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Silver-Catalyzed Direct Thiolation of Quinones by Activation of Aryl Disulfides to Synthesize Quinonyl Aryl Thioethers

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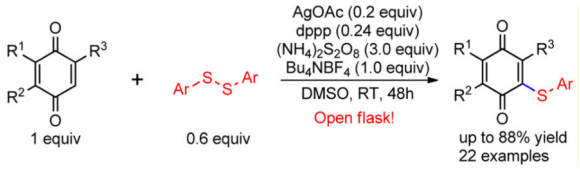
Abstract

A silver-catalyzed coupling reaction of quinones with aryl disulfides for the synthesis of quinonyl aryl thioethers is described. In the presence of AgOAc (0.2 equiv)/dppp (0.24 equiv) as the catalyst, $(NH_4)_2S_2O_8$ (3.0 equiv) as the oxidant, and Bu_4NBF_4 (1.0 equiv) as the additive, the reaction is simple, provides high yield (up to 88% yield), and possesses a broad substrate scope. The reaction is believed to proceed via direct activation of disulfides evidenced by observation of a metathesis reaction between two different disulfides placed together under the reaction conditions and ^{13}C NMR spectroscopy analysis.

Graphical abstract



INTRODUCTION

Thioethers are ubiquitous structural motifs that play important roles in catalytic,[1] material,[2] and biological chemistries.[3] To date, many strategies have been reported for the synthesis of such compounds, and these strategies can be classified into photocatalyzed,[4] transition-metal catalyzed,[5] and metal-free reactions.[6] In addition, organocatalytic, asymmetric reactions to chiral thioethers have also been intensively studied.[7] Among these innovative synthetic methods, transition-metal catalyzed reactions have been the focus of many recent studies. Utilizing various transition metals as catalysts, most of which are Pd[5b–h] and Cu,[5i–o] synthesis of several types of thioethers has been achieved. The quinonyl aryl thioether is an

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ASSOCIATED CONTENT

Supporting Information

Synthesis of starting materials, reactions for mechanism probing, LC/MS, HRMS, ^1H NMR, and ^{13}C NMR spectra for thioethers. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00247.

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important class of biologically active compounds,[8] and the most popular synthetic methods for these compounds rely on the direct coupling reaction of quinones with thiols (Scheme 1).[9] Despite these advances, however, exploration into transition-metal mediated synthesis of quinonyl aryl thioethers has rarely been reported, and the substrate scope with respect to quinones is limited.[10] In fact, quinones have very specific electronic properties allowing them to act as both ligands and oxidants in reactions,[11] and therefore it is more difficult for quinones to be effectively applied in transition-metal catalyzed reactions. In this context, developing effective transition-metal catalyzed methods to synthesize the quinonyl aryl thioethers remains challenging, yet highly desirable.

Compared to Pd and Cu, silver is a much less explored transition metal for the synthesis of thioethers. To our knowledge, there have been only three examples of silver-catalyzed synthesis of thioethers. In 2012, Charkraborty et al.[12] reported a class of C–S coupling reactions of boronic acids with thiols to form thioethers with good yields in the presence of AgOTf as a catalyst in DMF, but under harsh reaction conditions: a high reaction temperature (150 °C) and strong base (KOH), which is usually a shared feature of these transition-metal catalyzed C–S bonds formation reactions (Scheme 2, reaction 1a). Very recently, $AgNO_3$ and AgOAc were reported as being successfully employed in thiolation reactions by Xu et al. and Deng et al, respectively. In the thiolation of alkyl carboxylic acids with aryl disulfides, stoichiometric $AgNO_3$ and excessive $K_2S_2O_8$ assisted in generating alkyl radicals from alkyl carboxylic acids, and the radicals reacted with aryl disulfides to afford the thioethers (Scheme 2, reaction 1b).[13] In the sulfenylation of enamides with disulfides, excessive AgOAc facilitates the generation of vinyl radicals from the enamides at high temperature (120 °C), and the vinyl radicals reacted with disulfides to provide the corresponding thioethers (Scheme 2, reaction 1c).[14] In all three examples, aryl, alkyl, and vinyl free radicals are generated from boronic acids, carboxylic acids, and enamides respectively under the assistance of silver, and these radicals react with thiols or disulfides to form thioethers, instead of direct activation of thiols and disulfides. With our great interest in quinone based small molecules as biologically active compounds[15] and to further expand the library of C–S coupling reactions, we report herein a silver(I)-catalyzed direct thiolation of quinones with aryl disulfides to form quinonyl aryl thioethers, in which disulfide-silver intermediates are believed to be generated to initiate the reactions under the assistance of AgOAc/$(NH_4)_2S_2O_8$ in DMSO at room temperature (Scheme 2, reaction 2).

RESULTS AND DISCUSSION

At the outset of our investigation, the direct coupling reaction of 1,4-naphthoquinone (**1a**) with phenyl disulfide (**2a**) in the presence of $AgNO_3$ (0.2 equiv) and $(NH_4)_2S_2O_8$ (3.0 equiv) for 24 h was chosen as our test reaction to examine the effects of several solvents. Surprisingly, only DMSO is a suitable solvent with **3a** being obtained in 18% isolated yield (Table 1, entry 1),[16] while CH_2Cl_2, CH_3CN, THF, MeOH, and DMF do not furnish any desired products.[17] Additionally, an organic/aqueous environment also proves to be unfavorable for the reaction (entry 2). Next we evaluated the catalytic activity of various transition metals for the coupling reaction. The results showed that replacing $AgNO_3$ with AgOAc (0.2 equiv) is also effective for the reaction, affording **3a** with a slightly better yield than that of $AgNO_3$ (entry 3). However, $Cu(OAc)_2{\cdot}H_2O$, CuBr, and $Ni(OAc)_2{\cdot}4H_2O$ were

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found to be completely inefficient for the reaction.[17] We then turned our attention to exploring the effects of oxidants. Several other typical oxidants, $K_2S_2O_8$, TBHP, H_2O_2, and MnO_2, were also tested with the coupling reaction, but no desired product was observed with these oxidants.[17] The ineffectiveness of $K_2S_2O_8$ compared to $(NH_4)_2S_2O_8$ is likely due to its poor solubility in DMSO (entry 4). An increased reaction time and a slightly elevated reaction temperature provide better yields of **3a** (entries 5–7); however, a further increase in temperature is harmful to the reaction (entry 8). It was also found that the combination of AgOAc with a mono- or diphosphine ligand, such as $P(Cy)_3$, dppp, dppe, and dppf, significantly improves the yield of thioether **3a** (entries 9–12). A nitrogen-based bidentate ligand, however, such as 2,2′-bipyridine completely abrogates the generation of the thioether **3a** (entry 13). With an aim of removing extra water from the reaction system and increasing the solubility of the reagents, several additives were also investigated, ultimately showing that Bu_4NBF_4 accelerates the reaction more effectively than other additives (entries 14–17). We also found that lower concentrations of the catalyst or oxidant lead to lower yields of the thioether (entries 18–21). The reaction under N_2 protection did not have much influence on the yield of **3a**, which indicated that air is not an influential factor for the reaction (entry 22).

With the optimized reaction conditions in hand, the substrate scope with respect to various kinds of aryl disulfides was examined (Scheme 3). The aryl disulfides with electron-donating groups at the 4-position on the phenyl ring afford the thioethers in high yields (**3b, 3c**, and **3h**), while an electron-withdrawing substituent at the 4-position leads to a significant decrease in efficiency of the catalytic system (**3d**). However, when the electron-withdrawing groups are at the 3-position, the reaction proceeds smoothly and affords the thioethers with comparable yields to that of **3b** and **3c** (**3e, 3f**, and **3k**). Heterocyclic disulfide **2g** also proves to be a suitable reaction partner for this reaction, providing thioether **3g** with high yield. Highly electron-deficient groups at the 2- or 4- position greatly compromise the reaction, and the corresponding thioethers are not obtained in isolated yields. However, when these electron-deficient disulfides are subjected to 2-methyl-1,4-naphthoquinone, the corresponding thioethers are obtained with moderate yields (**3i, 3j**, and **3l**). Disappointingly, alkyl disulfides seem to be challenging substrates for this catalytic system. Under identical reaction conditions, very little desired thioether (**3w**) is detected via LC/MS when using 2-methyl-1,4-naphthoquinone (**1b**) and benzyl disulfide (**2m**) as the starting materials (Scheme 4).[17]

As outlined in Scheme 5, we have also explored the reactions of phenyl disulfide **2a** with several kinds of quinones. Adding an electron-donating group at the 3-position of 1,4-naphthoquinone (**1a**), such as an alkyl substituent, affords the thioether (**3m**) with improved yield. Whereas adding a phenyl group at the 3-position does not show much influence on the reaction (**3n**). However, if the substrates bearing an electron-withdrawing substituent at the 2- or 4-position of the phenyl ring are used, the reaction yields are significantly reduced (**3o** and **3q**). The presence of an electron-withdrawing substituent at the 3-position on the phenyl ring does not show much influence on the yield of the corresponding thioether (**3p**). In contrast, the phenyl group which is bearing an electron-donating substituent at its 4-position results in improvement of the reaction efficiency (**3r**). Dimethyl substituted 1,4-benzoquinones are found to afford slightly lower yields of the corresponding thioethers than

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1,4-naphthoquinones (**3s** and **3t**). In addition, the catalytic system is also effective with functionalized quinones, affording the corresponding thioethers (**3u** and **3v**) with moderate to high yields.

