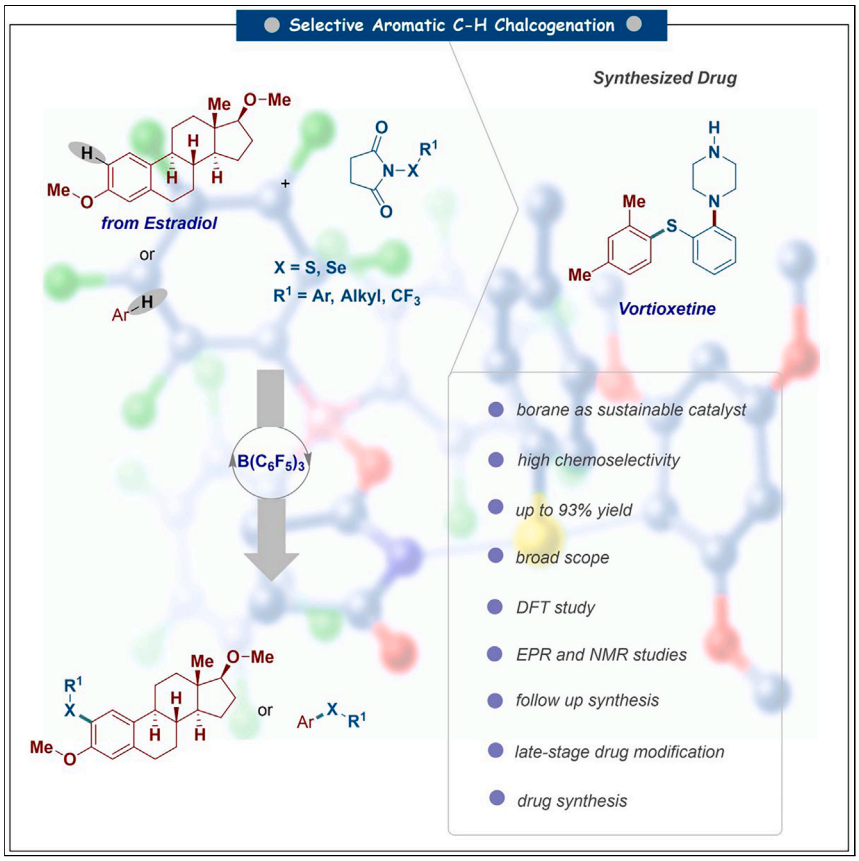
Chem

CellPress
OPEN ACCESS

Article

$B(C_6F_5)_3$-catalyzed selective C–H chalcogenation of arenes and heteroarenes



This study discloses the borane-catalyzed synthesis of organochalcogenides using readily available arenes, heteroarenes, and pharmacophores, and the installation of the industrially relevant trifluoromethylthio group, in high yields. Furthermore, the protocol enables the late-stage selective chalcogenation of drug derivatives such as naproxen and estradiol and offers a metal-free synthetic route for synthesizing vortioxetine as an antidepressant drug. The comprehensive NMR, EPR, and DFT study indicate a stable ion pair mechanism with the exitance of off-cycle radical species in the catalytic process.

Milan Pramanik, Sampurna Das, Rasool Babaahmadi, Sanjukta Pahar, Thomas Wirth, Emma Richards, Rebecca L. Melen

wirth@cf.ac.uk (T.W.)
richardse10@cardiff.ac.uk (E.R.)
melenr@cardiff.ac.uk (R.L.M.)

Highlights

Borane catalysis in selective Csp^2–H chalcogenation of arenes and heteroarenes

Late-stage chalcogenation of drug molecules such as naproxen and estradiol derivatives

A metal-free synthetic route to synthesizing vortioxetine

Comprehensive NMR, EPR, and DFT studies to elucidate radical vs. ionic mechanisms

Pramanik et al., Chem *10*, 1–15
September 12, 2024
Published by Elsevier Inc.
https://doi.org/10.1016/j.chempr.2024.05.025

Please cite this article in press as: Pramanik et al., $B(C_6F_5)_3$-catalyzed selective C–H chalcogenation of arenes and heteroarenes, Chem (2024), https://doi.org/10.1016/j.chempr.2024.05.025

Chem

CellPress
OPEN ACCESS

Article

$B(C_6F_5)_3$-catalyzed selective C–H chalcogenation of arenes and heteroarenes

Milan Pramanik,[1] Sampurna Das,[1] Rasool Babaahmadi,[1] Sanjukta Pahar,[1] Thomas Wirth,[2,*] Emma Richards,[1,2,*] and Rebecca L. Melen[1,3,*]

SUMMARY

The synthesis of organochalcogenides remains a valuable area of research due to their widespread biological applications, particularly in pharmaceuticals. Herein, our study details the $B(C_6F_5)_3$-catalyzed Csp^2–H functionalization of diverse arenes, heteroarenes, and pharmacophores with thiosuccinimides or selenosuccinimides, providing selective access to chalcogenated products. This protocol enables the selective late-stage chalcogenation of drug molecules such as the anti-inflammatory drug naproxen, the estrogen steroid hormone estradiol derivatives, and the industrially relevant trifluoromethylthiolation reaction. Furthermore, this C–S coupling methodology provides a facile and metal-free route to synthesize vortioxetine, an antidepressant drug, and a plethora of significant organic motifs. Detailed NMR, EPR analyses, and density functional theory (DFT) computational studies indicate that the elongation of the thiosuccinimide N–S bond is assisted by a boron-centered adduct, which then leads to a stable ion pair with an arene. The EPR analysis shows that a transient radical pair, potentially an off-cycle species, is not directly involved in the catalytic process.

