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Radical−Radical Cross-Coupling for C−S Bond Formation

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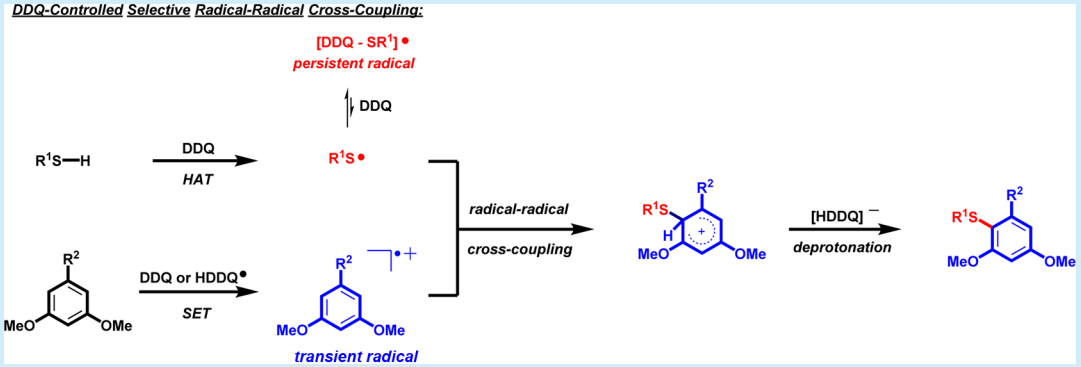
Supporting Information



ABSTRACT: A new method was demonstrated to overcome the selectivity issue of radical−radical cross-coupling toward the synthesis of asymmetric diaryl thioethers. The preliminary mechanism was revealed by radical-trapping experiments, DFT calculations, and kinetics, etc., indicating that the C−S bond formed through cross-coupling of a thiyl radical and an aryl radical cation. Moreover, the formation of an aryl radical cation instead of the C−H bond cleavage was determined as the rate-limiting step.

Radicals have attracted a lot of attention due to their high reactivity and strong tendency to form chemical bonds.[1] In the last few decades, numerous effective processes, such as radical addition, substitution, and cyclization, were successfully demonstrated for the construction of C−X (X = C, N, O etc.) bonds when radicals were utilized as the key intermediates.[2] However, the radical−radical cross-coupling reaction, which also emerged as a powerful tool for new chemical bonds, still remains in its infancy when compared with those highly developed reactions.[3]

Generally, the activation energy of the radical−radical coupling reaction is nearly zero.[4] Therefore, when two types of reactive radicals are employed to couple with each other, three pathways afford two homocoupling products and one cross-coupling product; i.e., the poor selectivity is the main issue for the radical−radical cross-coupling reaction.[3c,5] Usually, in order to control the selective bond formation, a persistent radical and a transient radical should be engaged according to the persistent radical effect.[6] In this regard, if one of the reactive radicals could be stabilized to a persistent one, selective cross-coupling of two reactive radicals could succeed.[3b] Recently, there have been some clues in the literature reporting the stabilization of reactive radicals by using transition metals (Cu, Ni, etc.) or molecular I_2 in oxidative radical−radical cross-coupling reactions.[3b,7] Nevertheless, these examples only focused on the carbon- or nitrogen-centered radicals. Thus, it is still highly important to develop new strategies for stabilizing other reactive radicals, such as thiyl radicals, and make them suitable for the radical−radical cross-coupling reaction.

It is well-known that the addition of thiyl radical to alkene is fast and reversible.[8] Therefore, we envisioned that it is possible to transfer the reactive thiyl radical to a persistent one by stabilizing it through radical addition to a unique alkene. Then, once a transient carbon-centered radical is added, a selective radical−radical cross-coupling reaction could be achieved.[6a] DDQ is an excellent single-electron oxidant that could oxidize thiol and electron-rich arene, etc., to the corresponding radicals.[9] Moreover, the unique quinone structure of DDQ shows great potential in stabilizing the reactive thiyl radical.[10] Regarding this information, a new DDQ-controlled selective radical−radical cross-coupling between arene and thiol toward C−S bond formation is proposed in this work (Scheme 1).