To further elucidate the mechanism of this reaction, we performed some preliminary experiments as depicted in Scheme 6. Under the assumption that the reaction proceeded using a free radical pathway, we utilized TEMPO, a typical radical-trapping reagent, to trap radicals generated in the reaction. With this method, however, there were no trapped intermediates being observed, and only thioether **3a** was obtained with a similar yield to that without TEMPO (Scheme 6, reaction 1), indicating that the reaction might not proceed by a free radical pathway. We then hypothesized that the reaction might be initiated by disulfide–silver intermediates formed through silver–disulfides interactions. To test the hypothesis, we placed two different disulfides together under the optimal reaction conditions. Gratifyingly, we successfully obtained the expected unsymmetrical disulfide **4a** (Scheme 6, reaction 2), but it is very unstable at room temperature.[17] In order to further confirm the formation of disulfide–silver intermediates, two controlled experiments were carried out. In one experiment, the aryl disulfide **2a**, AgOAc, $(NH_4)_2S_2O_8$, and Bu_4NBF_4 were stirred in deuterated DMSO for 2 h (Scheme 6, reaction 3, I). The solution was filtered, and the filtrates were analyzed by ^{13}C NMR experiments. In the other experiment, the procedures are the same except for the absence of AgOAc (Scheme 6, reaction 3, II). The ^{13}C NMR spectrum showed that the chemical shifts for experiment I change significantly compared to those for experiment II.[17] All the results implied that disulfide–silver intermediates are being generated in the reaction,[18] and it may also explain why DMSO (a solvent with high polarity) is favorable for this reaction. Given the possibility that aryl disulfides might be oxidized in the reaction, we also carried out the reaction as depicted in Scheme 6, reaction 4; however, there was no sign of oxidized disulfides being detected. In addition, when 1,4-naphthoquinone (**1a**) was treated with silver thiolate **6b** (poor solubility in DMSO) under the standard reaction conditions, the thioether **3c** was obtained in 28% yield (Scheme 6, reaction 5), and it implied that silver thiolate might be the active intermediate. A kinetic isotope effect (KIE) experiment was also evaluated, and no kinetic isotope effect was observed (Scheme 6, reaction 6).[17] The result indicated that the abstraction of hydride at the 2-position of 1,4-naphthoquinone (**1a**) is not rate-determining.

With these results, we proposed a plausible mechanism shown in Scheme 7. Initially, silver complex [Ag(I)(dppp)]OAc (**5**) interacting with phenyl disulfide (**2a**) forms the active intermediate **6a**, which then generates silver thiolate **7** and sulphenyl acetate **8**.[19] The reaction of silver thiolate **7** with 1,4-naphthoquinone (**1a**) forms complex **9**, and it was then oxidized by sulphenyl acetate **8** to afford the desired thioether **3a**. At the same time, sulphenyl acetate **8** is reduced to thiophenol **10** with the regeneration of silver complex **5**, and the thiophenol **10** is oxidized back to phenyl disulfide (**2a**) by $(NH_4)_2S_2O_8$/DMSO for next reaction circle.[17]

Finally, the thiolation of 1,4-naphthoquinone (**1a**) with the unsymmetrical aryl disulfide (**4b**) was evaluated (Scheme 8).[17] Interestingly, much more electron-deficient thioether **3d** was obtained than electron-rich thioether **3c** (**3d**/**3c** = 3.4/1), which is contrary to the rule known before that electron-rich aryl disulfides afford higher yields of thioethers than electron-

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deficient disulfides do. However, this phenomenon is well explained by Scheme 8. There is more thiolate anion **12** generated than thiolate anion **11** in the reaction because the thiolate anion with an electron-withdrawing group is more stable than that with an electron-donating group. Therefore, more $ClPhS^-$ (**12**) is generated to react with 1,4-naphthoquinone (**1a**), yielding more thioether **3d**. In turn, this phenomenon is also additional indirect evidence for the proposed mechanism.

CONCLUSION

In conclusion, we have shown a silver-catalyzed direct coupling reaction of quinones with aryl disulfides to synthesize a variety of quinonyl aryl thioethers with moderate to high yields. The catalytic system required DMSO as the indispensable solvent and $(NH_4)_2S_2O_8$ as the indispensable oxidant to be effective under mild reaction conditions. Additionally the system is tolerant to a broad substrate scope of quinones and aryl disulfides. Furthermore, we have also provided preliminary mechanism studies that indicate the reaction is initiated by active disulfide–silver intermediates formed through interactions of the silver with aryl disulfides in DMSO.

EXPERIMENTAL SECTION

General Considerations

All reactions were carried out under air unless otherwise stated. Solvents were HPLC grade and used without purification. Commercial reagents were used without further purification. Flash chromatography was performed on silica gel. Thin layer chromatography (TLC) was performed on glass plates coated with silica gel. Chemical shifts for protons are reported in parts per million upfield to tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$ = δ 7.26, DMSO = 2.52). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$ = δ 77.07, DMSO = 39.9). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz (Hz), integration. HRMS data of compounds were recorded on a double focusing magnetic sector mass spectrometer using an electron ionization method (EI).

General Procedures

AgOAc (16.7 mg, 0.1 mmol), dppp (49.5 mg, 0.12 mmol), $(NH_4)_2S_2O_8$ (342 mg, 1.5 mmol), Bu_4NBF_4 (165 mg, 0.5 mmol), quinone (0.5 mmol), and aryl disulfide (0.3 mmol) were stirred in 2 mL of DMSO at room temperature for 48 h. The reaction mixture was poured into 10 mL of water and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. Volatiles were removed under vacuum, and the residue was purified on silica column with AcOEt/ Hexane to afford the desired thioether.

2-(Phenylthio)-1,4-naphthoquinone (3a).[9a]**—**Yellow solid: 108 mg, 81% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15–8.13 (m, 1H), 8.03–8.01 (m, 1H), 7.74–7.72 (m, 2H), 7.56–7.49 (m, 5H), 6.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.2, 182.0, 156.7, 135.8,

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134.4, 133.4, 132.3, 131.8, 130.6, 130.4, 128.2, 127.4, 126.9, 136.6; LC/MS: $[M + H]^+$ = 267.17.

2-[(4-Methyl)phenylthio]-1,4-naphthoquinone (3b).[20a]—Yellow solid: 121 mg, 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12–8.10 (m, 1H), 8.01–7.99 (m, 1H), 7.72–7.69 (m, 2H), 7.41–7.39 (m, 2H), 7.30–7.28 (m, 2H), 6.09 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.2, 182.0, 157.1, 141.0, 135.6, 134.3, 133.3, 132.3, 131.8, 131.2, 128.1, 126.8, 126.5, 123.7, 21.4; LC/MS: $[M + 1]^+$ = 281.08.

2-[(4-Methoxyl)phenylthio]-1,4-naphthoquinone (3c)—Yellow solid: 121 mg, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11–8.09 (m, 1H), 8.00–7.98 (m, 1H), 7.73–7.67 (m, 2H), 7.44–7.41 (m, 2H), 7.01–6.98 (m, 2H), 6.08 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.3, 182.0, 161.5, 157.5, 137.2, 134.3, 133.3, 132.3, 128.1, 126.8, 126.5, 117.5, 116.0, 55.5; LC/MS: $[M + 1]^+$ = 297.17; HRMS: calcd for $C_{17}H_{12}O_3S$ $[M]^+$, 296.0507; found, 296.0510.

2-[(4-Chloro)phenylthio]-1,4-naphthoquinone (3d).[20b]—Yellow solid: 96 mg, 64% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14–8.12 (m, 1H), 8.04–8.01 (m, 1H), 7.76–7.70 (m, 2H), 7.48 (s, 4H), 6.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.0, 181.9, 156.1, 137.3, 137.0, 134.5, 133.5, 132.2, 131.7, 130.7, 128.3, 126.9, 126.6, 125.9; LC/MS: $[M + 1]^+$ = 301.08.

