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*t*BuOK-triggered bond formation reactions†

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Recently, inexpensive and readily available *t*BuOK has seen widespread use in transition-metal-free reactions. Herein, we report the use of *t*BuOK for S–S, S–Se, N=N and C=N bond formations, which significantly extends the scope of *t*BuOK in chemical synthesis. Compared with traditional methods, we have realized mild and general methods for disulfide, azobenzenes imine *etc.* synthesis.
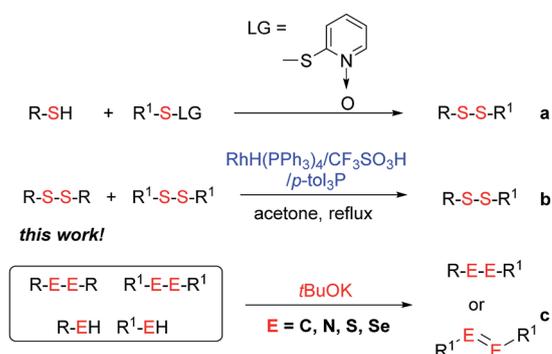
Introduction

Potassium *tert*-butoxide (*t*BuOK) is traditionally used as a strong and non-nucleophilic base in organic synthesis. In recent years, *t*BuOK has seen widespread use in transition-metal-free reactions. For example, *t*BuOK can mediate coupling reactions of haloarenes with arenes or styrenes to produce biphenyls or stilbenes *via* a single-electron reduction mechanism.[1–5] A *t*BuOK-mediated transition-metal-free alkoxycarbonylation of aryl halides has also been developed by Lei.[6] Furthermore, a *t*BuOK-mediated reductive cleavage of aryl C–O bonds in lignin models has been reported by Grubbs,[7] followed by their potential application in the hydrodesulfurization of fuels.[8] Interestingly, in 2015, Grubbs and Stoltz reported a *t*BuOK-catalyzed dehydrocoupling reaction of (hetero)arenes with silanes for heteroarylsilane synthesis.[9] More recently, Milstein reported the *t*BuOK-catalyzed C–C bond formation of benzyl alcohols and alkynes, which further extended the applications of *t*BuOK.[10] It is worth to mention that all the above procedure proceeded in a radical pathway[11,12] and most use *t*BuOK in large excess. Therefore, further development of methods using inexpensive and readily available *t*BuOK for chemical synthesis ids still needed.

Unsymmetrical disulfides, especially aryl alkyl disulfides, exhibit many biological activities.[13,14] For example, aryl alkyl disulfides have undergone clinical evaluation for tumor treatment.[15] Therefore, the synthesis of unsymmetrical disulfides is an important task in synthetic chemistry.[16] Traditionally, disulfides were prepared by oxidative coupling of thiols, while, unsymmetrical disulfide synthesis is challenging owing to the coproduction of symmetrical disulfides.[17–20] While, their synthesis is challenging owing to the coproduction of symmetrical disulfides. Traditionally, the nucleophilic

substitution of thiols with sulfenyl derivatives has been used for unsymmetrical disulfide synthesis (Scheme 1a).[21–27] However, these reactions suffer from low atom economy. In addition to the aforementioned methods, thio-disulfide interchange and disulfide (S–S bond) metathesis can also provide unsymmetrical disulfides (Scheme 1b). In 2003, Yamaguchi reported a RhH(PPh₃)₄ and trifluoromethanesulfonic acid system for disulfide metathesis reactions,[23] which proceeded in refluxing acetone. Since then, very few systems for disulfide metathesis have been developed.[28] Therefore, the development of clean, mild, and efficient methods for unsymmetrical disulfide synthesis remains of great interest.[29] Herein, we report the use of inexpensive and readily available *t*BuOK for the synthesis of unsymmetrical disulfides (S–S bond formation) and other bond formations (Scheme 1c).

