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Direct *ortho*-Thiolation of Arenes and Alkenes by Nickel Catalysis

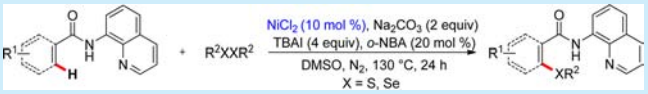
Cong Lin,[†] Danyang Li,[†] Binjie Wang,[†] Jinzhong Yao,[†] and Yuhong Zhang*[,†,‡]

[†]ZJU-NHU United R&D Center, Department of Chemistry, Zhejiang University, Hangzhou 310027, China

[‡]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

Supporting Information

ABSTRACT: The direct thiolation of arenes and alkenes with diaryl disulfides was developed by nickel catalysis. The reaction displayed exceptional compatibility with a wide range of functional groups to regioselectively give the diaryl sulfides and alkenyl sulfides in high yields.



The sulfur-containing molecules are of considerable importance as versatile intermediates in organic synthesis and possess particular pharmaceutical relevancies.[1] Consequently, the development of general methods for C−S bond formation has received a great deal of attention over the past decades.[2] Traditionally, the construction of aliphatic C(sp^3)−S bonds is generally limited to the condensation reaction between a metal thiolate and an organic halide. With the transition-metal-catalyzed coupling reaction, the formation of C(sp^2)−S bonds can be achieved to prepare many useful aryl sulfides and alkenyl sulfides.[3] Disadvantages of these transformations include the harsh reaction conditions, low substrate scope, and the preactivation of the substrates.

Recently, the chemical approach based upon direct C−H bond functionalization allows the formation of C−S bonds through more effective synthetic routes with high atom economy.[4] Given the biological and pharmaceutical properties of aryl sulfides and alkenyl sulfides, there is a strong impetus to discover chemical transformations that target C(sp^2)−H bonds for new and valuable C−S bond forming reactions.[5] The seminal study of Yu has demonstrated that the conventional cross-couplings of aryl halides with thiols (Ullmann coupling) can be accessed via the copper-catalyzed direct functionalization of aromatic C(sp^2)−H bonds by employing pyridinyl as the direct group.[6] This reaction inspired extensive efforts to discover alternative approaches to construct C(sp^2)−S bonds, which include the copper-mediated *ortho*-methylthiolation of arenes by Qing[7] and the copper-promoted *ortho*-sulfenylation of arenes by Daugulis.[8] Very recently, palladium[9] and rhodium[10] catalysts have been reported for the direct *ortho*-thiolation of arenes to give the diverse aryl sulfides. Despite the recent significant achievements in this area, a great challenge still remains with respect to the direct thiolation of alkenes, which would allow the straightforward synthesis of useful alkenyl sulfides.[11] To the best of our knowledge, a catalytic system that is capable of performing direct thiolation of alkenes has not been reported.

Similar to aryl sulfides, alkenyl sulfides are versatile intermediates in chemical synthesis and important motifs in bioactive compounds and pharmaceuticals. However, this privileged functional group is usually assembled by a limited number of methods such as hydrothiolation of alkynes and cross-coupling of alkenyl halides with organometallic compounds. A conceptually different approach to alkenyl sulfides is the direct thiolation of alkenes via C(sp^2)−H activation. Herein, we report a highly efficient method for the direct thiolation of arenes and alkenes. By using the nickel catalytic system, not only the direct thiolation of aromatic C(sp^2)−H bond could be smoothly approached but also the vinylic C(sp^2)−H bond participated in the transformation successfully to give the corresponding alkenyl sulfides in high yields, which provide an efficient alternative for the synthesis of alkenyl sulfides.

Nickel belongs to the low-cost and more abundant metals and is utilized as a prevalent catalyst in many organic transformations. Inspired by other nickel-catalyzed C−H functionalizations, we explored the thiolation of arenes by using nickel as the catalyst. The initial study using 10 mol % $NiCl_2$ in the presence of 2 equiv of Na_2CO_3 in the reaction of **1a** with 1,2-bis(4-methoxyphenyl)disulfane **2a** (Scheme 1) showed that the desired *ortho*-thiolation could indeed be carried out in DMSO at 130 °C, albeit in very low yield (see Supporting Information). The addition of 4 equiv of tetrabutylammonium iodide (TBAI) significantly promoted the thiolation to give the diaryl sulfide **3a** in 76% yield (see Supporting Information). Further optimization of the reaction conditions indicated that the diaryl sulfide **3a** could be isolated in 92% yield in the presence of 20 mol % of *o*-nitrobenzoic acid (*o*-NBA).