2-[(3-Fluoro)phenylthio]-1,4-naphthoquinone (3e).[20b]—Yellow solid: 117 mg, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14–8.12 (m, 1H), 8.03–8.01 (m, 1H), 7.75–7.72 (m, 2H), 7.50–7.48 (m, 1H), 7.35 (d, *J* = 8 Hz, 1H), 7.30–7.20, (m, 2H), 6.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.0, 181.9, 163.2 (d, *J* = 250 Hz), 155.9, 134.5, 133.5, 132.2, 131.8, 131.6 (d, *J* = 18 Hz), 131.6, 131.5, 129.4 (d, *J* = 8 Hz), 128.4, 126.8 (d, *J* = 28 Hz), 122.6 (d, *J* = 22 Hz), 117.9 (d, *J* = 21 Hz); LC/MS: $[M + 1]^+$ = 285.08.

2-[(3-Nitro)phenylthio]-1,4-naphthoquinone (3f)—Yellow solid: 125 mg, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45–8.44 (m, 1H), 8.40–8.37 (m, 1H), 8.15–8.13 (m, 1H), 8.04–8.02 (m, 1H), 7.91–7.89 (m, 1H), 7.77–7.71 (m, 3H), 6.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.7, 181.6, 155.0, 149.2, 141.7, 134.7, 133.7, 132.1, 131.5, 131.3, 130.6, 130.2, 128.6, 127.0, 126.8, 125.5; LC/MS: $[M+1]^+$ = 312.08; HRMS: calcd for $C_{16}H_9NO_4S$ $[M]^+$, 311.0252; found, 311.0259.

2-[(2-Furyl)thio]-1,4-naphthoquinone (3g)—Yellow solid: 114 mg, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13–8.10 (m, 1H), 8.04–8.01 (m, 1H), 7.76–7.70 (m, 2H), 7.65 (dd, *J* = 5 Hz, *J* = 1 Hz), 7.33 (dd, *J* = 3 Hz, *J* = 1 Hz), 7.21–7.18 (m, 1H), 6.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.1, 182.1, 156.5, 138.2, 134.5, 133.7, 133.5, 132.2, 131.6, 129.0, 129.0, 126.8, 126.6, 124.3; LC/MS: $[M + 1]^+$ = 273.08; HRMS: calcd for $C_{14}H_8O_2S_2$ $[M]^+$, 271.9966; found, 271.9970.

2-[2-Benzamido(phenylthio)]-1,4-naphthoquinone (3h)—Yellow solid: 146 mg, 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (br, 1H), 8.78–8.76 (m, 1H), 8.13–8.11 (m, 1H), 8.01–7.98 (m, 1), 7.81–7.79 (m, 2H), 7.75–7.69 (m, 2H), 7.61–7.55 (m, 2H), 7.51–7.48

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(m, 1H), 7.44–7.40 (m, 2H), 7.27–7.23 (m, 1H), 6.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.1, 181.6, 165.3, 153.0, 140.8, 137.0, 134.7, 134.4, 133.6, 132.8, 132.2, 132.2, 131.6, 129.6, 129.0, 127.1, 126.9, 126.8, 125.4, 121.4, 114.9; LC/MS: $[M + 1]^+$ = 386.08; HRMS: calcd for $C_{23}H_{15}NO_3S$ $[M]^+$, 385.0773; found, 385.0769.

3-Methyl-2-[2-phenylcarbamoyl(phenylthio)]-1,4-naphthoquinone (3i)—Yellow solid: 84 mg, 42% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.04 (br, 1H), 8.14–8.12 (m, 1H), 7.99–7.97 (m, 1H), 7.75–7.69 (m, 5H), 7.35–7.27 (m, 5H), 7.12–7.09 (m, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.6, 182.0, 166.4, 150.6, 145.8, 139.0, 138.6, 134.4, 133.8, 132.9, 132.4, 132.2, 130.8, 130.8, 130.3, 129.0, 128.8, 127.3, 127.0, 124.2, 119.7, 16.2; LC/MS: $[M + 1]^+$ = 400.08; HRMS: calcd for $C_{24}H_{17}NO_3S$ $[M]^+$, 399.0929; found, 399.0929.

3-Methyl-2-[2-nitro(phenylthio)]-1,4-naphthoquinone (3j)—Yellow solid: 68 mg, 42% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (dd, *J* = 8 Hz, *J* = 1 Hz, 1H), 8.15 (dd, *J* = 8 Hz, *J* = 1 Hz, 1H), 8.01 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H), 7.78–7.70 (m, 2H), 7.40–7.38 (m, 1H), 7.34–7.31 (m, 1H), 7.12 (dd, *J* = 8 Hz, *J* = 1 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.9, 179.8, 153.6, 146.7, 142.7, 134.2, 134.1, 133.4, 132.3, 132.1, 129.9, 127.3, 127.0, 126.4, 126.1, 16.2; LC/MS: $[M + 1]^+$ = 326.08; HRMS: calcd for $C_{17}H_{11}NO_4S$ $[M]^+$, 325.0409; found, 325.0411.

3-Methyl-2-[3-nitro(phenylthio)]-1,4-naphthoquinone (3k)—Yellow solid: 137 mg, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17–8.16 (m, 1H), 8.13–8.11 (m, 1H), 8.09–8.06 (m, 1H), 7.98–7.97 (m, 1H), 7.75–7.66 (m, 3H), 7.49–7.45 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.7, 179.9, 150.9, 148.5, 143.2, 136.9, 135.8, 134.1, 134.0, 132.3, 132.0, 129.9, 127.2, 126.9, 124.6, 122.1, 16.4; LC/MS: $[M + 1]^+$ = 326.08; HRMS: calcd for $C_{17}H_{11}NO_4S$ $[M]^+$, 325.0409; found, 325.0413.

3-Methyl-2-[4-nitro(phenylthio)]-1,4-naphthoquinone (3l)—Yellow solid: 72 mg, 44% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15–8.10 (m, 3H), 8.03–8.01 (m, 1H), 7.78–7.70 (m, 2H), 7.41–7.37 (m, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.7, 179.7, 152.2, 146.2, 143.9, 142.5, 134.2, 134.1, 132.3, 132.0, 128.9, 127.3, 127.0, 124.3, 16.4; LC/MS: $[M – 1]^-$ = 324.33; HRMS: calcd for $C_{17}H_{11}NO_4S$ $[M]^+$, 325.0409; found, 325.0407.

3-Methyl-2-(phenylthio)-1,4-naphthoquinone (3m).[20c]—Yellow solid: 123 mg, 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11–8.09 (m, 1H), 8.02–8.00 (m, 1H), 7.73–7.65 (m, 2H), 7.38–7.35 (m, 2H), 7.30–7.22 (m, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.1, 180.5, 149.2, 145.5, 134.1, 133.8, 133.7, 132.6, 132.1, 130.6, 129.2, 127.4, 127.1, 126,7, 16.0; LC/MS: $[M + 1]^+$ = 291.08.

3-Phenyl-2-(phenylthio)-1,4-naphthoquinone (3n)—Yellow solid: 140 mg, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15–13 (m, 1H), 8.07–8.05 (m, 1H), 7.77–7.70 (m, 2H), 7.38–7.35 (m, 3H), 7.24–7.21 (m, 4H), 7.18–7.14 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.1, 181.5, 148.1, 147.8, 134.1, 133.7, 133.6, 133.5, 132.6, 132.2, 131.6, 129.7,

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129.0, 128.9, 127.9, 127.5, 127.0, 127.0; LC/MS: $[M+1]^+$ = 343.08; HRMS: calcd for $C_{22}H_{14}O_2S$ $[M]^+$, 342.0715; found, 342.0720.

3-(2-Chlorophenyl)-2-(phenylthio)-1,4-naphthoquinone (3o)—Yellow solid: 117 mg, 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15–8.12 (m, 1H), 8.09–8.06 (m, 1H), 7.78–7.71 (m, 2H), 7.35–7.34 (m, 1H), 7.31–7.27 (m, 4H), 7.20–7.14 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.2, 181.0, 149.1, 145.9, 134.2, 133.7, 133.0, 132.5, 132.3, 132.2, 132.1, 130.7, 130.2, 129.4, 129.0, 128.0, 127.1, 127.1, 126.6; LC/MS: $[M + 1]^+$ = 377.08; HRMS: calcd for $C_{22}H_{13}ClO_2S$ $[M]^+$, 376.0325; found, 376.0321.