Results and discussion

Initially, the metathesis of *p*-tolyl disulfide (**1a**, 0.1 mmol) and di-*tert*-butyl disulfide (**2a**, 0.2 mmol) was conducted using 5 mol% *t*BuOK in THF at 100 °C. Pleasingly, desired compound **3a** was obtained in 96% yield (GC yield, Table S1, entry 1†). The reaction was also performed at 60 °C, with no decrease in the yield of **3a** (Table S1, entry 2†). Remarkably, we found that,

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Scheme 1 Methods for unsymmetrical disulfide synthesis and beyond.

Table 1 tBuOK-triggered unsymmetrical disulfide production *via* metathesis of aromatic disulfide **1** or thiols **1′** with alkyl disulfide **2**[a]

Entries	Disulfides 2	1 or 1′	Products 3	Yields[b] [%]
1		1a′ (Me)	3a	91
2		1b′ (MeO)	3b	92
3	2a (tBu–S–S–tBu)	1c′ (F)	3c	95
4		1d′ (Cl)	3d	88
5		1e′ (H₂N)	3e	86
6		1a	3a	90
7		1b	3b	87
8	2a (tBu–S–S–tBu)	1c	3c	92
9		1d	3d	89
10		1e	3e	90
11		1b′	3f	90
12	2b (Cy–S–S–Cy)	1c′	3g	89
13		1d′	3h	88
14		1e′	3i	90
15	2b (Cy–S–S–Cy)	1b	3f	91
16		1c	3g	89

[a] Reaction conditions: substituted aromatic thiols **1′** (0.2 mmol) or aromatic disulfides **1** (0.1 mmol), alkyl disulfides **2** (0.2 mmol), tBuOK (0.01 mmol), THF 1.0 mL with air in 38 mL pressure tube, 60 °C, 8 h. [b] Isolated yields after chromatography.

Paper

under these reaction conditions, p-thiocresol (**1a′**) and di-*tert*-butyl disulfide (**2a**) also produced **3a** in an equal yield (95%; Table S1, entry 3†). Notably, **3a** was not produced in the absence of *t*BuOK, indicating that *t*BuOK played a crucial role in this reaction (Table S1, entry 4†).[30] The generality of this method was then assessed by reacting different aromatic disulfides **1** or thiols **1′** with alkyl disulfides **2** under the optimized condition and were summarized in Table 1.

Di-*tert*-butyl disulfide **2a** successfully reacted with aromatic thiols bearing methyl and methoxy substituents, giving corresponding products **3a** and **3b** in 91% and 92% isolated yields, respectively (Table 1, entries 1 and 2). Fluorine and chlorine functional groups were also well tolerated, with **3c** and **3d** obtained in excellent yields (95% and 88%, entries 3 and 4). When using 4-aminobenzenethiol as the substrate, high site selectivity was observed with the –NH$_2$ group left untouched, affording **3e** in 86% yield (entry 5). We next studied the metathesis reactions of **2a** with different aromatic disulfides. Electron-donating groups, such as 4-Me, 4-MeO, and 4-NH$_2$, and electron-withdrawing group, such as 4-F and 4-Cl, on the aromatic disulfides were well tolerated, affording excellent yields (87–92%, entries 6–10). Changing the alkyl disulfide to dicyclohexyl disulfide **2b** gave similar yields to di-*tert*-butyl disulfide **2a**. Therefore, **2b** reacted readily with different aromatic thiols and disulfides to afford the corresponding unsymmetrical disulfides **3f–3i** in excellent yields (88–91%, entries 11–16).

