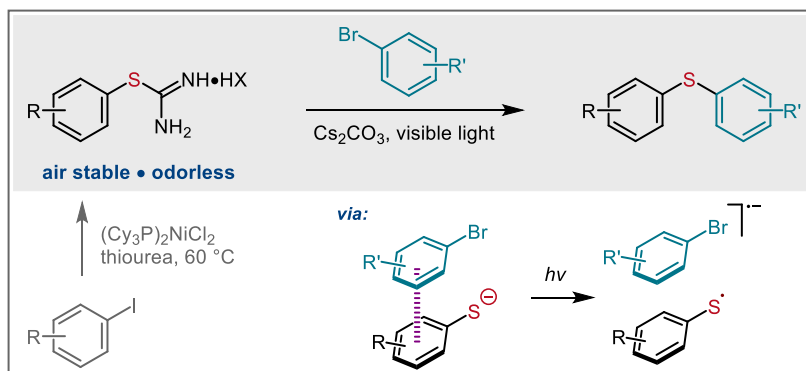


Generation of Thiyl Radicals from Air-Stable, Odorless Thiophenol Surrogates: Application to Visible-Light-Promoted C-S Cross-Coupling

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Abstract The synthetic versatility of thiophenols is offset by their air-sensitivity and foul odor. Here, we demonstrate that *S*-aryl isothiuronium salts can be used as precursors to thiyl radicals, extending the practical benefits of these air-stable, odorless salts from ionic to single electron manifolds. The isothiuronium salts are accessed *via* Ni-catalyzed cross-coupling of (hetero)aryl iodides and thiourea, and are isolated as free-flowing solids following anion exchange. Judicious choice of a redox-innocent counteranion enables use of these convenient thiophenol surrogates in radical processes, as is exemplified by the synthesis of non-symmetrical diaryl thioethers *via* light-promoted *S*-arylation.

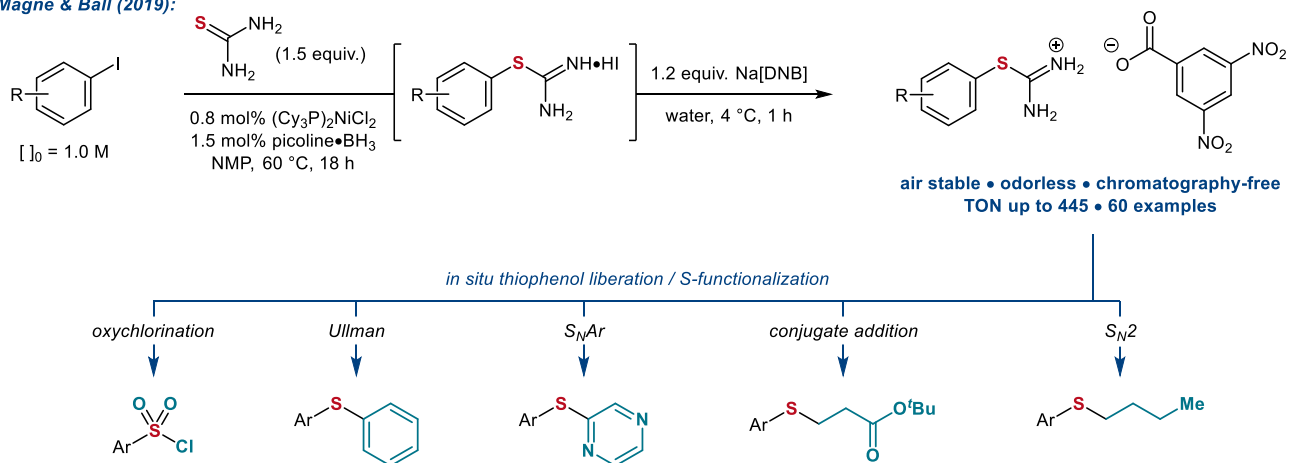
Key words Thiophenols, nickel catalysis, C-S cross-coupling, photochemistry, electron donor-acceptor complexes, thiyl radicals, diaryl sulfides.

The aryl-sulfur motif is common to a vast array of drugs, agrochemicals, materials and high impact odorants.^{1,2} Regardless of the substitution pattern or oxidation state at sulfur, all aryl-sulfur species can ultimately be derived from thiophenols *via* established synthetic protocols.^{3,4,5} However, the direct use of thiophenols in synthesis is often rendered impractical due to

their relatively low commercial availability, challenging syntheses, air-sensitivity, toxicity, and pungent malodor.