1,3,5-Trimethoxybenzene (**1a**) and 4-chlorobenzenethiol (**2a**) were initially employed as the substrates to test the proposal above. As expected, when DDQ was utilized, the

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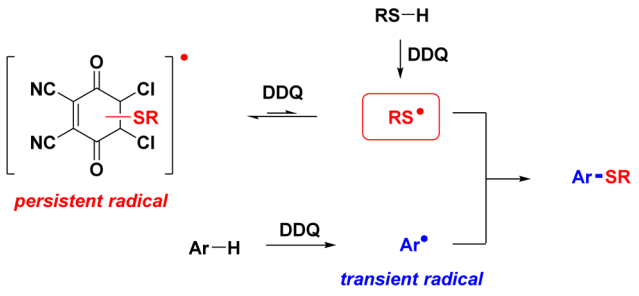
Scheme 1. Mechanism for Selective Radical−Radical Cross-Coupling between Arene and Thiol



cross-coupling product **3aa** could be obtained in 84% yield (eq 1). To further identify the role of DDQ, a set of experiments

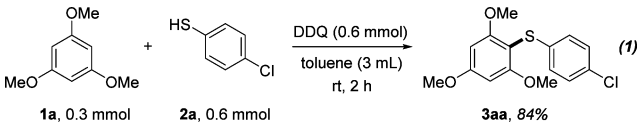


Table 1. Optimization for Oxidative Cross-Coupling of 1a and 2a[a]

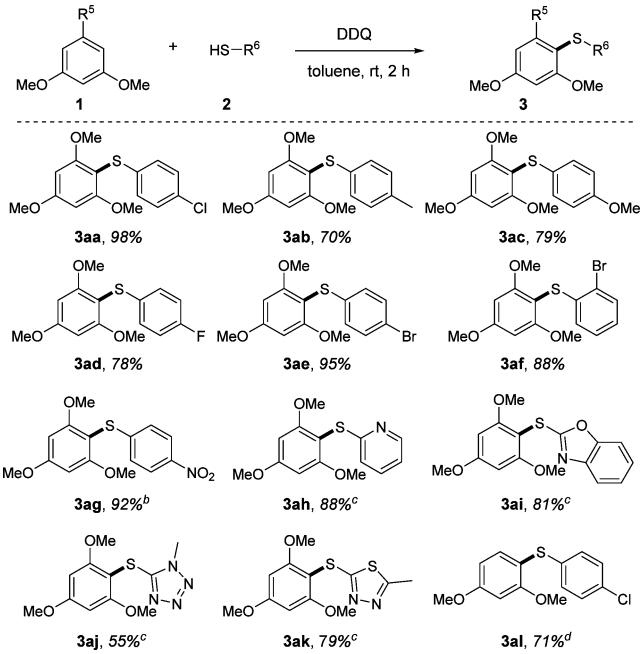
entry	oxidant	solvent	yield[b] (%)
1	$K_2S_2O_8$	toluene	trace
2	TBHP	toluene	trace
3	chloranil	toluene	trace
4[c]	DDQ	toluene	98
5[c]	DDQ	CH_3CN	86

[a]All of the reactions were performed with **1a** (0.3 mmol), **2a** (0.6 mmol), oxidant (0.6 mmol), and toluene (3.0 mL) in Schlenk tubes at room temperature for 2 h under N_2. [b]Yield determined by GC analysis with biphenyl as the internal standard. [c]A toluene solution of **2a** (0.6 mmol, 2 mL) was added to the mixture of **1a** (0.3 mmol), DDQ (0.6 mmol), and toluene (1 mL) by constant-flow pump in 10 min. Yield was obtained by isolating the pure product.

were carried out. As shown in Table 1, when $K_2S_2O_8$ or TBHP, which is a well-known single-electron oxidant but does not stabilize radicals,[11] was used instead of DDQ, only a trace amount of **3aa** could be produced (entries 1 and 2). Meanwhile, chloranil was unable to oxidize **1a**[12] and could only afford trace amounts of **3aa** (entry 3). With the addition of **2a** to the reaction mixture by constant-flow pump in 10 min, a 98% yield of **3aa** was obtained (entry 4), indicating that excess DDQ over thiol is beneficial for the cross-coupling reaction. The transformation could also proceed very well in acetonitrile (entry 5). All of these results are consistent with the proposed radical−radical cross-coupling reaction mechanism in which DDQ not only acts as a single-electron oxidant to produce the relevant radicals but also might stabilize the reactive thiyl radical.