From the above results, we concluded that there was almost no difference between the reactivities of aromatic thiols **1′** and disulfides **1** react with alkyl disulfides **2**. For thiols, disulfide formation was assumed to be the first step, followed by a disulfide metathesis reaction. To confirm this, the *t*BuOK-triggered oxidative coupling reaction of thiols to afford disulfides was conducted under ambient conditions, which proceeded readily in a short reaction time at 25 °C (Fig. 1 and for different base effect please see Table S2†). A series of functional groups were tolerated in this reaction system. Both electron-rich and electron-poor aromatic thiols gave the corresponding symmetrical disulfides in moderate to excellent isolated yields (**1a–1h**, 61–99%). Notably, alkyl thiols, such as *tert*-butylthiol, cyclohexanethiol, *n*-butylthiol, and benzylthiol, all gave the corresponding disulfides (**2a–2d**) in good to excellent yields (67–93%).[31] Then, the direct synthesis of unsymmetrical disulfides from thiols was also attempted.

We selected the reaction of p-thiocresol (0.2 mmol) with *tert*-butylthiol (0.4 mmol) at 25 °C as the model reaction. Unsymmetrical disulfide **3a** was produced in only 5% yield at room temperature with mixtures of symmetrical disulfides. Pleasingly, increasing the reaction temperature to 60 °C improved the yield of **3a** to 54%, while heating at 100 °C afforded **3a** in 75% yield (Table S3†).

With optimized conditions in hand, we next evaluated the scope and limitations of this method for direct unsymmetrical disulfide synthesis. A series of aromatic thiols were treated with different aliphatic thiols (Fig. 2). To our delight, unsymmetrical disulfides were obtained in moderate to good yields (48–90%), tolerating a good substrate scope. Methyl, methoxy, halide (–F, –Cl), and protic groups, such as –NH$_2$ and –OH, on the aromatic
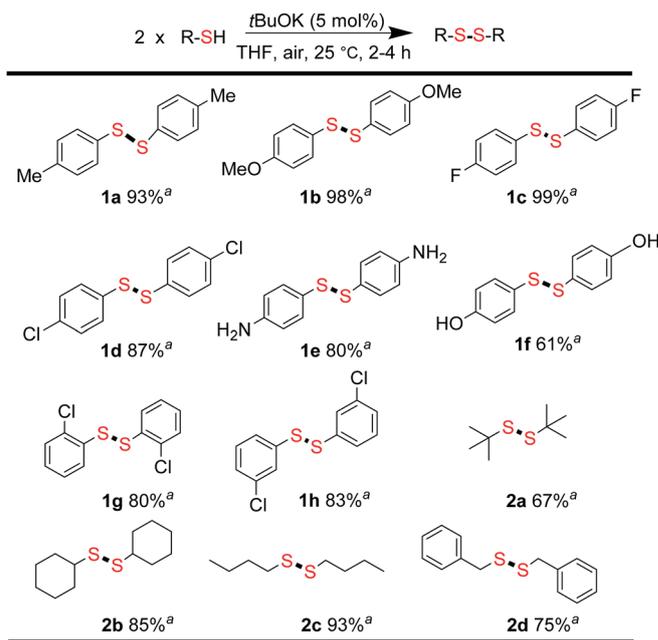

Fig. 1 Synthesis of symmetrical disulfides. Reaction conditions: thiols (0.2 mmol), *t*BuOK (0.01 mmol), THF 1.0 mL in 20 mL sample vial 25 °C, 2–4 h; [a]isolated yields.