With the established conditions in hand, the substrate scope of disulfides was evaluated (Scheme 1). Various diaryl disulfides with either electron-donating or -withdrawing groups could participate in the reaction smoothly to provide the corresponding monothiolated products in good yields (**3a**−**3k**). For example, the diaryl disulfides with OMe, *t*-Bu, or Me substituents at the *para*-position of the aryl ring produced the aryl sulfides in excellent yields (**3a**−**3c**). The steric hindrance of the diaryl disulfides influenced the reaction, and *o*-methyl substituted diaryl sulfide gave the thiolation product in lower

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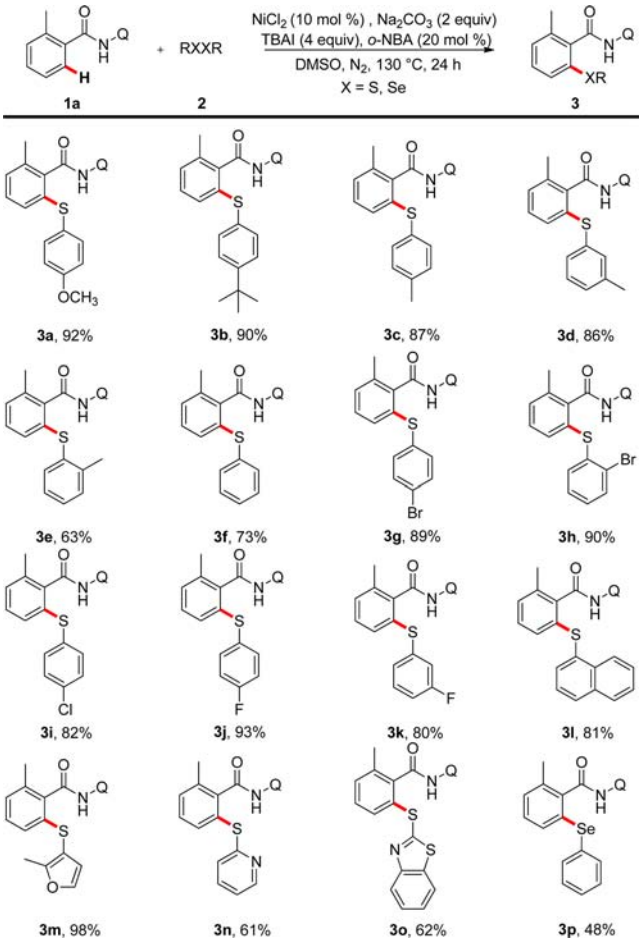
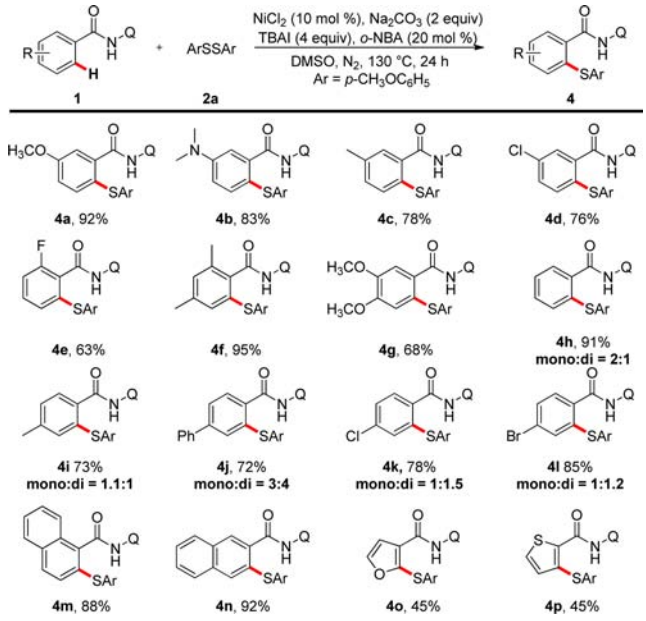
Scheme 1. Substrate Scope of Disulfides[a,b]



[a]Isolated yields are given. [b]Reaction conditions: benzamides **1a** (0.2 mmol), disulfide **2** (0.4 mmol), $NiCl_2$ (0.02 mmol), Na_2CO_3 (0.4 mmol), TBAI (0.8 mmol), *o*-NBA (0.04 mmol), DMSO (2.0 mL), 130 °C, N_2, 24 h.