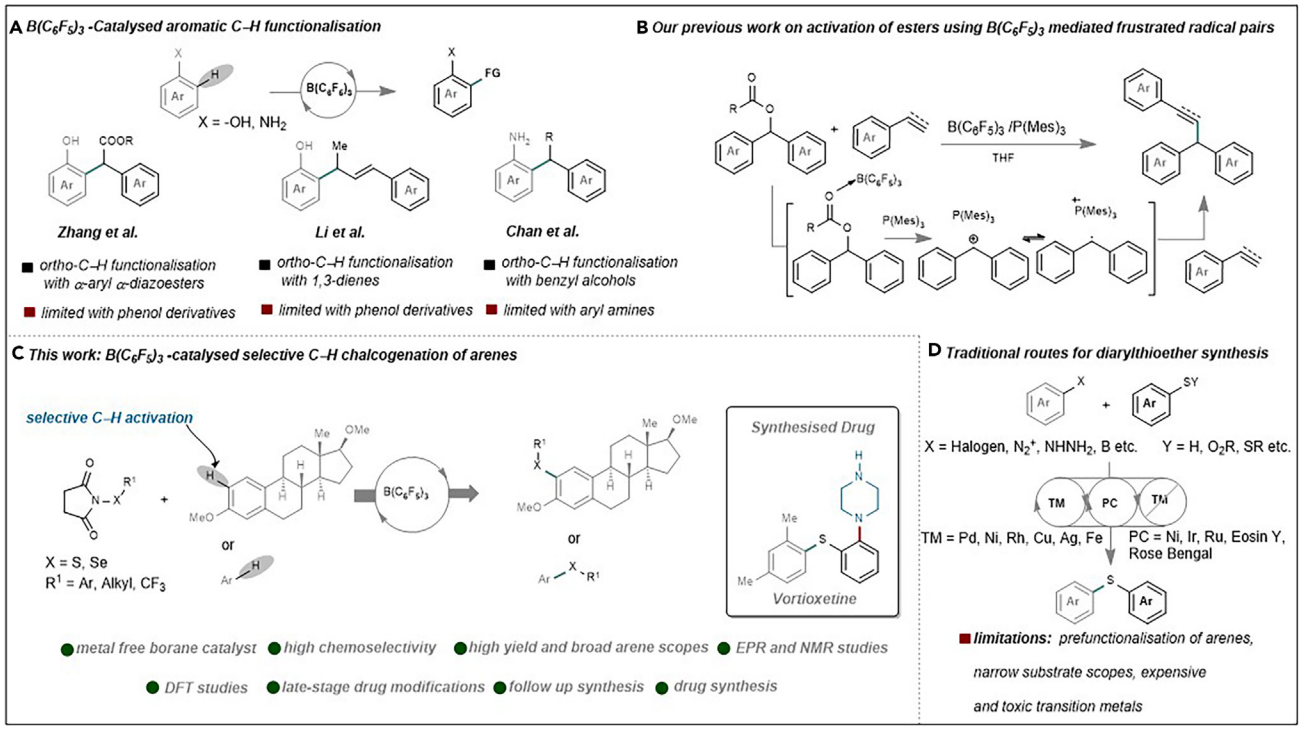
INTRODUCTION

The reactivity of tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] as a well-known electron acceptor can promote heterolytic bond scission via the formation of a dative bond with a Lewis basic donor atom.[1,2] Indeed, the utilization of frustrated Lewis pairs (FLPs) and, in particular, the combination of $B(C_6F_5)_3$ with hindered phosphines or amines has begun to expand the chemical toolbox in synthesis as it addresses a wide range of synthetic challenges inherent in transition metal catalysis.[3–6] Recent studies also disclose the indispensable function of $B(C_6F_5)_3$ in realizing the stability of reactive intermediates in radical-driven FLP mechanisms via an electron donor-acceptor complex.[7] Furthermore, $B(C_6F_5)_3$ also demonstrates versatile applications beyond FLP chemistry, such as hydride abstraction, hydroxy/ester group activation, CN coordination, and fluoride abstraction, which ultimately influence a diverse range of C–C and C–X (X = O, N, Si etc.) bond-forming transformations.[2,8–13] Despite the tremendous ability of $B(C_6F_5)_3$ in the formation of organic bonds, the $B(C_6F_5)_3$-catalyzed selective C–H functionalization of arenes continues to remain conspicuously scarce in the literature. An early example includes the $B(C_6F_5)_3$-catalyzed *ortho*-selective C–H functionalization of phenols with α-aryl-α-diazoesters reported by Zhang et al. (Scheme 1A).[14] Subsequent studies by Li demonstrate that borane-catalyzed hydroarylation of 1,3-dienes can lead to the *ortho*-selective C–H coupling of phenols (Scheme 1A).[15] Furthermore, Chan and Zhao reported the *ortho*-selective C–H alkylation of unprotected arylamines with benzylic alcohols

THE BIGGER PICTURE

The synthesis of organochalcogenides is an important area of investigation due to the intricacies inherent in their diverse biological applications, especially in pharmaceutical compounds. Herein, a metal-free Csp^2–H functionalization method using $B(C_6F_5)_3$ catalysis, yielding unsymmetrical diarylchalcogenides with high selectivity, is disclosed. This versatile approach works for various arenes, heteroarenes, and pharmacophores with borane-sensitive groups. Our protocol allows for the late-stage chalcogenation of drug derivatives, such as naproxen (anti-inflammatory), estradiol (estrogen steroid hormone), and vortioxetine (antidepressant). Additionally, we demonstrate post-synthetic modifications, providing access to valuable organic motifs. Mechanistic investigations suggest that $B(C_6F_5)_3$-induced N–S bond scission involves both ion pairs and off-cycle radical pathways. We anticipate that this finding will expand the scope of borane catalysis in organic synthesis.

Please cite this article in press as: Pramanik et al., $B(C_6F_5)_3$-catalyzed selective C–H chalcogenation of arenes and heteroarenes, Chem (2024), https://doi.org/10.1016/j.chempr.2024.05.025



Scheme 1. Development of the reaction strategy

(A) Previous report on $B(C_6F_5)_3$-catalyzed C–H functionalizations, (B) our previous work on the activation of diaryl esters using FLP chemistry, (C) present work on the $B(C_6F_5)_3$-catalyzed selective C–H chalcogenation of arenes and heteroarenes, and (D) traditional synthetic routes for thioarylation.

(Scheme 1A).[16] $B(C_6F_5)_3$-catalyzed arene C–H functionalizations are rare with either phenols or aryl amines due to the highly coordinating nature of the Lewis basic O/N center and the strong Lewis acid, and they have previously only been explored for *ortho*-selective C–C bond-forming reactions. Thus, the $B(C_6F_5)_3$-catalyzed chemoselective arene C–H functionalization for the construction of carbon–heteroatom bonds, in particular C–S and C–Se, is still an unknown transformation.

Our earlier investigations on the site-selective C_{sp3}–C_{sp} or C_{sp3}–C_{sp2} cross-coupling reaction between terminal alkynes or alkenes with aryl esters using the combination of $B(C_6F_5)_3$/$P(Mes)_3$ as FLPs implied that the activation of benzhydryl esters by $B(C_6F_5)_3$ could assist in the stabilization of the benzylic carbocation by $P(Mes)_3$ through the formation of ion pairs or radical pairs (Scheme 1B).[17,18] Inspired by this result, we postulated that thioarylsuccinimides could similarly be activated by $B(C_6F_5)_3$ to generate either a thiyl radical or sulfenium ion, potentially serving as a suitable sulfur synthon for a selective C–H thioarylation reaction of arenes (Scheme 1C).

Chalcogenide motifs exhibit profound versatility in various pharmaceuticals and bioactive molecules, agrochemicals, materials, and lubricants.[19–22] In particular, the thioaryl group is a prominent functionality in various commercially available FDA-approved pharmaceuticals.[23–25] Similarly, trifluoromethylthio (SCF_3) groups having high lipophilicity are prevalent in many veterinary medicines and pharmaceutically active molecules.[26–28] Because of the frequent application of diarylthioethers, synthetic chemists have made continuous efforts in shortening and modifying synthetic routes for their construction. The most commonly employed synthetic route for synthesis of thioethers currently relies on transition

[1]Cardiff Catalysis Institute, School of Chemistry, Cardiff University, Translational Research Hub, Maindy Road, Cardiff CF24 4HQ, Wales, UK

[2]School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff CF10 3AT, Wales, UK

[3]Lead contact

*Correspondence: wirth@cf.ac.uk (T.W.), richardse10@cardiff.ac.uk (E.R.), melenr@cardiff.ac.uk (R.L.M.)

https://doi.org/10.1016/j.chempr.2024.05.025

Please cite this article in press as: Pramanik et al., $B(C_6F_5)_3$-catalyzed selective C–H chalcogenation of arenes and heteroarenes, Chem (2024), https://doi.org/10.1016/j.chempr.2024.05.025

metal-catalyzed C–S cross-coupling of thiophenols (or other organosulfur surrogates) and aryl halides or arylboronic acids (Scheme 1D).[29,30] However, there are major disadvantages associated with these methods, including the use of expensive and toxic transition metals, and the requirements for additional base and ligand, high reaction temperatures, and long reaction times. It is further noted that thiophenol in the presence of metal or base is prone to overoxidation and can give undesired by-products. Again, the narrow scope is limited to the use of prefunctionalized arenes or heteroarenes and therefore hinders the broad accessibility of this cross-coupling strategy. To overcome these disadvantages of transition metal catalysis, several sustainable methods using photocatalysis and metal-free reagents have been investigated. Despite the great potential for catalyzing the thioarylation reaction by photocatalysis, these methods still have several drawbacks, including a narrow arene or heteroarene scope, the use of expensive and toxic metal-based photocatalysts, or the degradation of organic dyes.[31–36] In the pursuit of metal-free synthesis, there are substantial reports on metal-free thioarylation reactions based on a non-radical mechanism; however, most of them are plagued with inaccessibility of sulfur precursor, restricted substrate scopes, and the requirement for stoichiometric reagents.[29,37–41]