thiols were well tolerated in the reaction with *tert*-butylthiol, affording unsymmetrical disulfides (**3a–3e** and **3j**) in yields of 48–88%. Changing the alkyl thiol from *tert*-butylthiol to *n*-butylthiol resulted in somewhat lower yields; for example, **3b** (63%) *vs.* **3k** (48%) and **3c** (74%) *vs.* **3l** (55%). For the reaction of
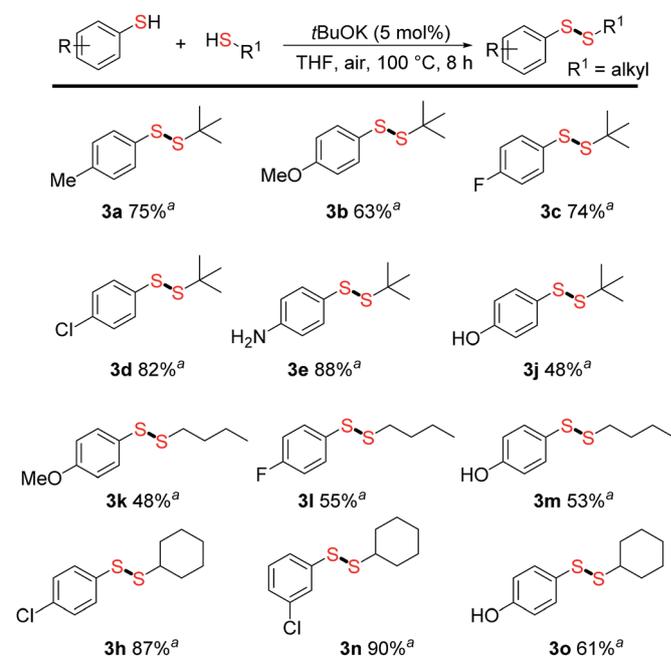

Fig. 2 Direct synthesis of unsymmetrical disulfides. Reaction conditions: substituted aromatic thiols (0.2 mmol, 24.8 mg), alkyl thiols (0.4 mmol), *t*BuOK (0.01 mmol), THF 1.0 mL in 38 mL pressure tube and then heat at 100 °C for 8 h; [a]isolated yields.
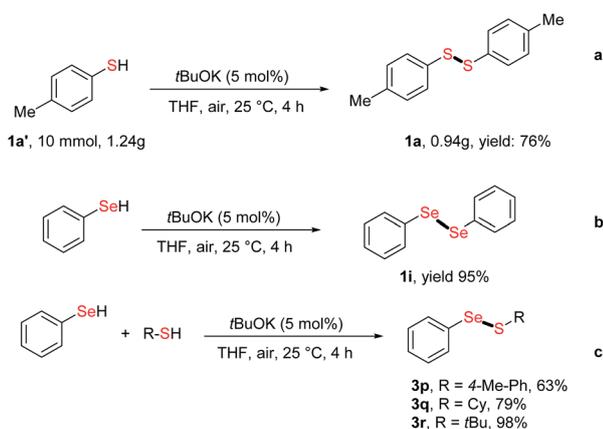
cyclohexanethiol with different aromatic thiols, good to excellent yields were obtained (**3h, 3n, 3o; 61–90%**) and substituents on the aromatic thiols were well tolerated.

The application of our strategy to large scale synthesis was assessed by performing a gram-scale reaction, which afforded disulfide **1a** in 76% yield (0.94 g) (Scheme 2a). In addition to thiols, the dehydrocoupling of benzeneselenol also afforded 1,2-diphenyldiselane **1i** in 95% yield (Scheme 2b). Finally, the cross-coupling reaction of benzeneselenol with aromatic and alkyl thiols was also realized at 25 °C, with cross-coupling products **3p–3r** readily obtained in up to 98% yield (Scheme 2c).

Having established different systems for S–S, Se–Se, and S–Se bond formations using *t*BuOK, we then turned our attention to N=N bond formation. Components bearing N=N bonds are ubiquitous motifs in therapeutic agents, food additives, dyes, pigments, photochemical switches, and radical reaction initiators.[32–34] A previous report using *t*BuOK was conducted in liquid ammonia which is dangerous and need to operate at −75 °C.[35] On the contrary, simply sealed the starting material in a pressure tube and heat at 60 °C we can obtain 95% azobenzene from hydrazobenzene. Then a series of aromatic azo compounds were successfully prepared in excellent yields in short reaction time (Fig. 3). Electron-donating and electron-withdrawing groups all afforded the corresponding azo compounds in high yields (**5a–5c**, 90–97%). In addition to symmetrical aromatic azo compounds, unsymmetrically substituted hydrazobenzenes showed a similar reactivity. Therefore, substrates with electron-donating groups, such as 4-MeO, and electron-withdrawing groups, such as 4-Cl and 4-F, were well tolerated, affording the corresponding aromatic azo compounds **5d–5f** in excellent yields (93–95%).