3-(3-Chlorophenyl)-2-(phenylthio)-1,4-naphthoquinone (3p)—Yellow solid: 156 mg, 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12–8.07 (m, 2H), 7.78 (m, 2H), 7.27–7.22 (m, 2H), 7.20–7.11 (m, 6H), 7.07–7.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.7, 149.2, 145.4, 134.9, 134.3, 133.8, 132.5, 132.3, 132.0, 129.8, 129.1, 129.0, 128.7, 127.9, 127.9, 127.0, 127.0; LC/MS: $[M + 1]^+$ = 377.00; HRMS: calcd for $C_{22}H_{13}ClO_2S$ $[M]^+$, 376.0325; found, 376.0320.

3-(4-Chlorophenyl)-2-(phenylthio)-1,4-naphthoquinone (3q)—Yellow solid: 128 mg, 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13–8.11 (m, 1H), 8.08 (m, 1H), 7.78–7.71 (m, 2H), 7.19–7.27 (m, 2H), 7.19–7.11 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.8, 181.5, 148.6, 146.3, 134.9, 134.2, 133.8, 133.0, 132.4, 132.0, 132.0, 131.7, 131.2, 129.0, 128.1, 127.8, 127.0, 127.0; LC/MS: $[M + 1]^+$ = 377.08; HRMS: calcd for $C_{22}H_{13}ClO_2S$ $[M]^+$, 376.0325; found, 376.0319.

3-(4-Methoxylphenyl)-2-(phenylthio)-1,4-naphthoquinone (3r)—Yellow solid: 160 mg, 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15–8.13 (m, 1H), 8.05–8.02 (m, 1H), 7.76–7.68 (m, 2H), 7.24–7.20 (m, 4H), 7.18–7.15 (m, 3H), 6.92–6.88 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.4, 181.5, 160.3, 147.8, 146.8, 134.0, 134.0, 133.7, 132.7, 132.2, 131.6, 131.3, 128.9, 127.4, 127.0, 126.9, 125,6, 113.4, 55.3; LC/MS: $[M + 1]^+$ = 373.08; HRMS: calcd for $C_{23}H_{16}O_3S$ $[M]^+$, 372.0820; found, 372.0819.

3,5-Dimethyl-2-(phenylthio)-1,4-benzoquinone (3s)—Yellow solid: 98 mg, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.20 (m, 5H), 6.62 (q, *J* = 2 Hz, 1H), 2.21 (s, 3H), 2.06 (d, *J* = 2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.9, 153.5, 147.2, 146.0, 142.6, 134.0, 133.9, 130.5, 129.2, 127.3, 16.0, 15.4; LC/MS: $[M + 1]^+$ = 245.17; HRMS: calcd for $C_{14}H_{12}O_2S$ $[M]^+$, 244.0558; found, 244.0562.

3,6-Dimethyl-2-(phenylthio)-1,4-benzoquinone (3t)—Yellow solid: 93 mg, 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.22 (m, 5H), 6.62 (q, *J* = 2 Hz, 1H), 2.18 (s, 3H), 2.01 (d, *J* = 2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.4, 183.1, 147.3, 146.7, 142.6, 134.0, 133.5, 130.5, 129.2, 127.3, 14.3, 15.1; LC/MS: $[M + 1]^+$ = 245.08; HRMS: calcd for $C_{14}H_{12}O_2S$ $[M]^+$, 244.0558; found, 244.0559.

3-Benzamido-2-(phenylthio)-1,4-naphthoquinone (3u)—Yellow solid: 131 mg, 68% yield. ^{1}H NMR (400 MHz, DMSO): δ 10.21 (br, 1H), 8.09–8.08 (m, 1H), 7.97–7.95 (m, 1H), 7.92–7.86 (m, 4H), 7.64–7.60 (m, 1H), 7.52–7.49 (m, 2H), 7.33–7.32 (m, 2H), 7.24–

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7.16 (m, 3H); ^{13}C NMR (100 MHz, DMSO): δ 181.1, 179.2, 165.1, 142.4, 138.5, 135.0, 135.0, 133.9, 133.0, 132.9, 132.6, 131.5, 130.8, 129.5, 128.9, 128.6, 127.7, 127.1, 127.0; LC/MS: $[M + 1]^+$ = 385.92; HRMS: calcd for $C_{23}H_{15}NO_3S$ $[M]^+$, 385.0773; found, 385.0776.

3-Phenoxymethyl-2-(phenylthio)-1,4-naphthoquinone (3v)—Yellow solid: 153 mg, 82% yield. ^{1}H NMR (400 MHz, DMSO): δ 8.11–8.08 (m, 1H), 7.92–7.82 (m, 3H), 7.45–7.43 (m, 2H), 7.34–7.26 (m, 5H), 7.03–6.97 (m, 3H), 5.18 (s, 2H); ^{13}C NMR (100 MHz, DMSO): δ 181.7, 180.2, 158.5, 149.3, 145.2, 135.1, 134.8, 134.2, 132.7, 132.0, 130.8, 130.1, 129.7, 127.9, 127.2, 126.9, 121.7, 115.1, 62.8; LC/MS: $[M + 1]^+$ = 373.00; HRMS: calcd for $C_{23}H_{16}O_3S$ $[M]^+$, 372.0820; found, 372.0816.

Experiments for Trapping Free Radical

AgOAc (16.7 mg, 0.1 mmol), dppp (49.5 mg, 0.12 mmol), $(NH_4)_2S_2O_8$ (342 mg, 1.5 mmol), Bu_4NBF_4 (165 mg, 0.5 mmol), 1,4-naphthoquinone (**1a**, 0.5 mmol), phenyl disulfide (**2a**, 0.3 mmol), and TEMPO (1 mmol) were stirred in 2 mL of DMSO at room temperature for 48 h. The reaction mixture was poured into 10 mL of water and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. Volatiles were removed under vacuum, and the residue was analyzed by LC/MS and purified by silica gel chromatography, and only thioether **3a** was obtained with an 82% isolated yield.

Metathesis Reaction of Disulfides

A mixture of AgOAc (16.7 mg, 0.1 mmol), dppp (49.5 mg, 0.12 mmol), $(NH_4)_2S_2O_8$ (342 mg, 1.5 mmol), Bu_4NBF_4 (165 mg, 0.5 mmol), disulfides **2h** (0.3 mmol), and **2b** (0.3 mmol) was stirred in 2 mL of DMSO at room temperature for 48 h. The reaction mixture was poured into 10 mL of water and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. Volatiles were removed under vacuum, and the residue was purified on a silica column with AcOEt/Hexane to afford the expected disulfide **4a**. Disulfide **4a** is very unstable: **4a** was obtained as a pure compound when just purified on a silica column (analyzed by LC/MS), but both NMR and LC/MS results showed that it had decomposed to its starting materials after it was dried on a rotorvapor and dissolved in $CDCl_3$.

Synthesis of Silver Thiolate (6b).[21]

Silver nitrate (4 mmol, 664 mg) was dissolved in 35 mL of CH_3CN, to which was added 4-methoxythiophenol (8 mmol, 0.984 mL) with vigorous stirring, followed by the addition of Et_3N (8 mmol, 1.2 mL), and the mixture was stirred at room temperature for 30 min. The white solid was collected by filtration, and it was washed with CH_3CN and dried under vacuum. The silver thiolate **6b** was obtained as white solids in quantitative yield.

Synthesis of Deuterated 1,4-Naphthoquinone (1a′).[22]

Naphthalene-d_8 (136 mg, 1 mmol) was suspended in 1.8 mL of CH_3COOD (90%, D_2O) at 5–10 °C, to which was added a solution of CrO_3 [0.589 g (6 mmol) in 1 mL of CH_3COOD

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(60%, D_2O)] dropwise; the temperature during the addition was maintained at 5–10 °C. After the addition, the mixture was stirred at room temperature for 1 h. The mixture was cooled and poured into 10 mL of D_2O and extracted with ethyl acetate. Volatiles were removed, and the residue was purified on silica gel with hexane/ethyl acetate = 10/1. A yellow solid (60 mg) was obtained (37% yield).

Kinetic Isotope Effect Experiment

AgOAc (6.7 mg, 0.04 mmol), dppp (19.7 mg, 0.048 mmol), $(NH_4)_2S_2O_8$ (137 mg, 0.6 mmol), Bu_4NBF_4 (65.9 mg, 0.2 mmol), 1,4-naphthoquinone **1a** (47.4 mg, 0.3 mmol), deuterated 1,4-naphthoquinone **1a′** (50 mg, 0.3 mmol), and aryl *p*-tolyl disulfide (0.2 mmol) were stirred in 2 mL of DMSO at room temperature for 10 min. The reaction mixture was poured into 10 mL of water and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. Volatiles were removed under vacuum, and the residue was purified on a silica column with AcOEt/Hexane = 1/13 to afford the desired thioether (11 mg). The yellow solid was analyzed by ^1H NMR spectroscopy.