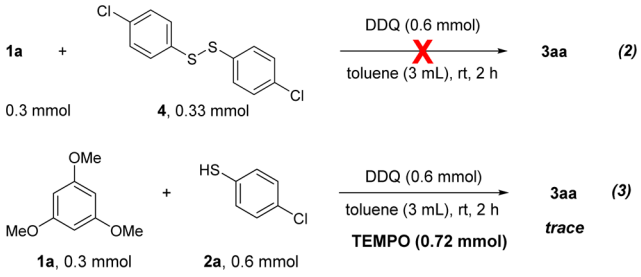
The scope of this oxidative C−H/S−H cross-coupling reaction was examined in detail under the optimized conditions. As shown in Scheme 2, various thiols could react with **1a** smoothly to produce the desired products in good to excellent yields. Thiols with electron-donating groups (−Me, −OMe) or electron-withdrawing groups ($-NO_2$) are suitable for this transformation, and 70%−92% yields were obtained (**3ab**, **3ac**, and **3ag**). It is noteworthy that −F, −Cl, and −Br substituents

Scheme 2. Oxidative C−H/S−H Cross-Coupling[a]



[a]In a Schlenk tube, a toluene solution of **2** (0.6 mmol, 2 mL) was added to the mixture of **1a** (0.3 mmol), DDQ (0.6 mmol), and toluene (1 mL) by constant-flow pump in 10 min. Then, the mixture was allowed to stir at rt for 2 h under N_2. The yields were obtained by isolating the pure products. [b]4-Nitrobenzenethiol (0.6 mmol) was added at once. [c]CH_3CN was used to replace toluene as the solvent. [d]DDQ (1.5 mmol), **2a** (1.5 mmol).

on the phenyl ring of benzenethiol are well tolerated, which enables a potential application in further functionalization (**3aa**, **3ad**, **3ae**, and **3af**). A mercapto group on the heteroaromatic ring is also an effective S−H source for this oxidative C−H/S−H cross-coupling reaction. For example, pyridine-2-thiol, benzo[*d*]oxazole-2-thiol, 1-methyl-1*H*-tetrazole-5-thiol, and 5-methyl-1,3,4-thiadiazole-2-thiol react with **1a** successfully to give the corresponding products in good to excellent yields (**3ah**, **3ai**, **3aj**, and **3ak**). 1,3-Dimethoxybenzene was also tested for this reaction, which afforded the product in 71% yield (**3al**). No desired product **3aa** could be obtained when bis(4-chlorophenyl) disulfide **4** was employed to react with **1a**, showing that **4** is not an intermediate in this cross-coupling reaction (eq 2).



Mechanistic investigations were carried out initially by conducting radical inhibition experiments. Only a trace amount of product **3aa** was observed when the reaction was carried out in the presence of radical scavenger TEMPO (eq 3), suggesting that radicals might be the key intermediates in the transformation. Hence, radical-trapping experiments were further