Scheme 2. Substrate Scope of Benzamides[a,b]



[a]Isolated yields are given. [b]Reaction conditions: benzamides **1** (0.2 mmol), disulfide **2a** (0.4 mmol), $NiCl_2$ (0.02 mmol), Na_2CO_3 (0.4 mmol), TBAI (0.8 mmol), *o*-NBA (0.04 mmol), DMSO (2.0 mL), 130 °C, N_2, 24 h.

yield (**3e**) under the standard conditions. Importantly, a halogen substituent in the diaryl disulfides was tolerated (**3g**–**3k**), which allowed the further modification of the diaryl sulfides to complex molecules. 1,2-Di(naphthalen-2-yl)disulfane participated in the reaction smoothly to give the corresponding sulfide **3l** in good yield. Besides the aromatic disulfides, the heteroaromatic disulfides, such as 1,2-di(furan-2-yl)disulfide, 1,2-di(pyridin-2-yl)disulfide, and 1,2-di(benzothiazol-2-yl) disulfide, showed good reactivity to give the corresponding sulfides containing heteroaromatics (**3m**–**3o**). The aliphatic disulfides were inactive under the reaction conditions. Notably, diphenyl diselane was compatible with the reaction conditions to afford the diphenyl diselane **3p** in 48% yield.

The reaction efficiency of different benzamides was evaluated by the use of 1,2-bis(4-methoxyphenyl)disulfane **2a** as the coupling partner (Scheme 2). Generally, benzamides bearing either electron-donating or -withdrawing groups were all compatible, but electron-rich substrates showed better reactivity to give higher yields (**4a**–**4l**). Multisubstituted benzamides were found to be excellent reaction substrates, in which up to a 95% yield was achieved with high monoselectivity (**4f**, **4g**). Steric hindrance played an important role in this transformation. For example, when *m*-substituted benzamides were used, the C–H bond thiolation took place at the less hindered position of benzamides (**4a**–**4d**). The unsubstituted and *p*-substituted benzamides resulted in a mixture of mono- and dithiolation, the products of which could be isolated to afford monothiolated products and dithiolated adducts (**4h**–**4l**). The thiolation proceeded selectively at the 2-position of naphthalene to provide the corresponding aryl thioethers in good yields (**4m**–**4n**). Moreover, the scope of this reaction was not limited to benzamide substrates. The functionalization of furan and thiophene derivatives could also proceed smoothly under the reaction conditions (**4o**, **4p**).

In recent years, significant progress has been made in the use of arenes as substrates in the transition-metal-catalyzed C–H activation. In contrast, direct fuctionalization reactions rarely employ alkene substrates.[12] Direct C–H functionalization by simple extension of the substrates from arenes to alkenes has proven to be difficult. Importantly, we found that the above-mentioned nickel catalytic system was also applicable to the more challenging C–H bond of acrylamide substrates as shown in Scheme 3. Highly site-selective direct thiolation of alkenes could be achieved without modification to the protocol developed for arenes. Various α-substituted acrylamides participated in the reaction smoothly to give the *Z*-alkenyl sulfides efficiently (**6a**–**6e**). It is worth noting that α,β-disubstituted alkenes showed high reactivity to deliver the tetrasubstituted thiolated alkene (**6b**). Electron-rich and -poor diaryl disulfides are compatible with the reaction conditions to give the products regioselectively in high yields (**6fa**–**6ff**, **6ga**–**6gb**). Selective thiolation in the presence of a halogen is possible, providing a useful handle for further cross-coupling reactions (**6fd**–**6ff**, **6gb**).

It is known that disulfides are easy to decompose at high temperature to generate a radical and therefore induce a Ni(I)/Ni(III) catalytic cycle as presented by Ge and co-workers in a reaction of nickel-catalyzed alkylation.[13] We performed a radical trapping experiment by the reaction of **1a** and **2a** in the