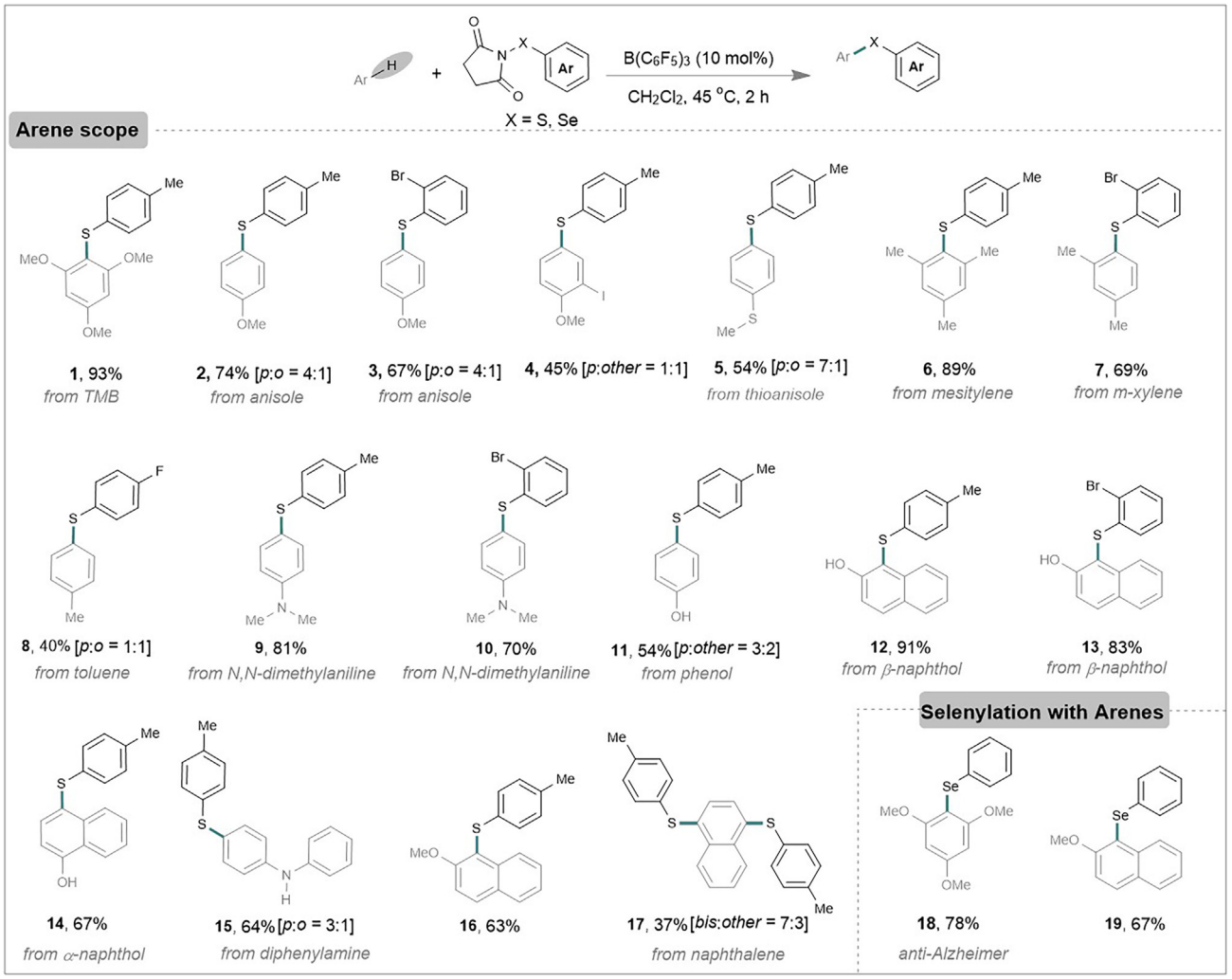
Although various synthetic routes, including electrochemical chalcogenations,[42] are documented in the literature, there is still a lack of effective and sustainable synthetic strategies for the chalcogenation reaction that can access challenging and valuable molecules from readily available feedstocks. Recently, Maiti et al. have demonstrated dual-ligand-assisted palladium-catalyzed nondirected C–H chalcogenation.[23] Kumar et al. have described the synthesis of organochalcogenides using potassium persulfate as stoichiometric oxidant and trifluoroacetic acid (TFA) as the solvent.[43] Wang et al. introduced a copper-catalyzed synthesis of diarylchalcogenides from diaryl dichalcogenides as the chalcogenating source, using a dechalcogenization reaction strategy.[44] Nevertheless, the use of a ligand-chelated metal, stoichiometric oxidants, and high reaction temperatures make these methods less attractive.

To address the constraints linked with the selective aromatic C–H functionalization strategy in chalcogenation reactions, and to continue our efforts on advancing borane catalysis in developing novel synthetic methodologies, we opted to use $B(C_6F_5)_3$ as a metal-free and sustainable catalyst for the selective C–H chalcogenation of arenes, heteroarenes, and various pharmaceutically active molecules.

RESULTS AND DISCUSSION

At the outset of our study, we optimized the reaction conditions using model substrates trimethoxybenzene (TMB) as the arene partner and tolylthiosuccinimide as the sulfenylating source for the thioarylation reaction. A maximum yield of 92% of the product diarylthioether **1** was obtained under the optimized conditions using 10 mol % $B(C_6F_5)_3$ at 45°C for 2 h in CH_2Cl_2 as the solvent (for details and full optimization protocol, see the supplemental information, Table S1). With the standardized optimum conditions in hand, we commenced the evaluation of the substrate scope employing commercially available (non)activated arenes for the selective C–H chalcogenation reactions with different arylthiosuccinimides (Scheme 2). A series of methoxy-substituted benzenes (TMB and anisole derivatives) were employed for the selective *para*-directed C–H functionalization and were pleasingly highly effective in producing C–H thioarylated products (**1–4**) with good to excellent yields (45%–93%). Thioanisole was also found to be productive toward the *para*-C–H

Please cite this article in press as: Pramanik et al., B(C_6F_5)$_3$-catalyzed selective C–H chalcogenation of arenes and heteroarenes, Chem (2024), https://doi.org/10.1016/j.chempr.2024.05.025



Scheme 2. Evaluation of the scope of commercially available arenes for the selective C–H chalcogenation reaction

All reactions were performed on a 0.2 mmol scale; selectivity was determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture.

sulfenylation producing the methyl 4-tolyl phenyl sulfide **5** (54%) as the major product. Surprisingly, the chemically inert aromatic hydrocarbons mesitylene, xylene, and toluene are also converted into useful thioarylated products (**6**–**8**) with 40%–89% yields. Notably, the more electron-rich systems resulted in higher product yields for (**1**–**8**). Of note, neither the addition of excess toluene nor thiosuccinimide could lead to the enhancement of the yield for **8**, rather the formation of disulfide as an additional byproduct was observed when excess thiosuccinimide was used. Our optimized conditions further led to the *para*-selective C–H sulfenylation of *N*,*N*-dimethyl aniline (compounds **9** and **10**). This unique observation is distinct to the radical reactivity of *N*,*N*-dimethyl aniline examined by Ooi et al. where α-aminoalkyl radicals initiated by single electron transfer with B(C_6F_5)$_3$ and *N*,*N*-dialkylanilines led to α-aminomethyl functionalization.[45] Our results are also divergent from the amine C–H functionalization realized by Erker et al.[46] B(C_6F_5)$_3$ is often intolerant toward alcohols or unhindered primary amines due to strong Lewis acid-base coordination. However, we observe that unprotected aromatic alcohols such as phenol or α/β-naphthol were also active for the chemoselective C–H-sulfenylation reactions (**11**–**14**) with reasonable to excellent yields (54%–91%). Interestingly, this *para*-selectivity