In seeking to address these manifold challenges, we recently reported a convenient and scalable method for the synthesis of *S*-aryl isothiuronium salts, which serve as air-stable, odorless surrogates to thiophenols (Scheme 1).⁶ Inspired by the work of Takagi,⁷ we showed that Ni-catalyzed C-S coupling of thiourea and diverse (hetero)aryl iodides proceeds under mild, base-free conditions to afford the corresponding isothiuronium iodides in excellent yields. These salts can be isolated without column chromatography simply by precipitation upon anion metathesis with sodium 3,5-dinitrobenzoate (Na[DNB]). The corresponding thiophenol is released *in situ* under the basic conditions typically employed for established ionic and metal-catalyzed *S*-functionalization protocols, including S_N2, conjugate addition, S_NAr, Ullman arylation and oxidation (Scheme 1).⁶ In this way, our methodology eliminates the need for experimentalists to isolate or otherwise manipulate noxious thiophenols *en route* to the target aryl-sulfur species.

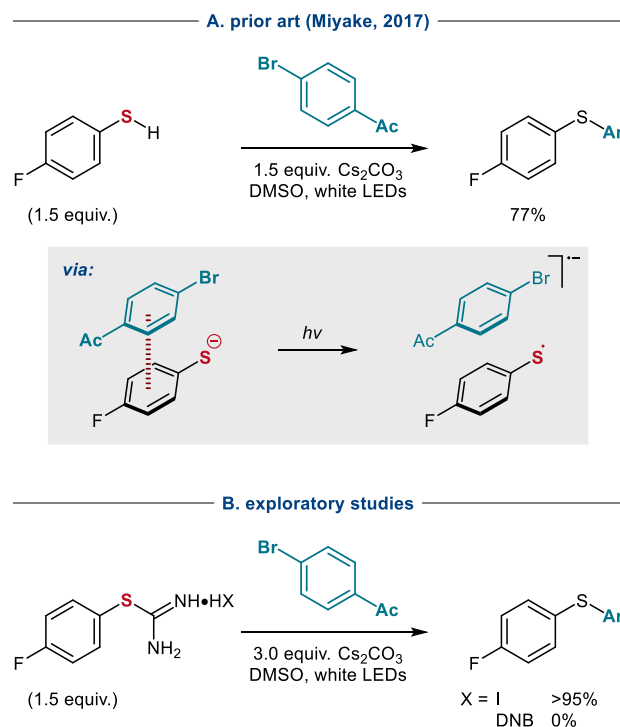
Magne & Ball (2019):



Scheme 1 Air-stable, odorless *S*-aryl isothiuronium salts are readily accessible *via* Ni-catalyzed C-S cross-coupling / precipitation, and serve as convenient surrogates for thiophenols in synthesis.⁶ DNB, 3,5-dinitrobenzoate.

However, attempts to employ these isothiuronium salts in single electron chemistry proved unsuccessful, precluding their use not only in conventional radical chemistry, but also in photoredox catalysis. We recognised that this apparent restriction to ionic *S*-functionalization processes represents a significant limitation in the applicability of isothiuronium salts, especially given the ease of formation of thiyl radicals from thiophenols and their versatile reactivity.⁸ Here, we seek to address this shortcoming such that the practical benefits of isothiuronium salts can be extended to single electron chemistry.

The visible light-mediated C-S coupling of thiophenols and aryl halides was selected as an archetypal radical process in which to test the isothiuronium salts. Recently reported by Miyake,^{9,10} this methodology provides facile access to non-symmetrical diaryl thioethers under mild conditions and in the absence of a transition metal catalyst (Scheme 2A); the ability to replace the thiophenol with an isothiuronium salt would therefore provide a practical improvement to this already powerful methodology. Moreover, combined experimental and computational studies suggest that the reaction proceeds *via* photo-stimulated electron transfer within a transient thiophenolate/aryl halide electron donor-acceptor (EDA) complex,¹¹ confirming that it is an appropriate testbed for the development of redox-compatible isothiuronium salts.

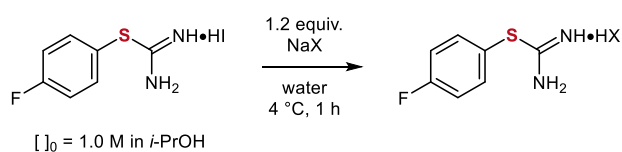


Scheme 2. (A) Miyake's light-mediated synthesis of diaryl thioethers; yield refers to isolated material.⁹ (B) Extension to *S*-aryl isothiuronium salts; yields determined by ¹⁹F NMR spectroscopic analysis vs internal standard.