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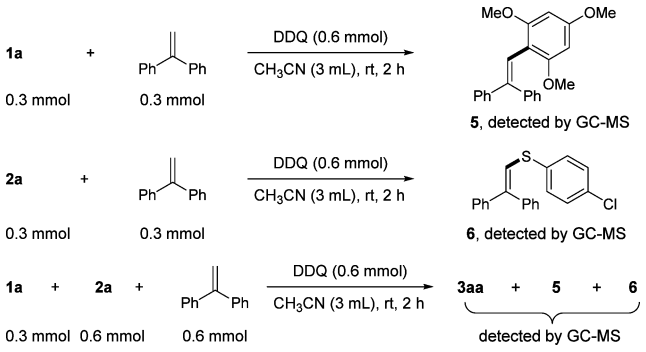
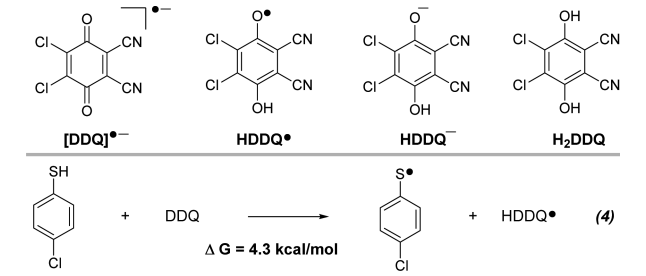
explored. As shown in Scheme 3, the product **5** (or **6**) was detected in the reaction of **1**, 1-diphenylethylene, and **1a** (or **2a**). Moreover, when 1,1-diphenylethylene was introduced into the coupling reaction of **1a** and **2a** as the radical trapping reagent under the standard conditions, **3aa**, **5**, and **6** were produced. These results indicated that both the 1,3,5-trimethoxyphenyl radical (or 1,3,5-trimethoxyphenyl radical cation) and the 4-chlorobenzenethiyl radical might be involved in this coupling reaction.

Scheme 3. Radical-Trapping Experiments



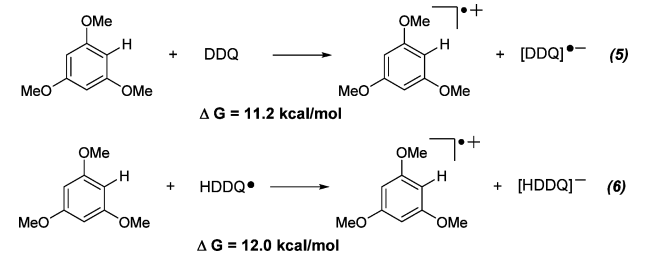
As a follow-up study, density functional theory (DFT) calculations were carried out to study the formation of these radicals using the M06 method. As shown in Scheme 4,

Scheme 4. Possible Pathway for the Formation of 4-Chlorobenzenethiyl Radical



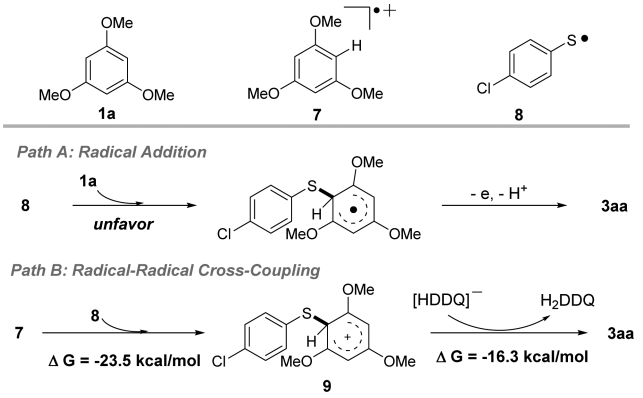
oxidizing 4-chlorobenzenethiol by DDQ to form the radical through a hydrogen atom transfer (HAT) pathway (eq 4) is favorable with an energy barrier of 4.3 kcal/mol (see the Supporting Information for more details). In contrast, for the formation of the 1,3,5-trimethoxyphenyl radical species, the electron-transfer (ET) pathway (Scheme 5) was recommended, since the energy barrier is only 11.2 or 12.0 kcal/mol, while the energy barrier in HAT pathway is up to 40.3 kcal/mol (see the SI for more details). Therefore, two competitive pathways for

Scheme 5. Possible Pathways for the Formation of 1,3,5-Trimethoxyphenyl Radical



the C−S bond formation were evaluated. As shown in Scheme 6, path A involving a radical addition step is initially considered

