Scheme 4d). To find out whether Ar–Ni(II)–I was involved in the catalytic cycle, the stoichiometric reaction of the Ar–Ni(II)–I complex **15** with *S*-phenyl benzenesulfonothioate **2a** was carried out in the presence or absence of Zn and no desired product **16** was detected (Scheme 4e).

Based on the above experimental results and literature reports, a plausible mechanism for the nickel catalyzed reductive thiolation that we developed was proposed (Scheme 5). Oxidative addition or single-electron transfer of $PhSO_2SPh$ to active Ni(0) (**I**) obtained from the reduction of Ni(II) by Zn furnishes the intermediate $PhSO_2$-Ni(II)-SR (**II**).[21] Disulfide was possibly formed through homocoupling of Ni(I)-SR (**III**) and it might act as a sulfur donor of thiolated groups.[16] Subsequently, reduction of $PhSO_2$-Ni(II)-SR (**II**) by Zn results in the formation of Ni(I)-SR (**III**), which undergoes oxidative addition into the weak C–I bond of organic iodides to furnish a Ni(III) species (**VI**) (pathway a).[16b] However, a stepwise single-



Scheme 4 Mechanistic studies.



Scheme 5 Plausible mechanism.

electron transfer might also occur to generate intermediate (**V**), and the Ni(III) species (**VI**) could also be generated through radical trapping (pathway b).[18] Finally, the reductive elimination of **VI** affords the final product and Ni(I) (**VII**), which could further regenerate the active Ni(0) (**I**) by reduction. At this stage, why the formation of the Ni(III) species (**VI**) proceeded through pathway a or pathway b especially when alkyl iodide was used because of its high tendency to react with Ni (I)-SR (**III**) *via* single-electron transfer is not clear, and more detailed experiments should be conducted.

Conclusions

In summary, we present a practical nickel catalyzed reductive thiolation and selenylation of various organic iodides with odorless and bench stable thiosulfonates and a selenosulfonate to construct diverse C–S/C–Se bonds under mild reaction conditions. A broad range of functional groups were tolerated under the reaction conditions, and excellent chemo-selectivity was achieved with a low loading of the catalyst. Moreover, the reaction provided an efficient approach for accessing functionalized sulfides and selenides and could be utilized for the late-stage modification of pharmaceuticals, synthesis of sulfoximine, and as precursors for preparing bipyridine and vortioxetine. A more detailed mechanism along with DFT calculations, structural modification and reactivities of electrophilic sulfur reagents, and expansion of more challenging substrates are currently being studied. These results will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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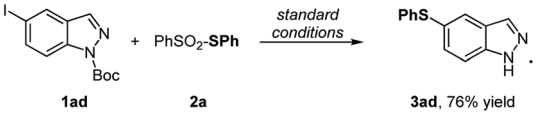
23 Deprotection of the Boc group was observed when **1ad** was used as the substrate.



1ad **2a** **3ad**, 76% yield

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