We found that, while Miyake's chemistry could be reproduced in excellent yield with isothiuronium iodide salts in place of thiophenols, it could not be extended to the corresponding DNB salts (Scheme 2B).¹² These results demonstrate the *de facto* suitability of isothiuronium salts as thiophenol surrogates in radical chemistry, but also reveal a sensitivity to the counteranion that prevents exploitation of the easily isolated DNB salts. We hypothesized that the failure of our DNB salts to engage in Miyake's methodology is likely due to the electron accepting ability of (poly)nitrobenzenes,¹³ which are commonly employed as radical traps.¹⁴ Of particular relevance, methyl 3,5-dinitrobenzoate readily undergoes two reversible single electron

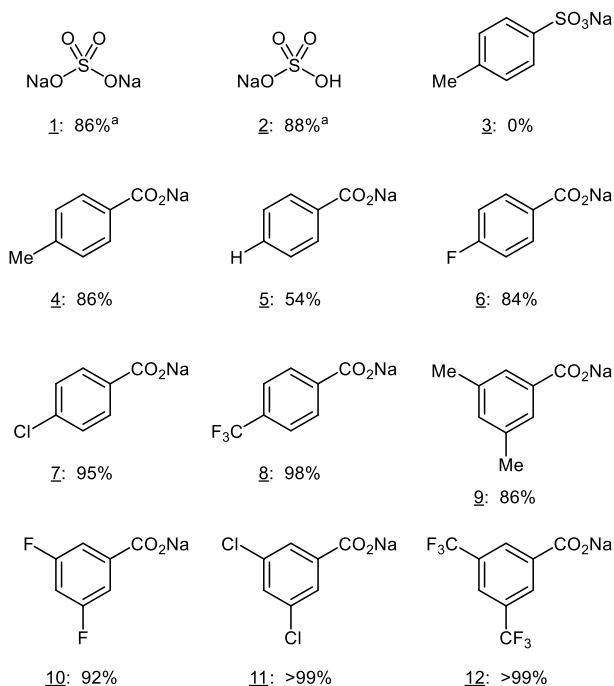
reductions ($E_{1/2}(I) = -1.215$ V vs Fc/Fc⁺, $E_{1/2}(II) = -1.620$ V vs Fc/Fc⁺),¹⁵ and the free acid is known to form EDA complexes¹⁶ that could interfere with the proposed mechanism of Miyake's *S*-arylation.⁹ Replacing DNB with an alternative, redox-innocent counteranion would avoid competing electron transfer processes and would ultimately enable the general use of isothiuronium salts in radical-based reactions.

Different counteranions were therefore assessed for their ability to precipitate the isothiuronium salt (Scheme 3). For this study, the initial Ni-catalyzed cross-coupling was performed in *isopropanol* rather than NMP (cf. Scheme 1),⁶ which is listed under REACH legislation as a Substance of Very High Concern and a candidate for authorization.¹⁷



assessment of counteranions X

entry number: % precipitation



Scheme 3. Assessment of different counteranions for the precipitation of *S*-aryl isothiuronium salts; yields determined by ¹⁹F NMR spectroscopic analysis vs internal standard. ^a Using 6 equiv. anion.

Although the inorganic anions sulfate and bisulfate provided high levels of precipitation (entries 1 and 2), the recovered isothiuronium salts proved sparingly soluble in organic media, precluding their characterization or subsequent use as thiophenol precursors in even very polar organic solvents. Metathesis with sodium tosylate failed to afford a precipitate (entry 3). In contrast, exchange of iodide for a benzoate counteranion generally resulted in high levels of precipitation (entries 4-12). While the majority of the isothiuronium benzoates formed gels or fine powders that prevented efficient isolation, salts of chloro- or trifluoromethyl-substituted

benzoates (entries 7, 8, 11 and 12) afforded free-flowing plate-like crystals amenable to filtration. The chlorobenzoates were ultimately rejected due to the potential reactivity of the C-Cl bond, and the trifluoromethylbenzoate salts were selected for further investigation.