Synthesis of Unsymmetrical Aryl Disulfide 4b

A mixture of AgOAc (33.4 mg, 0.2 mmol), $(NH_4)_2S_2O_8$ (684.6 mg, 3 mmol), Bu_4NBF_4 (329 mg,1 mmol), disulfides **2c** (287 mg, 1 mmol), and **2d** (278 mg, 1 mmol) was stirred in 3 mL of DMSO at room temperature for 48 h. The reaction mixture was poured into 10 mL of water and extracted with ethyl acetate (2 × 15 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. Volatiles were removed under vacuum, and the residue was purified on a silica column with AcOEt/Hexane to afford the expected disulfide **4b** (150 mg, 53% yield). The product was directly used in the next step reaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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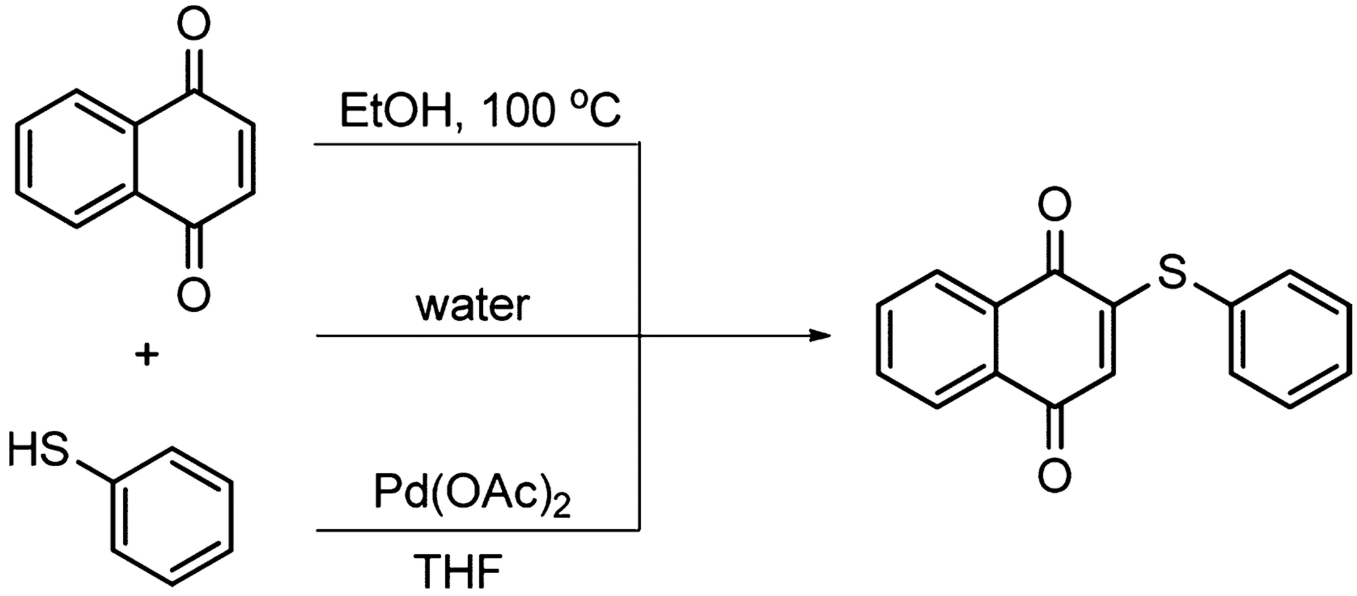

Scheme 1. Available Methods for the Synthesis of Thioethers by Direct Thiolation of Quinones

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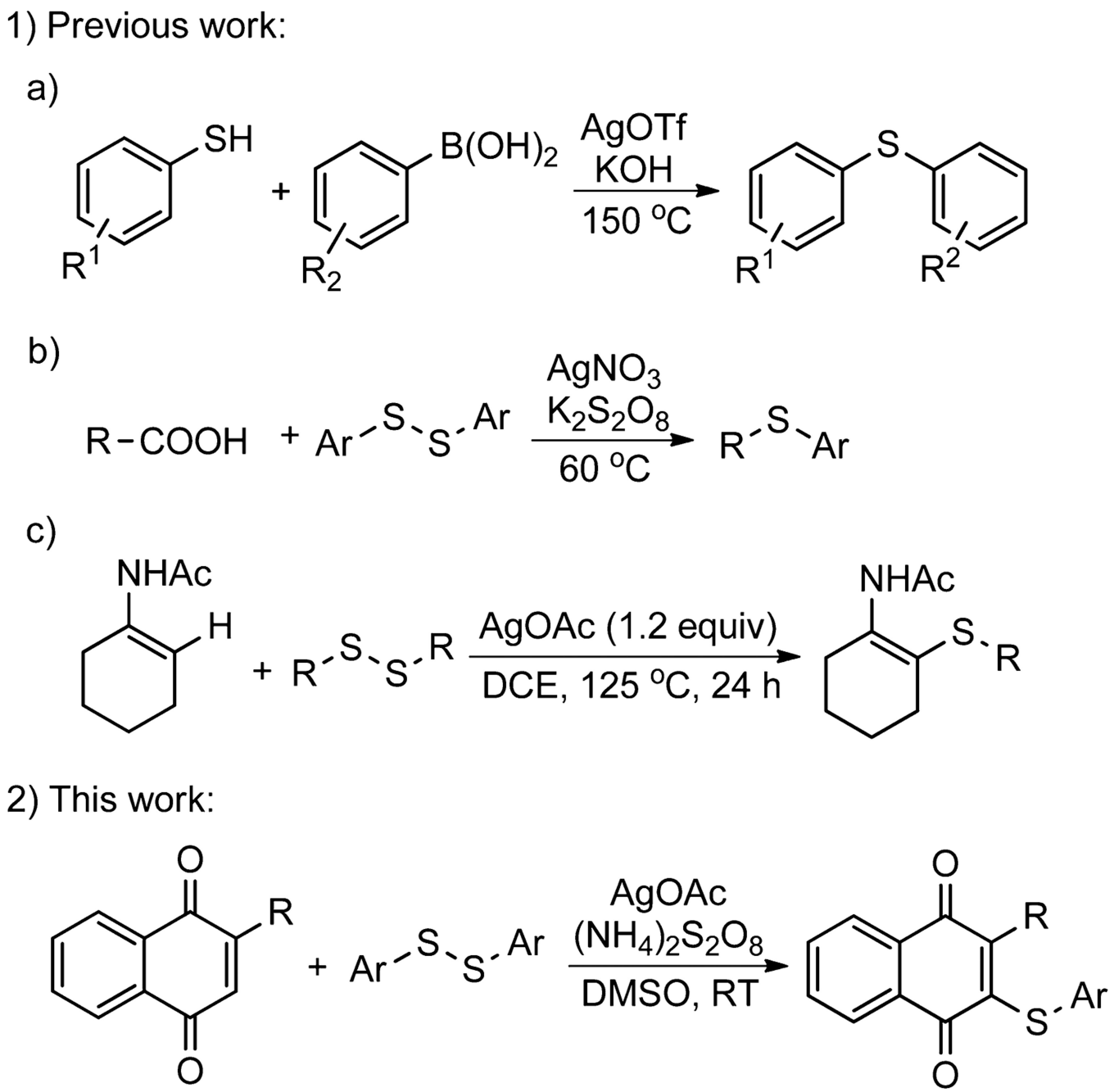
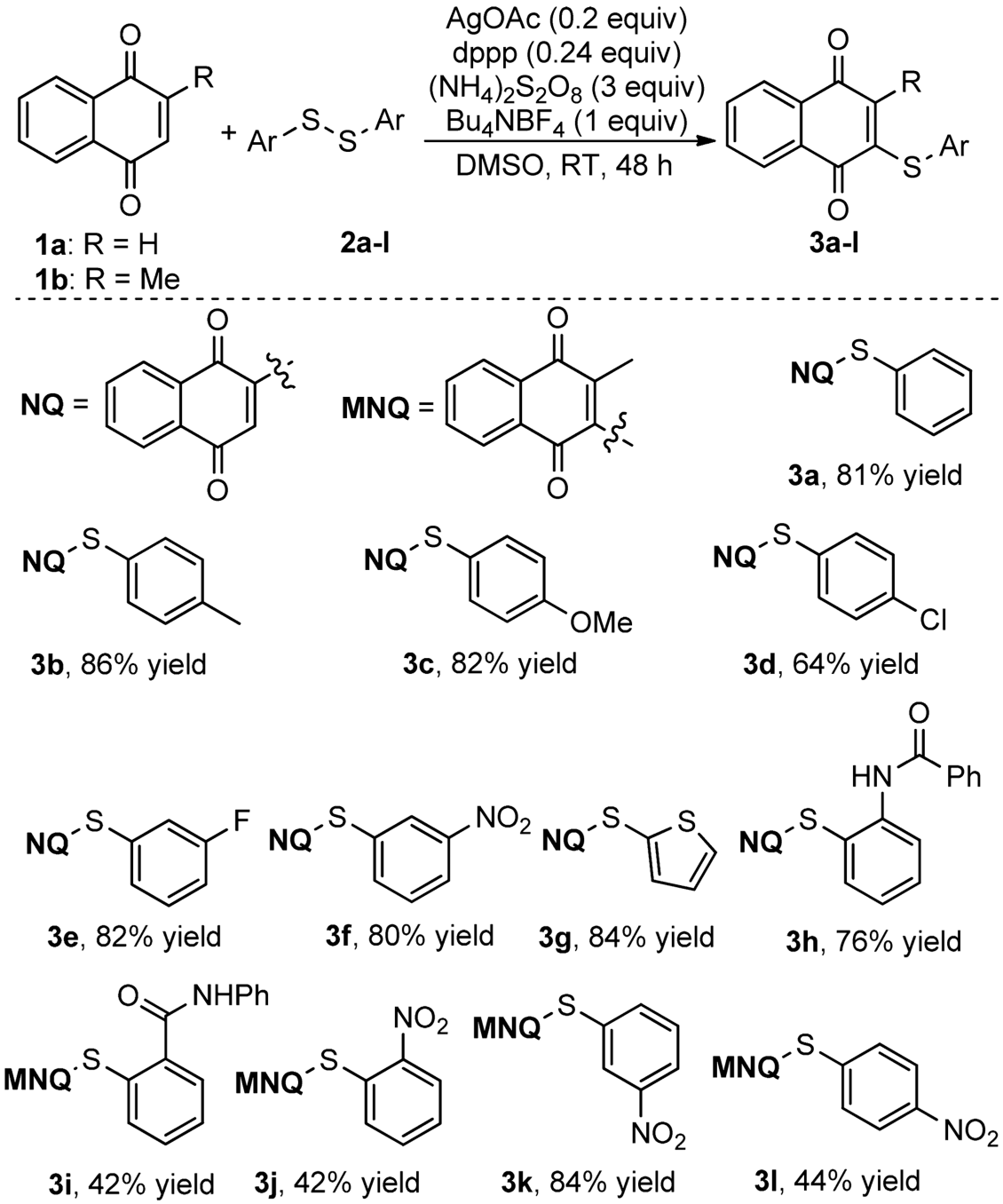