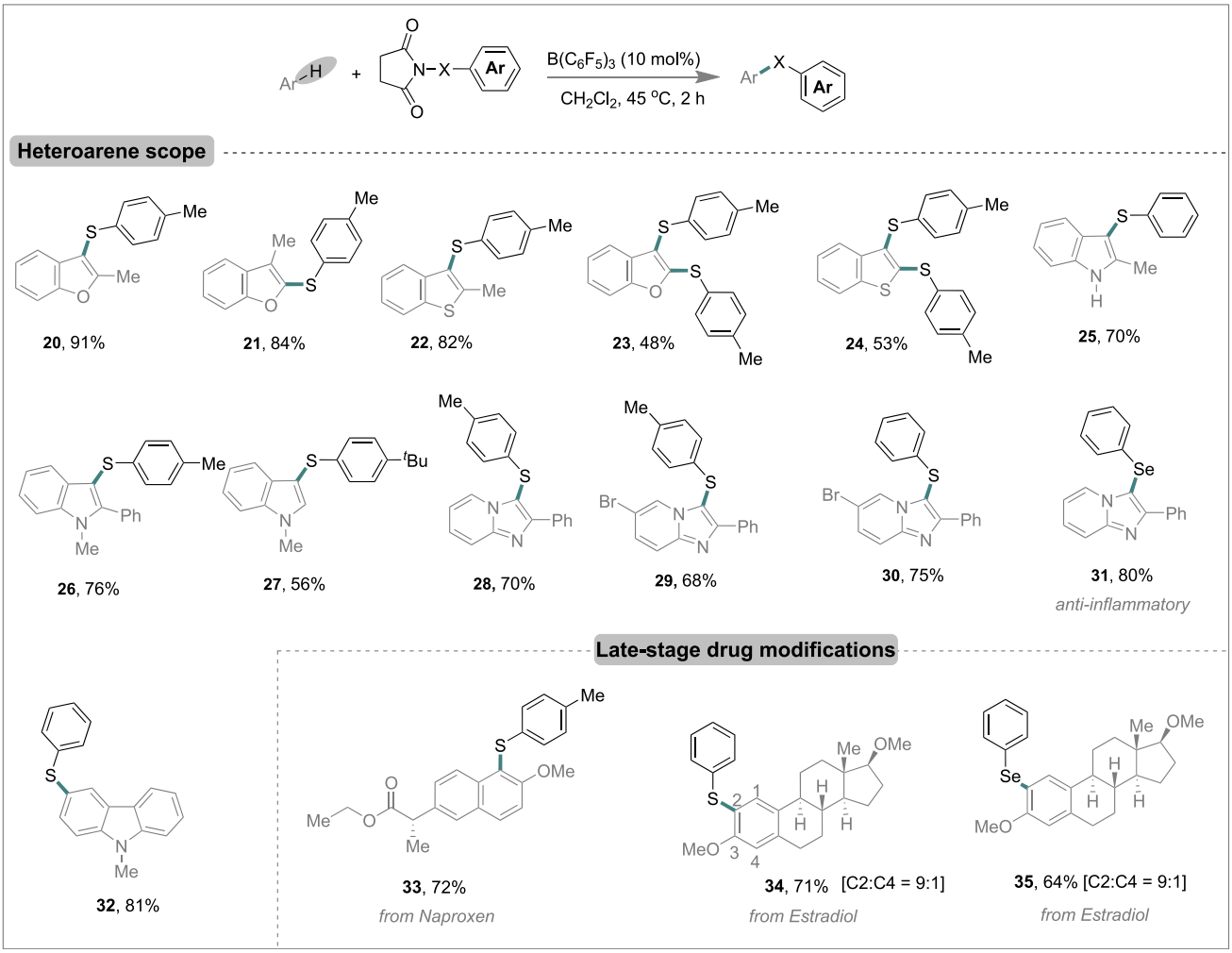
Please cite this article in press as: Pramanik et al., $B(C_6F_5)_3$-catalyzed selective C–H chalcogenation of arenes and heteroarenes, Chem (2024), https://doi.org/10.1016/j.chempr.2024.05.025

of the reaction with phenol is in contrast to Zhang's investigations on the $B(C_6F_5)_3$-catalyzed *ortho*-selective C–H functionalization of phenols with diazo compounds,[14] and the hydroarylation of 1,3-dienes as previously observed by Wang et al.[15] This is presumably due to the lack of coordination between the phenolic hydroxy group and $B(C_6F_5)_3$ in our study. Based upon our previous investigations of $B(C_6F_5)_3$-catalyzed *N*-alkylation of amines with aryl esters,[47] we expected N–S coupling to proceed rather than C–S coupling when the reaction was conducted with a secondary amine such as diphenylamine and thiosuccinimide. However, in these cases C–S coupling was predominantly observed. Pleasingly, we could accomplish a chemoselective aromatic mono C–H sulfenylation with 64% yield of compound **15** as the major product. Finally, we examined the arenes 2-methoxynaphthalene and naphthalene as substrates. Although 63% yield of selective and mono C–S coupled **16** was achieved for 2-methoxynaphthalene, a low-yielding bisthioarylated product **17** was formed with naphthalene due to the symmetrical and unbiased electronic configuration of the unsubstituted system. It should be noted that this reaction strategy is limited to more electron-rich arenes (unsuccessful substrates are listed in the supplemental information, Scheme S3), which is supported by the density functional theory (DFT) mechanism (see later). This can be observed with decreasing yields when moving from the more electron-rich mesitylene to xylene and to toluene. To further broaden the scope beyond thiyl derivatives, biologically active organoselenium compounds such as compounds **18** (an Alzheimer's medication)[48] and **19** were synthesized in 78% and 67% yield, respectively, when the C_{sp2}–H selenylation strategy was employed.

One of the key emphases of this manuscript was to draw attention to the radical reactivity of thiosuccinimide by utilizing $B(C_6F_5)_3$, potentially beneficial for frustrated radical pair chemistry. Remarkably, while $BF_3{\cdot}Et_2O$ failed to yield reasonable signal intensity in the electron paramagnetic resonance (EPR) measurements, $B(C_6F_5)_3$ consistently produced reliable EPR signals, thus prompting us to explore the radical reactivity (*vide infra*). It is also worth mentioning that $B(C_6F_5)_3$ and $BF_3{\cdot}Et_2O$ formed compound **1** with 93% and 69% yields, respectively, for electron-rich TMB (see also Table S2); therefore, we further evaluated the efficiency of both catalysts considering less electron-rich arenes. For instance, thioanisole, *m*-xylene, and β-naphthol in the presence of 10 mol % $BF_3{\cdot}Et_2O$ demonstrated lower reactivity (compounds **5**, **7**, and **12**) than $B(C_6F_5)_3$ as a catalyst, indicating the superiority of $B(C_6F_5)_3$ in this C–S coupling reaction strategy. Given these differences in reactivity, we have opted to employ $B(C_6F_5)_3$ as the catalyst herein. However, the regioselectivity observed in compound **5** remained unaltered for both borane catalysts, suggesting that the selectivity is not influenced by the borane catalyst.

Next, we sought to examine the reactivity of heteroarenes toward the selective C–H chalcogenation reaction (Scheme 3). With C2- and C3-methyl substituted benzofurans and C2-methyl substituted benzothiophene, the monosulfenylated products (**20**–**22**) were isolated in 82%–91% yield. By contrast, unsubstituted benzofuran and benzothiophene formed bis-sulfenylated products **23** (48%) and **24** (53%), demonstrating similar behavior to that observed for unsubstituted naphthalene (**17**). Unprotected and substituted indoles showed compatibility toward the C3-sulfenylation affording compounds **25**, **26**, and **27** in 70%, 76%, and 56% yield, respectively. It is noteworthy that no N–S coupling was observed through N–H functionalization of the C2-substituted indole during the formation of **25**.[49] By contrast, the C2- and C3-unsubstituted indole surprisingly exhibited the regioselective C3 mono sulfenylation instead of bis-sulfenylation observed earlier for

Please cite this article in press as: Pramanik et al., $B(C_6F_5)_3$-catalyzed selective C–H chalcogenation of arenes and heteroarenes, Chem (2024), https://doi.org/10.1016/j.chempr.2024.05.025