To ascertain their compatibility with single electron processes, the redox properties of the different benzoate counteranions were investigated (Figure 1). Cyclic voltammetry was conducted in DMSO to ensure relevance to Miyake's methodology. As anticipated, sodium DNB readily undergoes two chemically-reversible single electron reductions (Figure 1A; $E_{1/2}(I) = -1.321$ V vs Fc/Fc⁺, $E_{1/2}(II) = -1.702$ V vs Fc/Fc⁺), whereas 4-trifluoromethylbenzoate (TB) and 3,5-bis(trifluoromethyl)benzoate (BTB) each undergo a single, irreversible reduction event at much lower potentials (Figures 1B and 1C; $E_{red} = -2.487$ V vs Fc/Fc⁺ and $E_{red} = -2.570$ V vs Fc/Fc⁺, respectively). The resistance of the trifluoromethylbenzoates to reduction suggest that both would be compatible with typical single electron processes, and therefore that they would be suitable as redox-innocent counterions in both photoredox and conventional radical reactions.

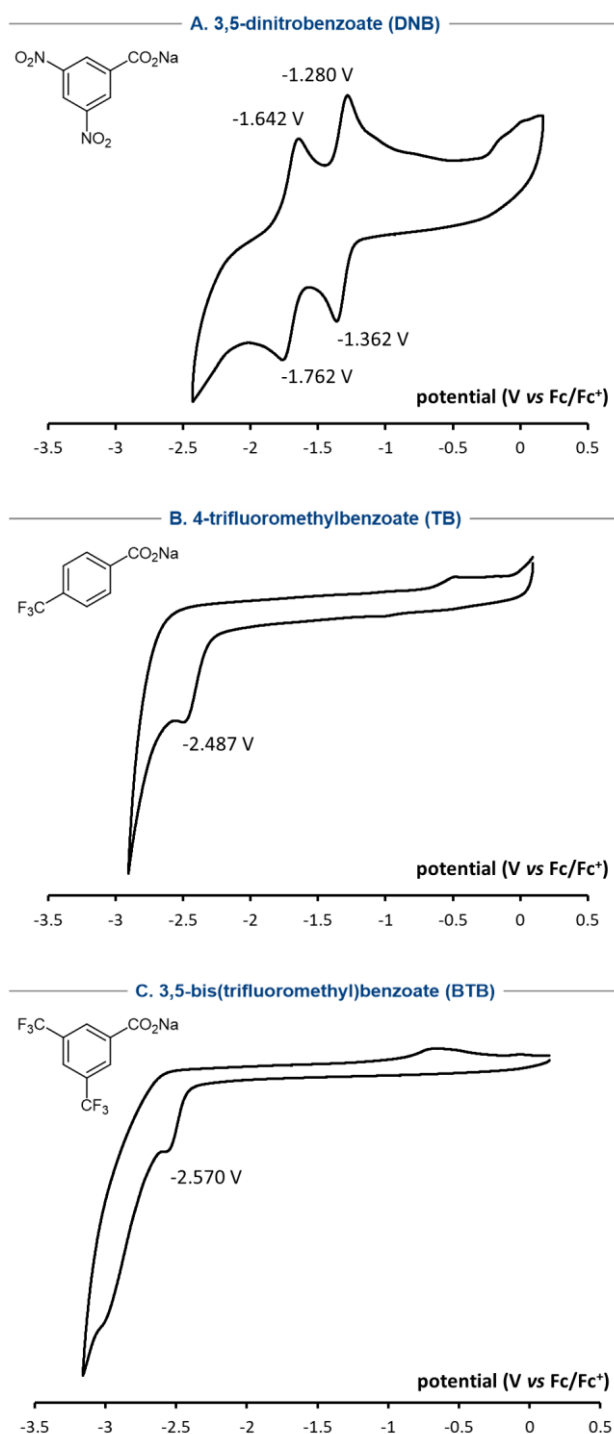


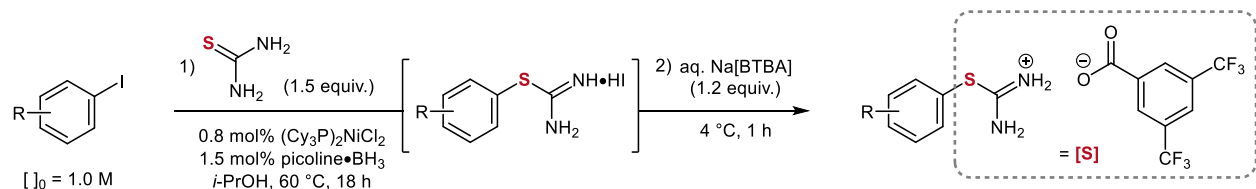
Figure 1. Cyclic voltammetry of sodium benzoate salts (0.1 M $[\text{NBu}_4][\text{PF}_6]$ in DMSO).