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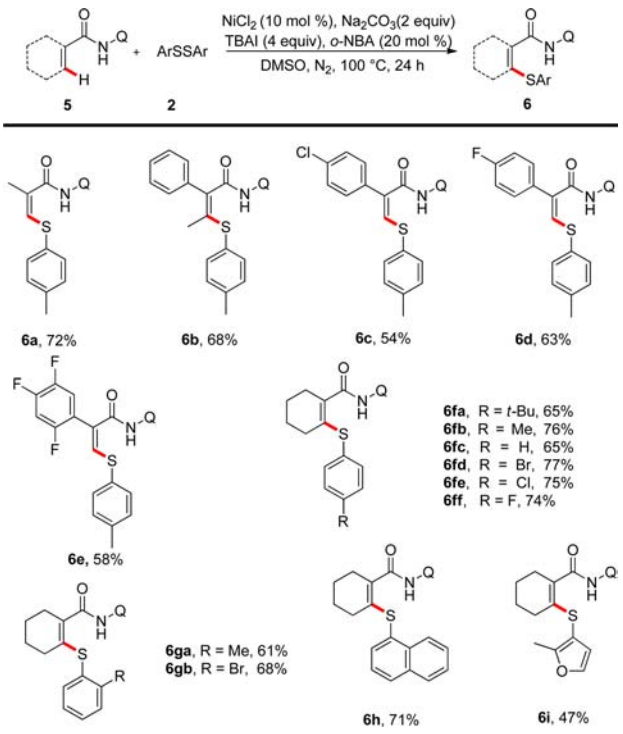
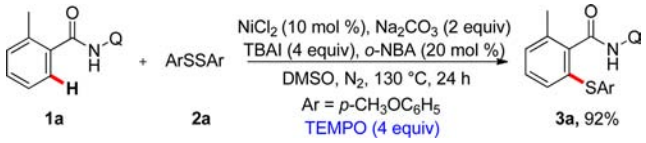
Scheme 3. Thiolation of C−H Bond in α,β-Unsaturated Amides[a,b]



[a]Isolated yields are given. [b]Reaction conditions: benzamides **5** (0.2 mmol), disulfide **2** (0.4 mmol), $NiCl_2$ (0.02 mmol), Na_2CO_3 (0.4 mmol), TBAI (0.8 mmol), *o*-NBA (0.04 mmol), DMSO (2.0 mL), 100 °C, N_2, 24 h.

presence of 4 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under the standard reaction conditions. It was found that the reaction was not influenced by the addition of TEMPO, and a 92% isolated yield of **3a** was obtained (Scheme 4).

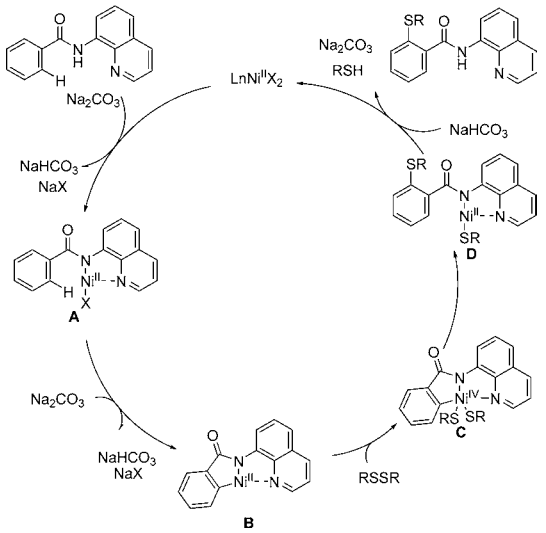
Scheme 4. Radical Trapping Experiment



This result excludes the possibility of a radical involved Ni(I)/Ni(III) pathway. On the other hand, this reaction progressed smoothly without the use of an oxidant. Based on these results and the previous report by Chatani and co-workers,[14] we tentatively believe a Ni(II)/Ni(IV) pathway may be implicated in this thiolation reaction (Scheme 5). With the assistance of an 8-aminoquinolyl auxiliary, the five-membered nickelacycle **B** is formed through a proton abstract by an *o*-nitrobenzoic anion coodinated to nickel.[15] The subsequent oxidative addition of disulfide into the Ni(II) species and reductive elimination construct the C−S bond. The thiolation product is obtained after the ion exchange and protonation. Further study is required for the elucidation of the detailed reaction mechanism.

In summary, a highly efficient thiolation of aromatic and vinylic C(sp^2)−H bonds was developed with the assistance of an 8-aminoquinolyl auxiliary by the nickel catalysis.[16] The

Scheme 5. A Plausible Reaction Pathway



reaction was not only compatible with arenes and heteroaromatic compounds but also efficient with a range of alkenes, which provides a viable method for the straightforward synthesis of alkenyl sulfides. Further research on the detailed mechanism of the reaction as well as the extension of the substrates to aliphatic compounds is currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectral and analytical data, copies of ^1H and ^{13}C NMR spectra for new compounds. These materials are available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yhzhang@zju.edu.cn.

Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

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