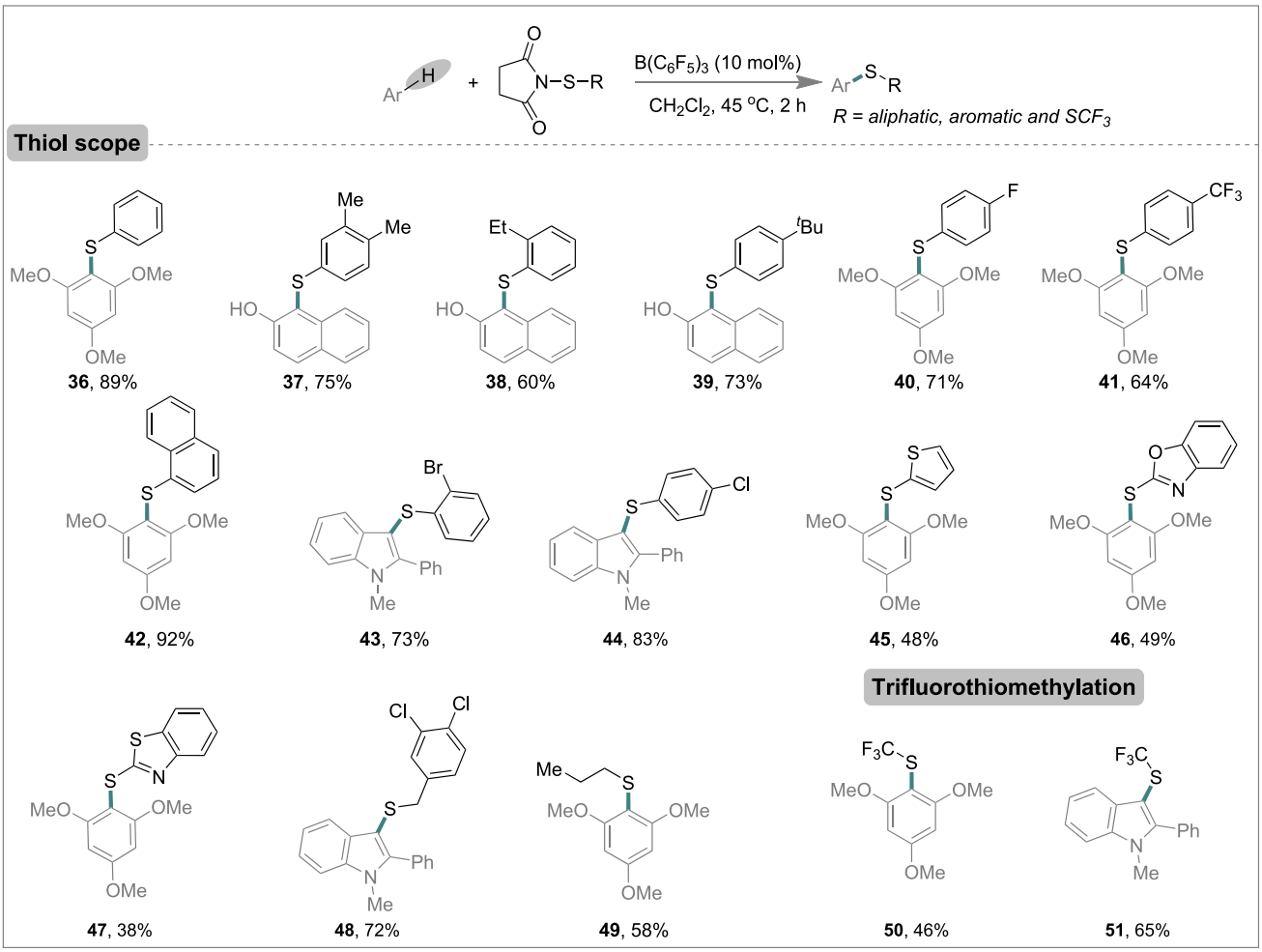


Scheme 3. Evaluation of the scope of heteroarenes and pharmaceuticals for selective C–H chalcogenations

All reactions were performed on a 0.2 mmol scale; selectivity was determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture.

the C2- and C3-unsubstituted benzofuran and benzothiophene. Imidazopyridine, a core structure of several pharmaceuticals, was selectively chalcogenated to produce the corresponding C–S/C–Se coupled products (**28**–**31**) with moderate yields (68%–80%). Importantly, selenylated imidazo[1,2-a]pyridine **31** has shown potential efficacy as an anti-inflammatory agent.[50,51] *N*-Protected carbazole also led to the regioselective C_{sp2}–H functionalization as demonstrated by Koenigs in the reactions of carbazole with aryldiazoacetates catalyzed by $B(C_6F_5)_3$.[52] In our reaction, we observe 81% of the C–S coupled product **32** when using *N*-methylcarbazole as the arene substrate.

With the broad substrate scope and optimized reaction conditions investigated, we next applied our new methodology to enable the selective late-stage diversification of commercially available pharmaceuticals such as naproxene and estradiol derivatives (entries **33**–**35**). Naproxen, a nonsteroidal anti-inflammatory (NSAID) drug used as a painkiller, could be regioselectively thioarylated in 72% yield without affecting other functionalities, and estradiol, a steroid hormone used to treat menopause symptoms, could selectively be chalcogenated with 71% (C–S) and 64% yield (C–Se), respectively.



Scheme 4. Evaluation of the scope of thiosuccinimides for regioselective C–H chalcogenations and trifluoromethylation with arenes and heteroarenes

All reactions were performed on a 0.2 mmol scale.

Having fully explored the arene and heteroarene substrate scopes, attention was turned to expanding further the scope of the thiosuccinimide partner (Scheme 4). The implementation of various thioaryl coupling partners having electron donating/withdrawing substituents such as -Me, -Et, -^{t}Bu, -F, -CF_3, or polyaromatic groups (e.g., naphthalene) revealed that a wide range of selective C_{sp2}–H thioarylated products with 60%–92% yields could be isolated when reacted with TMB or 2-naphthol as the arene coupling partner (products **36**–**42**). The protocol was also effective in forming thioarylated indoles (products **43** and **44**) with 73% and 83% yield when thioaryl partners substituted with electron-withdrawing groups (*o*-Br or *p*-Cl) were coupled with indoles. Thioheteroaryl coupling partners such as thiophene, benzothiazole, and benzoxazole were well amenable to the reaction conditions to furnish thioheteroarylated products (**45**–**47**), albeit with slightly decreased yields (38%–49%). Aliphatic thiosuccinimides were investigated with indoles and TMB, which pleasingly afforded regioselective C–H sulfenylated products (**48** and **49**) with 72% and 58% yield, respectively. Finally, it is noted that the SCF_3 group, found in many bioactive molecules, could also be installed using our metal-free reaction strategy, generating the selective trifluorothiomethylated compounds **50** and **51** with reasonable yields (46% and 65%, respectively).[53]

Please cite this article in press as: Pramanik et al., $B(C_6F_5)_3$-catalyzed selective C–H chalcogenation of arenes and heteroarenes, Chem (2024), https://doi.org/10.1016/j.chempr.2024.05.025

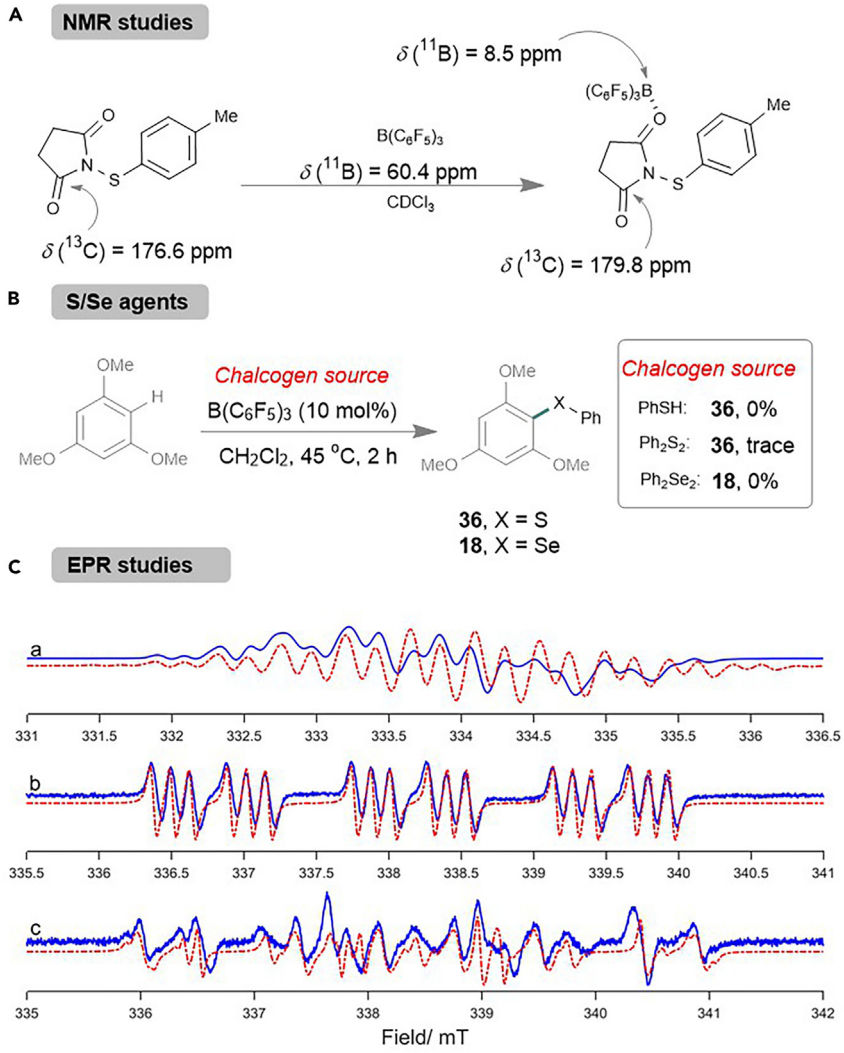


Figure 1. Control experiments conducted to elucidate the reaction mechanism

(A) NMR spectroscopic studies indicating the involvement of borane dative adduct, (B) examination of other sulfenylating agents, and (C) X-band CW EPR (T = 298 K) of $B(C_6F_5)_3$ with *p*–tolylthiosuccinimide, in addition with (a) toluene, (b) mesitylene and PBN spin trap, and (c) DMPO spin trap (no arene). Experimental (blue, solid); simulated (red, dashed).
See supplemental information for full details of simulation parameters.