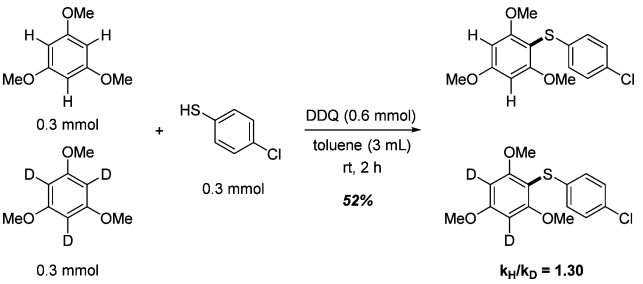
Scheme 6. Possible Reaction Pathways for C−S Bond Formation



in calculation. However, neither the transition state nor the addition intermediate was located after many attempts, which implies the thiyl radical addition to **1a** is unfavorable. In path B, the combination of radical **7** with radical **8** is exothermic by 23.5 kcal/mol, followed by deprotonation of **9**, which is also exothermic by 16.3 kcal/mol. Consequently, the radical−radical cross-coupling mechanism is finally recommended for this C−S bond formation reaction.[13]

A kinetic isotope effect (KIE) experiment was also performed to further study this oxidative C−H/S−H cross-coupling reaction. As shown in Scheme 7, the KIE of 1.30 is observed

Scheme 7. Measurement of KIE



from an intermolecular competition, suggesting that C−H bond cleavage of **1a** is not involved in the rate-limiting step. Further detailed kinetic behavior of **1a** was tested by utilizing in situ IR. As illustrated in Figure 1, plotting initial rate vs [**1a**] shows a linear relationship, indicating that the reaction is first order on [**1a**]. These results are consistent with our DFT calculations, suggesting the single-electron-transfer (SET) process between **1a** and DDQ (or HDDQ•) with a 11.2 kcal/mol (or 12.0 kcal/mol) barrier is the rate-determining step, and the C−H bond cleavage is a facile process with a 16.3 kcal/mol exothermic barrier, which proceeds after radical−radical cross-coupling of **7** and **8**.

On the basis of the above results, a putative mechanism was proposed (see Scheme S1 for more details). For example, cross-coupling between **1a** and **2a** begins with DDQ oxidizing **2a** through a HAT process to produce the thiyl radical **8**, which could be stabilized by forming the radical [DDQ−**8**]•. Simultaneously, **1a** undergoes a SET process to afford the aryl radical cation **7**. Thereafter, cross-coupling between **7** and

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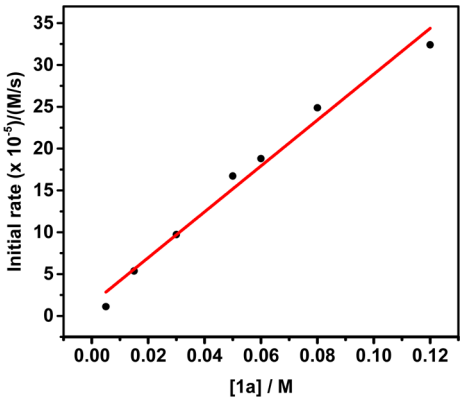

Figure 1. Kinetic plots of the reactions with different concentrations of **1a** from 0.005 to 0.120 M; **2a** (0.60 mmol, 0.12 M); DDQ (0.60 mmol, 0.12 M).

8 occurs, following by a deprotonation of **9** to release the desired product **3aa**.

In conclusion, a new DDQ-controlled selective radical−radical cross-coupling between electron-rich arenes and thiols was demonstrated. With this new method, various asymmetric diaryl sulfides were synthesized in good to excellent yields. Preliminary mechanistic studies were also performed. Radical-trapping experiments indicated that radicals are involved in the transformation. DFT calculations and kinetic studies suggested the SET process between **1a** and DDQ (or HDDQ$^{\bullet}$) with a 11.2 kcal/mol (or 12.0 kcal/mol) barrier is the rate-determining step, and the C−H bond cleavage is a facile process with a 16.3 kcal/mol exothermic barrier, which proceeds after cross-coupling of aryl radical cation **7** and thiyl radical **8**. This transformation provides a new method for selective radical−radical cross-coupling, which is beneficial for further radical reaction design. The detailed mechanism is currently under investigation in our laboratory and will be reported in the near future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00764.

General procedures, calculation details, kinetic studies, and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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(13) Another possible pathway, which involves the deprotonation process before radical combination, is also calculated and ruled out due to the higher energy barrier. See the Supporting Information (eqs S3 and S4) for more details.

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