Further evaluation indicated that both TB and BTB confer low solubility in apolar solvents (Table 1), facilitating purification of the precipitated isothiuronium salt simply by washing. However, although the isothiuronium salts of both TB and BTB are stable in the solid state, the TB salts undergo slow decomposition in solution (13% over 3 weeks; 0.05 M in DMSO, RT). As such, the BTB counteranion was employed in subsequent studies.

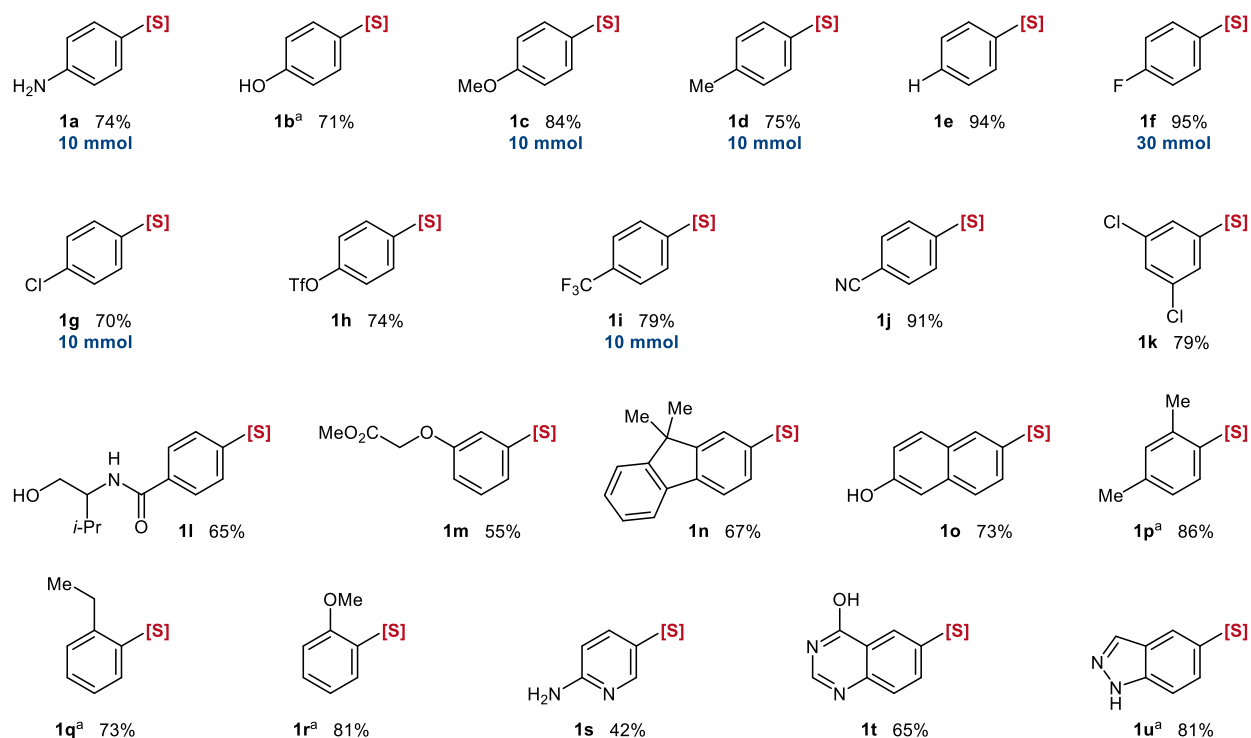
Table 1. Solubilities of Isothiuronium Salts.

Entry	Solvent	Solubility at 25 °C (mg mL ⁻¹)	
		TB	BTB
1	<i>i</i> -PrOH	5.8	3.9
2	MTBE	1.0	2.5
3	<i>i</i> -PrOAc	3.6	7.2
4	MeCN	4.1	2.5
5	PhMe	0.20	0.19
6	THF	83	45
7	CyH	0.15	0.18

Both the Ni-catalyzed coupling in *isopropanol*, and precipitation of the isothiuronium salt by exchange of iodide for BTB, proved general (Scheme 4). Thus, excellent isolated yields are obtained for couplings of aryl iodides featuring electron-donating (**1a-1d**, **1m**, **1o**) and -withdrawing (**1f-1l**) functionality, acidic protons (**1b**, **1l**, **1o**, **1s**, **1t**), and Lewis basic heteroatoms (**1l**, **1s-1u**). Couplings of *ortho*-substituted or very electron rich aryl iodides required NMP as the reaction solvent, but still provided excellent isolated yields upon anion metathesis (**1b**, **1p-1r**). The reaction efficiency is maintained or improved at multigram scales (**1a**, **1c**, **1d**, **1f**, **1g**, **1i**), and all products proved stable to air, moisture and ambient light for over 18 months.