After exploring the substrate scope, we performed a series of experimental and theoretical studies to elucidate the reaction mechanism (Figures 1 and 2). A shift in the ^{11}B NMR spectrum from δ = 60.4 ppm for free $B(C_6F_5)_3$ to δ = 8.5 ppm is observed upon addition of *p*–tolylthiosuccinimide to the borane (see also Data S1). In addition, there was a corresponding shift from δ = 176.6 ppm to δ = 179.8 ppm in the ^{13}C NMR spectrum for the carbonyl carbon of *p*–tolylthiosuccinimide when $B(C_6F_5)_3$ and phenylthiosuccinimide were mixed in a 1:1 ratio (Figure 1A; see also Data S1). These observations confirm that $B(C_6F_5)_3$ is involved in a dative interaction between the boron center and the carbonyl oxygen of *p*–tolylthiosuccinimide, which assists in the N–S bond scission. To prove the requirement of the succinimide group, it was found that addition of thiophenol instead of *p*–tolylthiosuccinimide under the standard reaction conditions did not lead to the desired product.

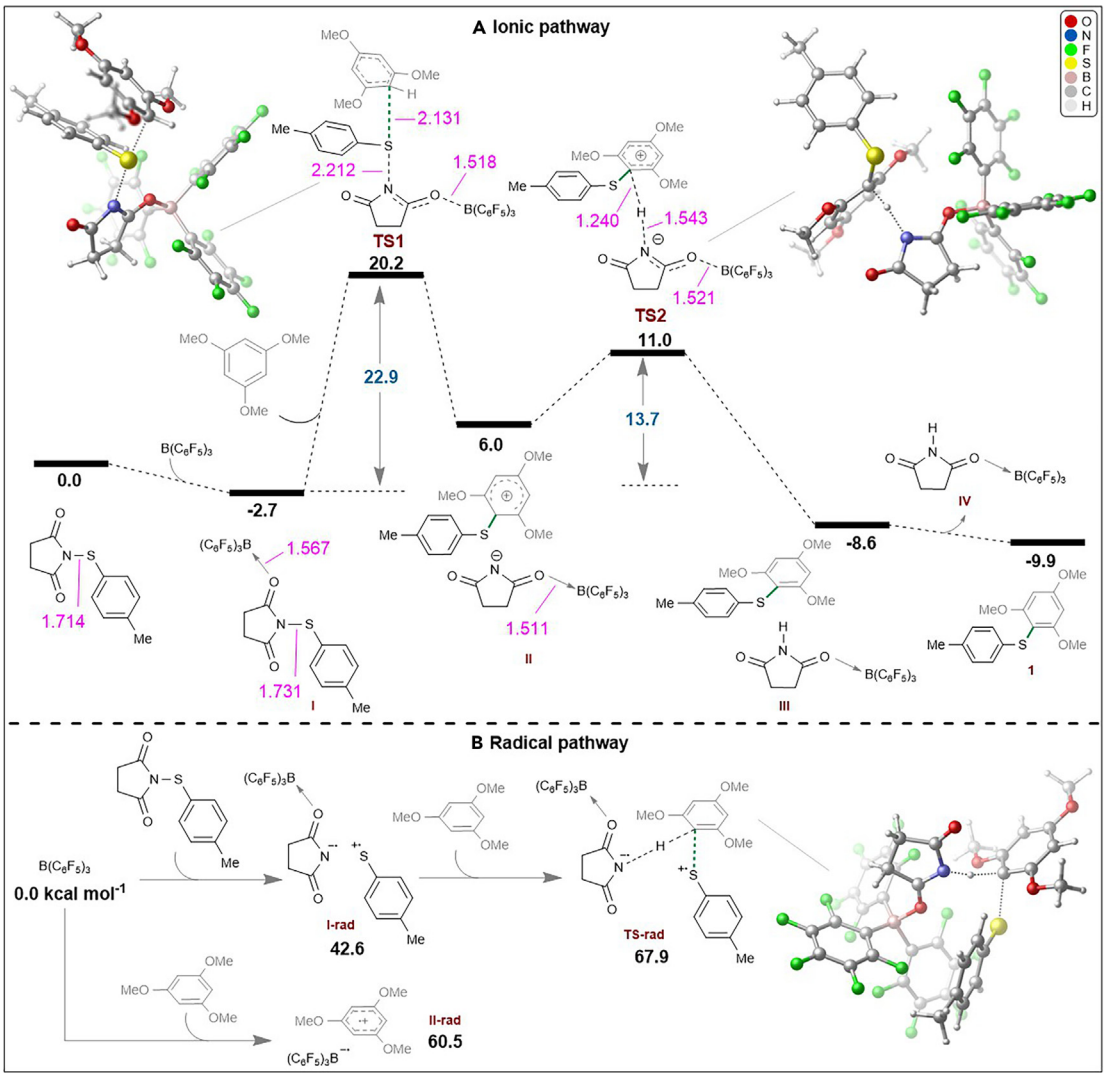


Figure 2. The mechanism shows ionic vs. radical routes using DFT studies

Energy profiles for the DFT calculated (A) ionic and (B) radical pathways at the SMD/M06-2X /def2-TZVP//SMD/M06-2X/6-31G(d) level of theory. Bond lengths (pink color) shown in (Å). Relative energies given in kcal mol^{-1}.

Additionally, formation of the desired C–H chalcogenated products **36** or **18** (Schemes 2 and 4) was unsuccessful upon employment of diphenyl disulfide and diphenyl diselenide, respectively, instead of phenylchalcogenosuccinimide as chalcogenating reagents (see also Scheme S2). These experiments indicate that in this study $B(C_6F_5)_3$ can neither assist S–H bond scission in thiophenol nor S–S/Se–Se cleavage in diphenyl disulfide or diphenyl diselenide (Figure 1B).

Recently, the participation of $B(C_6F_5)_3$ and FLPs in single electron transfer processes has become a prominent topic of research.[7,54] To explore if the reaction was taking place by a radical mechanism, a series of EPR experiments were performed to identify the potential involvement of single electron transfer events. The addition of toluene to a dichloromethane solution of *p*–tolylthiosuccinimide with $B(C_6F_5)_3$ yielded a transient EPR signal with a rich hyperfine structure (Figures 1C and S2). Upon comparison with a DFT calculated structure (*vide infra*), this signal was

Please cite this article in press as: Pramanik et al., $B(C_6F_5)_3$-catalyzed selective C–H chalcogenation of arenes and heteroarenes, Chem (2024), https://doi.org/10.1016/j.chempr.2024.05.025

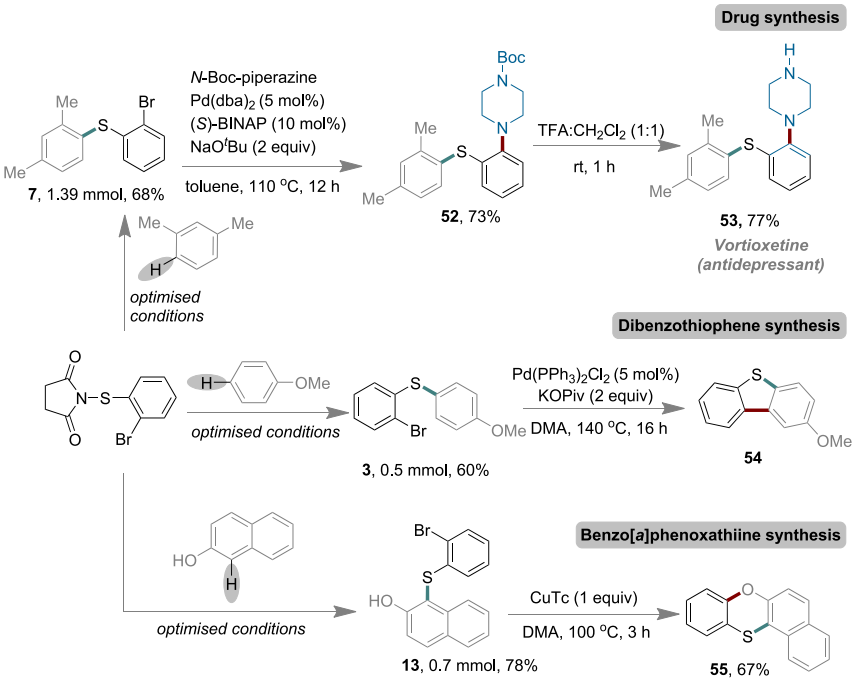
assigned to a neutral radical formed upon N–S bond cleavage in the thiosuccinimide following $B(C_6F_5)_3$ coordination through the carbonyl group, in agreement with the ^{11}B and ^{13}C NMR spectroscopic evidence (*vide infra*). It is worth noting that the EPR spectrum of the early time trace after toluene addition gives an identical spectrum to the neutral $B(C_6F_5)_3$−succinimide radical adduct in the absence of arene (see also Figure S2A).