Scheme 2. Silver-Catalyzed Synthesis of Thioethers



Scheme 3. Silver-Catalyzed Thiolation of Quinones (1a or 1b): Disulfides Scopea,b

[a]Reaction conditions: **1a** or **1b** (0.5 mmol), **2** (0.3 mmol), AgOAc (0.1 mmol), dppp (0.12 mmol), $(NH_4)_2S_2O_8$ (1.5 mmol), and Bu_4NBF_4 (0.5 mmol) were stirred in 2 mL of DMSO at room temperature for 48 h.

[b]Isolated yield.

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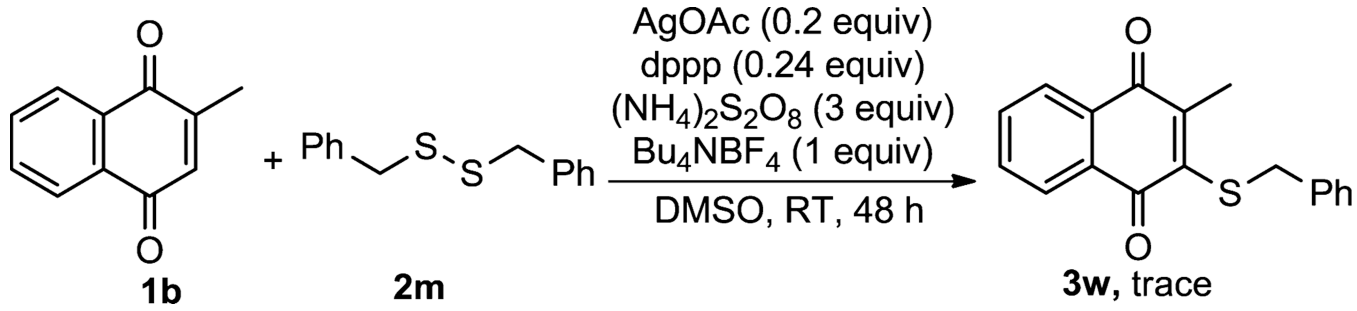

Scheme 4. Silver-Catalyzed Thiolation of 2-Methyl-1,4-naphthoquinone (1b) with Alkyl Disulfide (2m)a

[a]Reaction conditions: **1b** (0.5 mmol), **2m** (0.3 mmol), AgOAc (0.1 mmol), dppp (0.12 mmol), $(NH_4)_2S_2O_8$ (1.5 mmol), and Bu_4NBF_4 (0.5 mmol) were stirred in 2 mL of DMSO at 40 °C for 60 h.