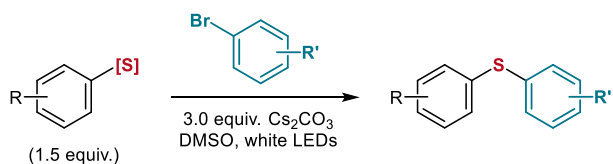


scope of Ni-catalyzed C-S coupling / precipitation

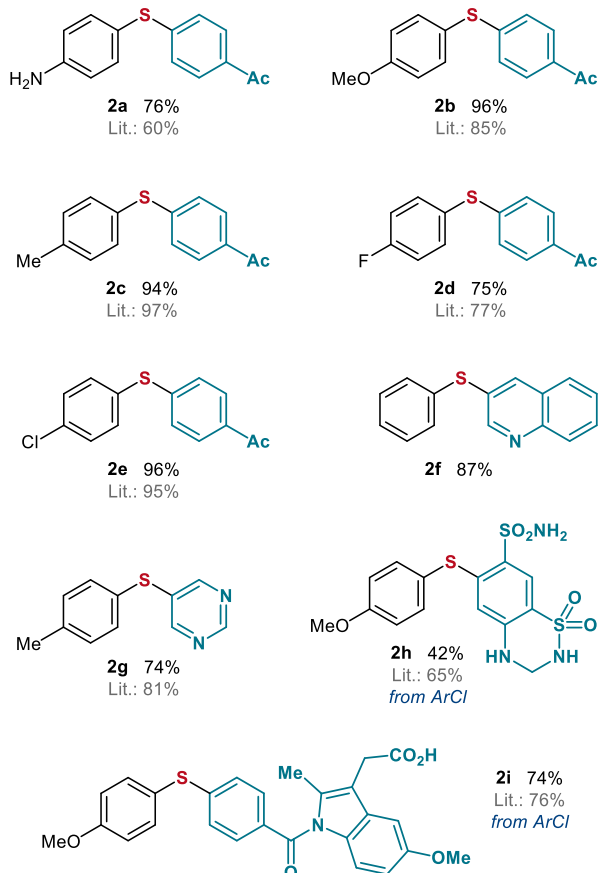


Scheme 4. Scope of the Ni-catalyzed synthesis of *S*-aryl isothiuronium bis(trifluoromethyl)benzoates; yields refer to isolated material. ^a Using 2 mol% $(\text{Cy}_3\text{P})_2\text{NiCl}_2$ and 4 mol% picoline-borane in NMP.

The isothiuronium BTB salts proved entirely compatible with Miyake's *S*-arylation (Scheme 5),^{9,12} with yields equivalent to or better than those obtained from thiophenols. In this way it is therefore possible to access non-symmetrical diaryl sulfides without the use of transition metal catalysts or the need to handle malodorous thiophenols. Moreover, these results illustrate that – by judicious choice of a redox-innocent counteranion – *S*-aryl isothiuronium salts can be exploited more generally as convenient and user-friendly surrogates for thiophenols in single electron chemistry.



application to 1-e⁻ chemistry



Scheme 5. Application of S-aryl isothiuronium bis(trifluoromethyl)benzoates to Miyake's light-mediated synthesis of diaryl thioethers; yields refer to isolated material. Literature yields as reported by Miyake.⁹

In summary, we have demonstrated that S-aryl isothiuronium salts can be employed as convenient thiophenol surrogates in single electron chemistry. The practical benefits of these salts – their ease of preparation and isolation, stability to air and moisture, and odorlessness – can therefore now be extended to a wide range of additional transformations. Crucial to achieving compatibility with radical processes has been identification of an alternative counteranion that is not only redox-innocent, but that also confers stability in solution and facilitates high-yielding isolation of the products.

The utility of the new isothiuronium salts is showcased by their application to Miyake's light-promoted S-arylation methodology, thereby giving concise access to non-symmetrical diaryl sulfides without the need to handle free thiophenols. We anticipate that

the practicality and convenience of our redox-compatible isothiuronium salts will be of broad utility within photoredox catalysis, electrocatalysis and conventional single electron chemistries.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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