Further evidence to support the N–S bond cleavage was provided by the results of spin-trapping measurements, employing α-phenyl *N*-tert-butyl nitrone (PBN) and 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) as spin-trapping agents, in which strong EPR signals corresponding to the succinimidyl spin adduct were observed in the presence of toluene or TMB (Figures 1C, S3, and S4).

Although direct detection of the corresponding thiyl radical partner via solution phase EPR measurements is not possible due to significant line broadening arising from large **g**-anisotropy and unquenched orbital angular momentum,[55,56] indirect detection of the corresponding thiyl-spin adduct was confirmed upon addition of PBN. The experimental EPR results therefore give clear evidence for the formation of succinimidyl and thiyl radicals, indicating the potential involvement of single electron transfer events in this chemistry. Addition of (2,2,6,6-tetramethylpiperidin-1-yl) oxyl (TEMPO) as a radical scavenger to the reaction led to a significant reduction in overall yield of **1** (13% vs. 93%; see also Scheme S1), which could be interpreted as evidence of an on-cycle radical pathway; however, it must also be noted that the TEMPO can itself interact with the $B(C_6F_5)_3$ and act to deactivate the catalyst.[57]

As the experimental results alone do not provide conclusive evidence for the nature of the on-cycle reaction pathway, and mindful of recent reports comparing ionic vs. radical routes in FLP chemistry,[58] we sought to gain further understanding of the thermodynamic and kinetic accessibility of the reaction through DFT calculations (Figure 2; see also Data S2). Calculations were performed using the SMD/M06-2X/def2-TZVP//SMD/M06-2X/6-31G(d) level of theory in dichloromethane solvent and tolylthiosuccinimide and TMB as model substrates (yielding **1**). Based on our calculations for the ionic pathway (Figure 2A), the reaction commences with the coordination of the borane catalyst to tolylthiosuccinimide, forming the adduct **I** with the energy of −2.7 kcal mol^{-1}. Intermediate **I** was found to have an elongated N−S bond length of 1.731 Å, which results in heterolytic bond cleavage and the generation of ion pair **II** in the presence of TMB. This concerted step occurs with an activation barrier of 22.9 kcal mol^{-1} through **TS1**. This slightly high barrier aligns with the required elevated temperature (45°C) in the standard reaction conditions. Afterward, deprotonation of **II** resulted in rearomatization and the formation of **III** via **TS2**, accompanied by an activation barrier of 13.7 kcal mol^{-1}. Subsequently, the release of **IV** and product **1** takes place with an energy of −9.9 kcal mol^{-1}. On the other hand, calculations into the radical pathway through formation of radical pairs as experimentally observed by EPR spectroscopy could also be computed (Figure 2B). However, the formation of the first diradical intermediate (**I-rad**) is found to be energetically high (42.6 kcal mol^{-1}), and the subsequent C–S bond-forming step through **TS-rad** shows a large activation barrier 67.9 kcal mol^{-1}. We have also excluded the possibility of radical-ion pair formation from the combination of TMB and $B(C_6F_5)_3$ through EPR and DFT studies. It is noted that the combination of TMB with $B(C_6F_5)_3$ (in the absence of the thiosuccinimide reagent) did not yield any evidence of radicals in the room temperature EPR spectrum under direct detection conditions, nor in the presence of PBN as a spin-trapping agent. This supports the DFT evidence, which indicates a high energy of 60.5 kcal mol^{-1} for the formation of diradical

Please cite this article in press as: Pramanik et al., B(C_6F_5)$_3$-catalyzed selective C–H chalcogenation of arenes and heteroarenes, Chem (2024), https://doi.org/10.1016/j.chempr.2024.05.025

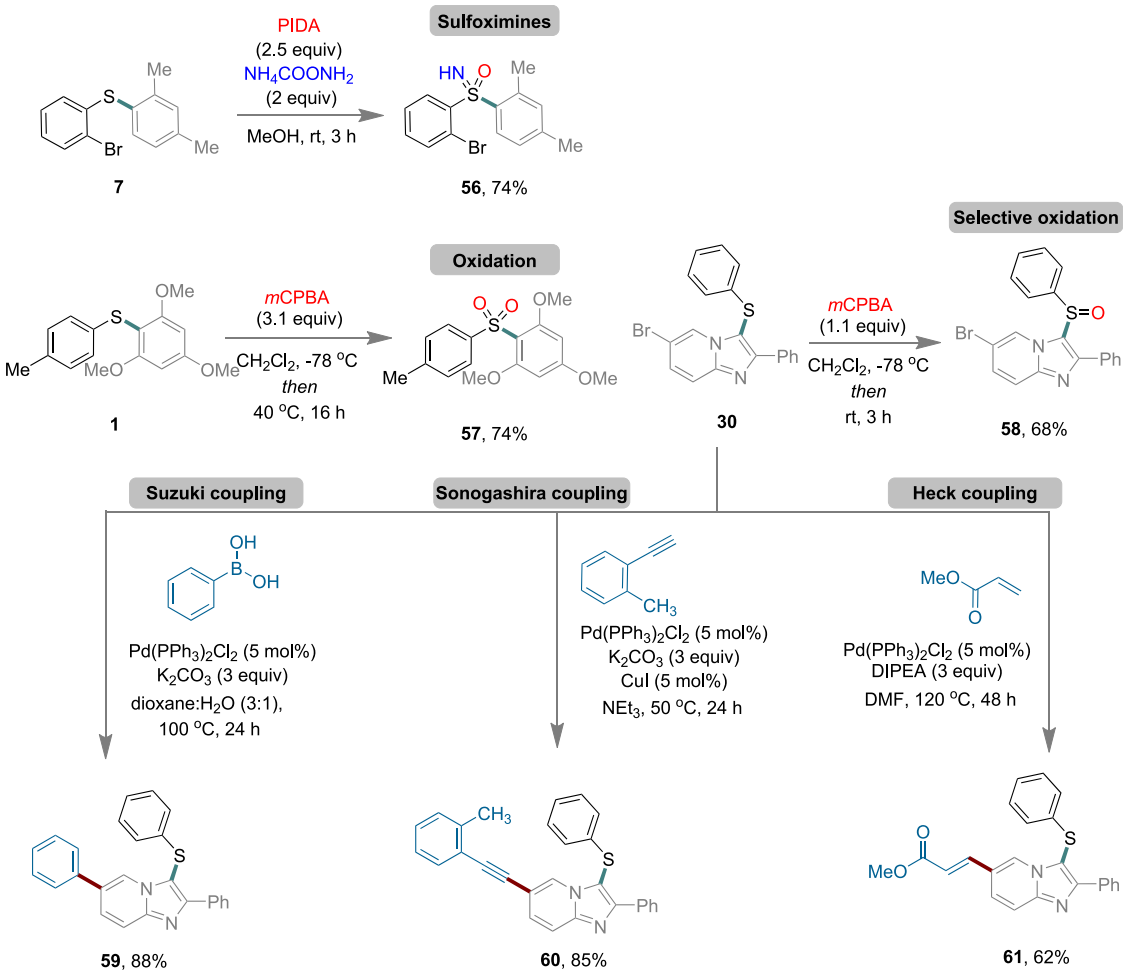


Scheme 5. Synthetic applications of the thioarylated products in multistep synthetic routes to useful molecules

II-rad from these substrates (Figure 2B). These combined results therefore strongly suggest that the ionic pathway is favorable for product formation, and the previous experimental EPR results may instead by indicative of an off-cycle pathway. As confirmed by DFT, the reaction proceeds through a stable ion pair II originating from nucleophilic attack by the electron-rich arene to the sulfur atom of the borane-coordinated thiosuccinimide. As a result, the desired thioarylated products were not observed for electronically deactivated systems listed in the supplemental information (Scheme S3).