In addition to hydrazobenzenes, the oxidative dehydrogenative coupling of aniline can also afford azobenzene, but traditional methods require excess amounts of strong and environmentally unfriendly oxidants (BaMnO$_4$, Pb(OAc)$_4$, AgO, HgO, *N*-chlorosuccinimide,[36] *tert*-butyl hypoiodite[37]) or transition metals (Au,[38] Pd,[39] Cu[40]) under harsh reaction conditions. On the contrary, using *t*BuOK with only 1 bar of O$_2$, azobenzene was obtained in 72% yield from aniline (Scheme 3a). Moreover, the oxidative dehydrogenation of *N*-benzylaniline to imine was also realized (Scheme 3b).
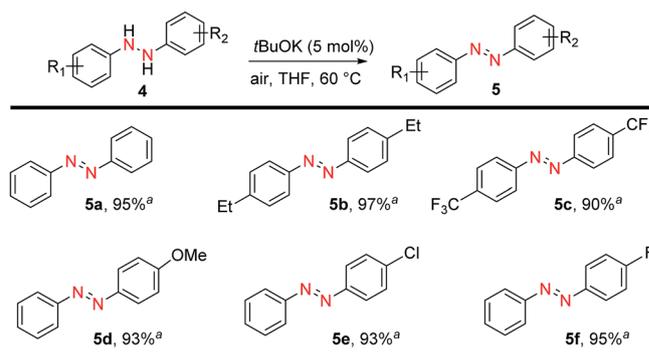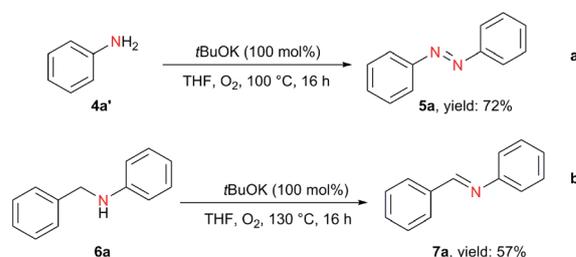

Fig. 3 *t*BuOK-triggered azobenzene synthesis from hydrazobenzene. Reaction conditions: hydrazobenzene (0.2 mmol), *t*BuOK (0.01 mmol), THF 1.0 mL in 38 mL pressure tube 60 °C, 8 h; [a]isolated yields.

Scheme 3 *t*BuOK-mediated oxidative coupling of aniline to azobenzene and imine formation.

Conclusions

We have demonstrated that inexpensive and readily available *t*BuOK can trigger a series of bond formation reactions, including S–S, S–Se, Se–Se, and N=N and C=N bonds. Our strategies significantly extend the scope of *t*BuOK in chemical synthesis. For S–S bond formation, both symmetrical and unsymmetrical disulfides were produced in good to excellent yields (up to 99%) with general functional group tolerance. Further applications, such as the synthesis of a bioactive glycosyl disulfide, were also realized. Furthermore, *t*BuOK was found to be able to mediate the disulfide metathesis reaction of aromatic disulfides or thiols with alkyl disulfides, providing another new reaction pathway for unsymmetrical disulfide synthesis. These findings extended the application scope of our strategy. Moreover, this strategy was applicable to azobenzene synthesis *via* the oxidative dehydrocoupling of NH–NH bonds which is more practical than reported process. Interestingly, the direct N=N bond formation from aniline and C=N formation from *N*-benzylaniline were also achieved.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Scheme 2 Gram-scale synthesis of disulfides and further applications of our strategy.

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30 For a comparison of our results with other developed oxidative dehydrogenation of thiols, please see Table S4 in the ESI.†

31 For a proposed mechanism please see the ESI Scheme S2.†

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