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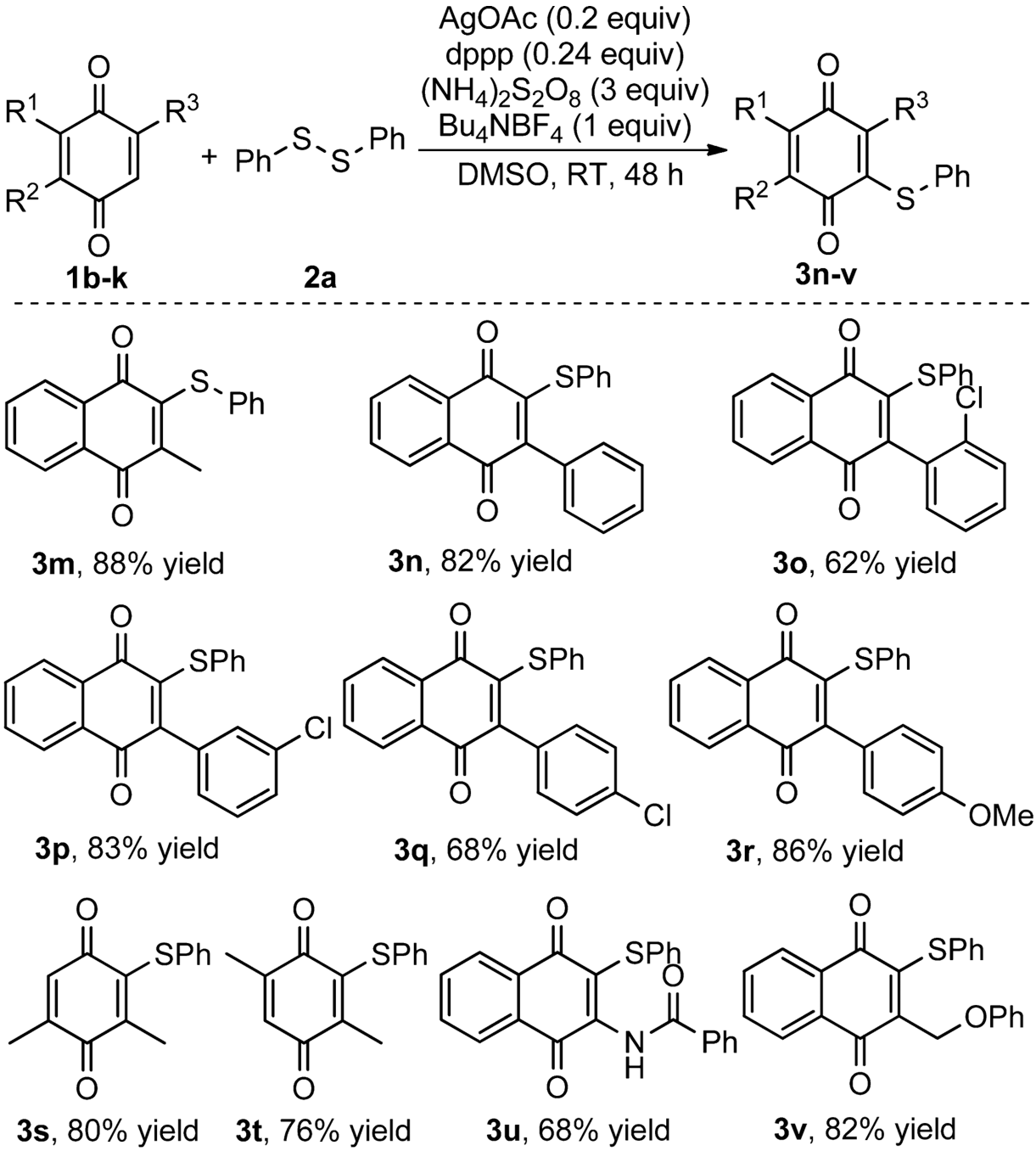
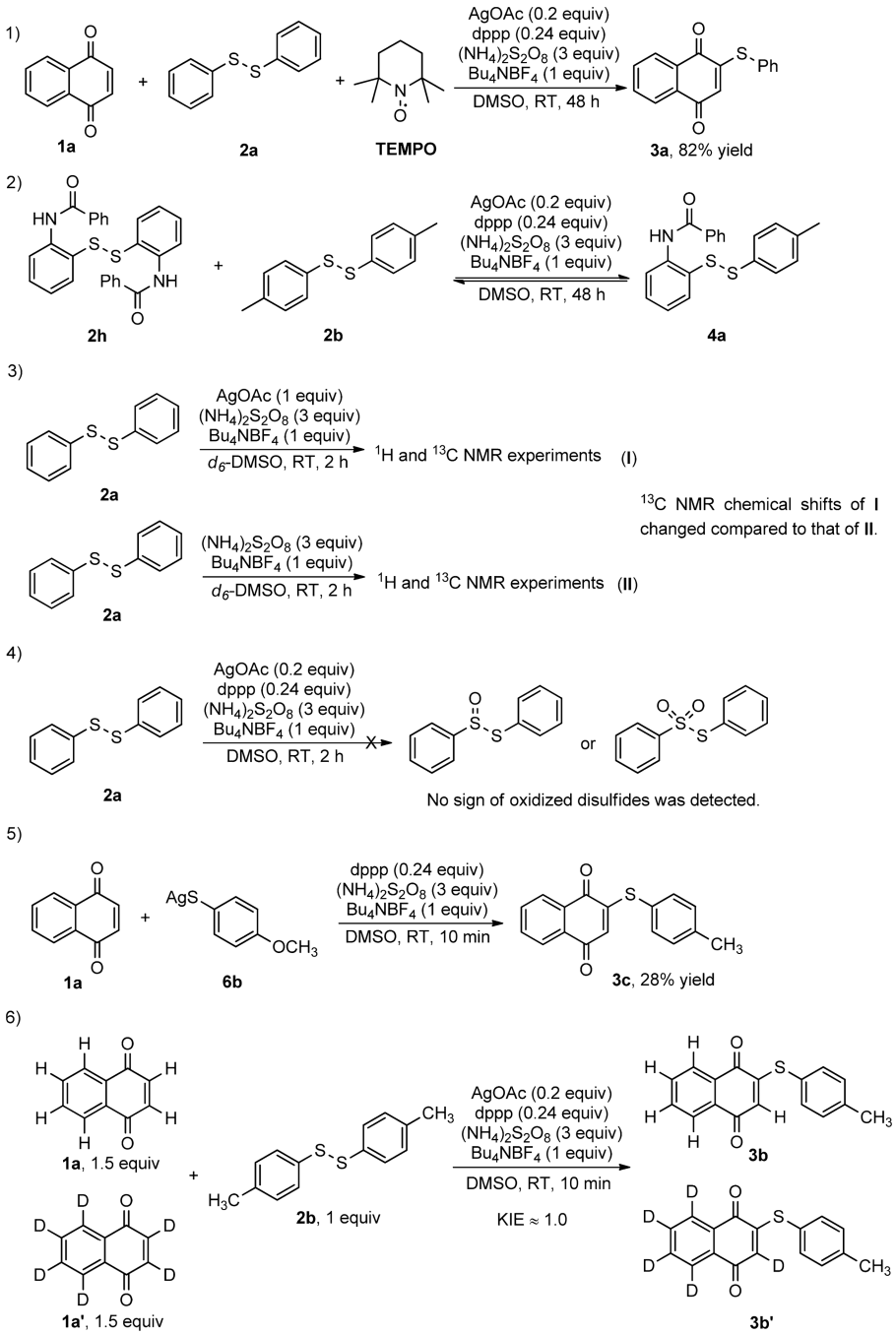


Scheme 5. Silver-Catalyzed Thiolation of Quinones (1) with Disulfides (2a): Quinones Scopea,b

[a]Reaction conditions: **1b–k** (0.5 mmol), **2a** (0.3 mmol), AgOAc (0.1 mmol), dppp (0.12 mmol), $(NH_4)_2S_2O_8$ (1.5 mmol), and Bu_4NBF_4 (0.5 mmol) were stirred in 2 mL of DMSO at room temperature for 48 h.

[b]Isolated yield.



Scheme 6. Preliminary Experiments for Probing the Mechanism

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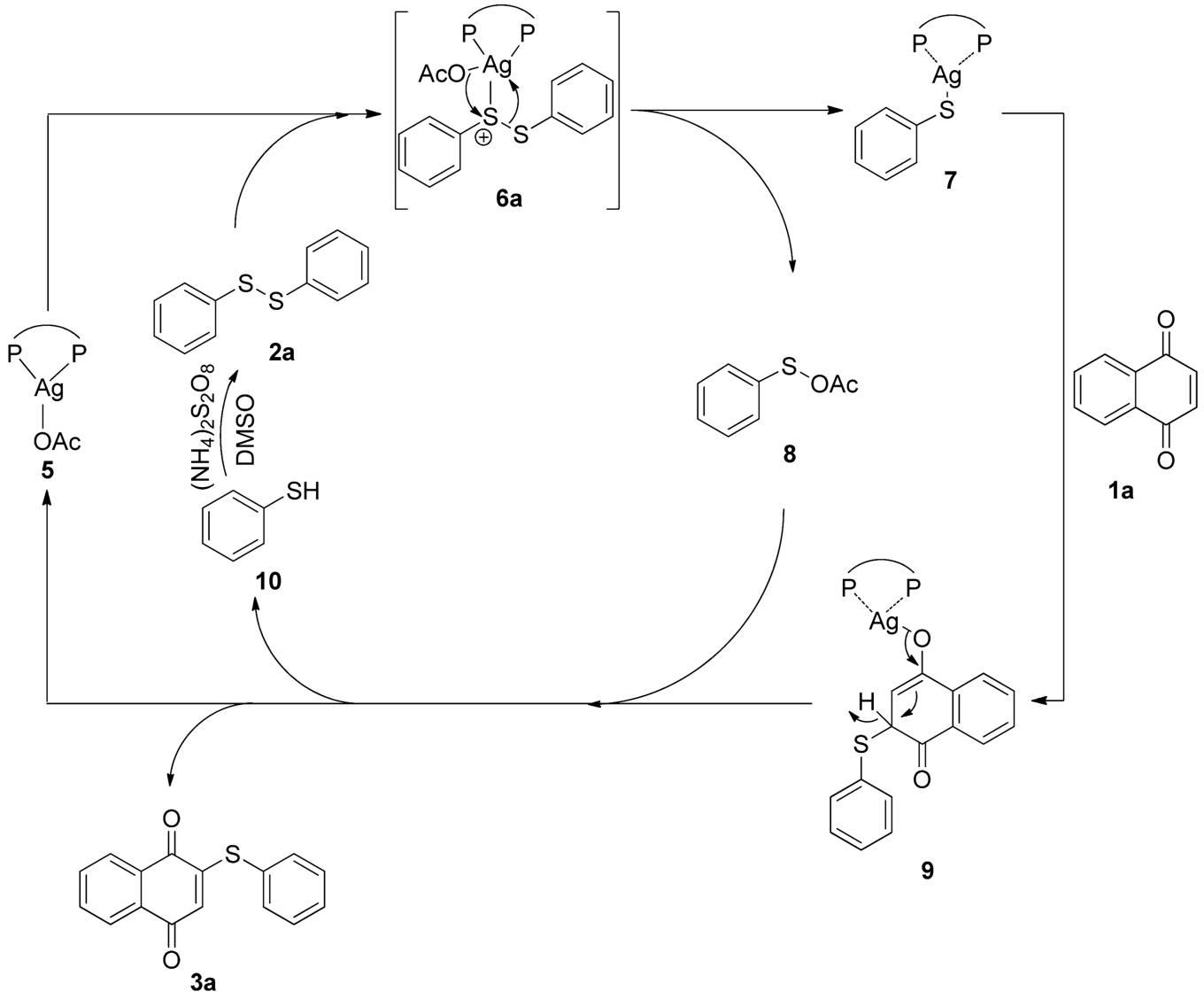

Scheme 7. Proposed Mechanism for Thiolation of Quinones with Disulfides

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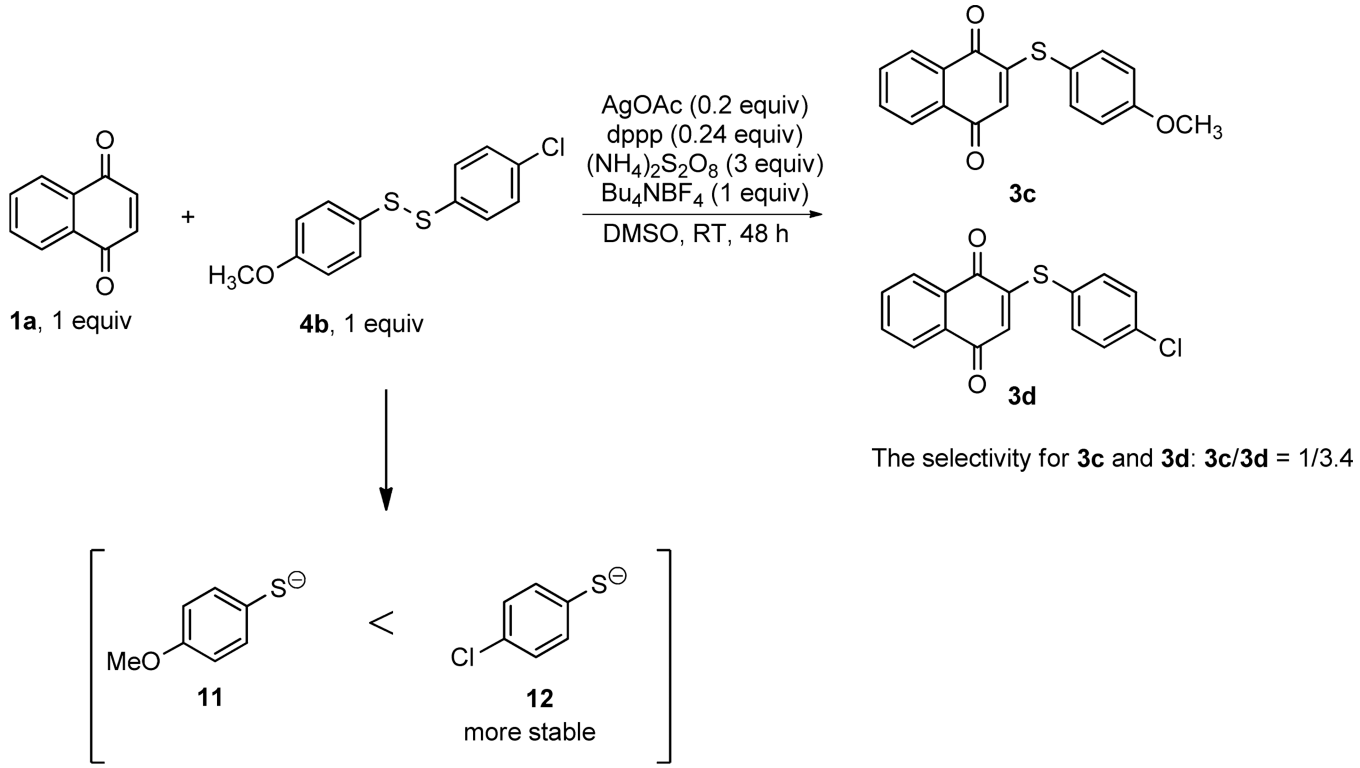

Scheme 8. Thiolation of 1,4-Naphthoquinone (1a) with the Unsymmetrical Disulfide (4b)

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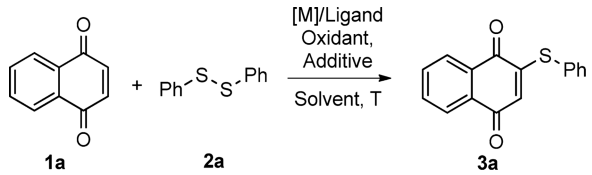
Table 1

Screening of Optimal Reaction Conditions for the Thiolation of 1,4-Naphthoquinone (1a) with Phenyl Disulfide (2a)[a]



entry	[M] (equiv)	ligand (equiv)	oxidant (equiv)	additive (equiv)	solvent	*T* (°C)	*t* (h)	yield (%)[b]
1	$AgNO_3$ (0.2)	–	$(NH_4)_2S_2O_8$ (3)	–	DMSO	25	24	18
2	$AgNO_3$ (0.2)	–	$(NH_4)_2S_2O_8$ (3)	–	DMSO/H_2O	25	24	–
3	AgOAc (0.2)	–	$(NH_4)_2S_2O_8$ (3)	–	DMSO	25	24	24
4	AgOAc (0.2)	–	$K_2S_2O_8$ (3)	–	DMSO	25	24	–
5	$AgNO_3$ (0.2)	–	$(NH_4)_2S_2O_8$ (3)	–	DMSO	25	48	22
6	AgOAc (0.2)	–	$(NH_4)_2S_2O_8$ (3)	–	DMSO	25	48	30
7	AgOAc (0.2)	–	$(NH_4)_2S_2O_8$ (3)	–	DMSO	40	48	36
8	AgOAc (0.2)	–	$(NH_4)_2S_2O_8$ (3)	–	DMSO	60	48	26
9	AgOAc (0.2)	$P(Cy)_3$ (0.24)	$(NH_4)_2S_2O_8$ (3)	–	DMSO	25	48	51
10	AgOAc (0.2)	dppp (0.24)	$(NH_4)_2S_2O_8$ (3)	–	DMSO	25	48	60
11	AgOAc (0.2)	dppe (0.24)	$(NH_4)_2S_2O_8$ (3)	–	DMSO	25	48	59
12	AgOAc (0.2)	dppf (0.24)	$(NH_4)_2S_2O_8$ (3)	–	DMSO	25	48	60
13	AgOAc (0.2)	bipy (0.24)	$(NH_4)_2S_2O_8$ (3)	–	DMSO	25	48	–
14	AgOAc (0.2)	dppp (0.24)	$(NH_4)_2S_2O_8$ (3)	DCC (1)	DMSO	25	48	13
15	AgOAc (0.2)	dppp (0.24)	$(NH_4)_2S_2O_8$ (3)	4 Å MS (1)	DMSO	25	48	10
16	AgOAc (0.2)	dppp (0.24)	$(NH_4)_2S_2O_8$ (3)	$CuSO_4$ (1)	DMSO	25	48	72
17	AgOAc (0.2)	dppp (0.24)	$(NH_4)_2S_2O_8$ (3)	Bu_4NBF_4 (1)	DMSO	25	48	81
18	AgOAc (0.1)	dppp (0.12)	$(NH_4)_2S_2O_8$ (3)	Bu_4NBF_4 (1)	DMSO	25	48	58
19	AgOAc (0.05)	dppp (0.06)	$(NH_4)_2S_2O_8$ (3)	Bu_4NBF_4 (1)	DMSO	25	48	34
20	AgOAc (0.01)	dppp (0.012)	$(NH_4)_2S_2O_8$ (3)	Bu_4NBF_4 (1)	DMSO	25	48	trace
21	AgOAc (0.2)	dppp (0.24)	$(NH_4)_2S_2O_8$ (2)	Bu_4NBF_4 (1)	DMSO	25	48	64

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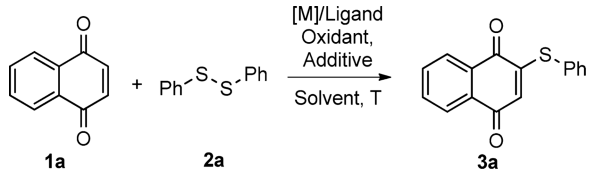
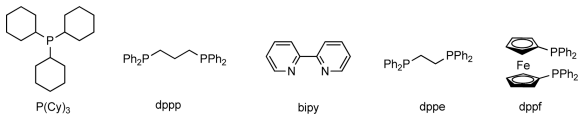


entry	[M] (equiv)	ligand (equiv)	oxidant (equiv)	additive (equiv)	solvent	*T* (°C)	*t* (h)	yield (%)[b]
22[c]	AgOAc (0.2)	dppp (0.24)	$(NH_4)_2S_2O_8$ (3)	Bu_4NBF_4 (1)	DMSO	25	48	80

[a]Reaction conditions: 1,4-naphthoquinone (**1a**, 0.5 mmol, 1 equiv), phenyl disulfides (**2a**, 0.3 mmol, 0.6 equiv), silver, ligand, oxidants, and additives were loaded, as listed in the table, and stirred together in the designated solvent.

[b]Isolated yield.

[c]The reaction was carried out under N_2 protection, and DMSO was bubbled with N_2 for 30 min before use.