To showcase the further potential application of our newly developed metal-free C−S bond-forming strategy, we targeted the synthesis of commercially available vortioxetine (an antidepressant medication) and other valuable organic skeletons (Scheme 5). Using the metal-free, mild, and sustainable reaction strategy, *meta*-xylene was selectively coupled with *N*-(2-bromophenylthio)succinimide on a larger scale to afford thioarylated product **7** with a 68% yield (1.39 mmol). Subsequent Buchwald-Hartwig cross-coupling conditions between **7** and *N*-Boc-piperazine were employed to yield the C–N coupled product **52**, which upon removal of the Boc-protecting group by TFA enabled access to vortioxetine **53** in 77% yield. Our metal-free protocol could further be utilized as a key step in the synthesis of dibenzothiophene and benzo[*a*]phenoxathiine via a two-step reaction sequence. Thioarylated compound **3** (0.5 mmol, 60% yield) was derived from *N*-(2-bromophenylthio)succinimide and anisole as a useful precursor for an intramolecular C−H arylation to provide benzothiophene derivative **54** (used as a semiconductor). However, an inseparable mixture of **54** was observed, consistent with previously reported methodology.[59] On the other hand, with the scalable synthesis of diarylsulfide **13** (0.7 mmol, yield 78%), the synthesis of benzo[*a*]phenoxathiine **55** was exemplified through a copper-mediated C−O cross-coupling route in 67% yield.

Please cite this article in press as: Pramanik et al., B(C_6F_5)$_3$-catalyzed selective C–H chalcogenation of arenes and heteroarenes, Chem (2024), https://doi.org/10.1016/j.chempr.2024.05.025



Scheme 6. Synthetic manipulation of thioarylated products using a one-step synthetic route
All reactions were performed in 0.2 mmol scale.

Furthermore, the thioarylated product compounds were exposed to other post-synthetic transformations, including oxidation and traditional cross-coupling reactions, to derivatize the thioarylated products into other useful sulfur-containing compounds (Scheme 6). As an example, thioarylated compound **7** afforded the sulfoximine **56** through an O and NH transfer strategy, which could be useful for further *N*-functionalization to attain various synthetically valuable organic moieties.[60] Alternatively, addition of different quantities of *meta*-chloroperbenzoic acid (*m*CPBA) to compounds **1** and **30** led to sulfone **57** and sulfoxide **58**. Suzuki, Sonogashira, and Heck coupling reactions could also be performed on **30** to yield compounds **59**, **60**, and **61** with 88%, 85%, and 62% yield, respectively.

In summary, we have developed a metal-free C_{sp2}–H functionalization reaction of aromatic compounds using B(C_6F_5)$_3$ catalysis, which pave the way to high yielding, selective diarylchalcogenides as products when *N*-thio or *N*-selenoarylsuccinimides are used as chalcogenating agents. This methodology was broadly applicable to a range of commercially available arenes, heteroarenes, and pharmacophores, including those having other borane-sensitive functional groups. This newly developed protocol also presented a route toward the selective late-stage chalcogenation of drug derivatives such as naproxen and estradiol derivatives.

Please cite this article in press as: Pramanik et al., $B(C_6F_5)_3$-catalyzed selective C–H chalcogenation of arenes and heteroarenes, Chem (2024), https://doi.org/10.1016/j.chempr.2024.05.025

Furthermore, a facile and metal-free synthetic route to the key step in the synthesis of vortioxetine was realized along with the synthesis of other valuable heterocycles such as dibenzothiophene and benzo[a]phenoxathiine. Additionally, the post-synthetic modification of thioarylated products offered potential access toward various valuable organic motifs such as sulfoximines, sulfoxides, and sulfones as well as traditional C–C cross-coupled products. The insights from our mechanistic investigations suggest that $B(C_6F_5)_3$ induced N–S bond scission involves a class of ion pairs, with off-cycle radical pathways also accessible, which could be implemented in future work to advance the streamlined application of borane in catalysis and organic synthesis.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information should be directed to the lead contact, Rebecca Melen (melenr@cardiff.ac.uk).

Materials availability

All unique/stable materials generated in this study may be made available on request, but we may require a payment and/or a completed materials transfer agreement if there is potential for commercial application.

Data and code availability

All data sets generated within this study are available in the supplemental information. Information about the data that underpins the results presented in this article, including how to access them, can be found at http://doi.org/10.17035/d.2024.0312078537.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.chempr.2024.05.025.

ACKNOWLEDGMENTS

M.P. and R.L.M. would like to thank the Engineering and Physical Sciences Research Council (EPSRC) for funding (grant number: EP/R026912/1). S.D. would also like to thank EPSRC for funding (grant number: EP/W524682/1). S.P., E.R., and R.L.M. would like to thank the Leverhulme Trust for funding (grant number: RPG-2020-016). R.B., T.W., and R.L.M. would like to thank the Royal Society for an International Newton Fellowship (grant number: NIF/R1/21130) and the support of the Supercomputing Wales project, which is partially funded by the European Regional Development Fund (ERDF).

AUTHOR CONTRIBUTIONS

All the authors contributed intellectually to the manuscript and jointly wrote and edited the article. M.P. conceptualized the idea and carried out initial experiments. M.P., S.D., and S.P. performed the experiments and data analysis. E.R. performed EPR measurements and analyzed the data. R.B. performed DFT calculations. T.W., E.R., and R.L.M. supervised the project. R.B., T.W., E.R., and R.L.M. secured funding for the project. All authors have approved the final version of the manuscript.

DECLARATION OF INTERESTS

R.L.M. is a member of the journal's advisory board.

Received: March 14, 2024
Revised: May 2, 2024
Accepted: May 31, 2024
Published: June 27, 2024

REFERENCES

1. Lawson, J.R., and Melen, R.L. (2017). Tris(pentafluorophenyl)borane and Beyond: Modern Advances in Borylation Chemistry. Inorg. Chem. *56*, 8627–8643. https://doi.org/10.1021/acs.inorgchem.6b02911.

2. Kumar, G., Roy, S., and Chatterjee, I. (2021). Tris(pentafluorophenyl)borane catalyzed C–C and C–heteroatom bond formation. Org. Biomol. Chem. *19*, 1230–1267. https://doi.org/10.1039/D0OB02478C.

3. Ju, M., Lu, Z., Novaes, L.F.T., Martinez Alvarado, J.I., and Lin, S. (2023). Frustrated Radical Pairs in Organic Synthesis. J. Am. Chem. Soc. *145*, 19478–19489. https://doi.org/10.1021/jacs.3c07070.

4. Heard, M.J., Stefkova, K., van Ingen, Y., and Melen, R.L. (2022). 11.14 - Frustrated Lewis Pairs in Organic Synthesis. In Comprehensive Organometallic Chemistry IV, G. Parkin, K. Meyer, and D. O'Hare, eds. (Elsevier), pp. 563–605. https://doi.org/10.1016/B978-0-12-820206-7.00041-X.

5. Stephan, D.W. (2015). Frustrated Lewis Pairs: From Concept to Catalysis. Acc. Chem. Res. *48*, 306–316. https://doi.org/10.1021/ar500375j.

6. Stephan, D.W. (2016). The broadening reach of frustrated Lewis pair chemistry. Science *354*, aaf7229. https://doi.org/10.1126/science.aaf7229.

7. van der Zee, L.J.C., Pahar, S., Richards, E., Melen, R.L., and Slootweg, J.C. (2023). Insights into Single-Electron-Transfer Processes in Frustrated Lewis Pair Chemistry and Related Donor–Acceptor Systems in Main Group Chemistry. Chem. Rev. *123*, 9653–9675. https://doi.org/10.1021/acs.chemrev.3c00217.

8. Kiyokawa, K., Noguchi, I., Nagata, T., and Minakata, S. (2023). Tris(pentafluorophenyl) borane-Catalyzed Stereospecific Bromocyanation of Styrene Derivatives with Cyanogen Bromide. Org. Lett. *25*, 2537–2542. https://doi.org/10.1021/acs.orglett.3c00727.

9. Liu, M., Yang, X., Sun, Q., Wang, T., Pei, R., Yang, X., Zhao, Y., Zhao, L., Frenking, G., and Wang, X. (2023). Lewis Acid-Mediated Radical Stabilization and Dynamic Covalent Bonding: Tunable, Reversible and Photocontrollable. Angew. Chem. Int. Ed. Engl. *62*, e202300068. https://doi.org/10.1002/anie.202300068.

10. Basak, S., Winfrey, L., Kustiana, B.A., Melen, R.L., Morrill, L.C., and Pulis, A.P. (2021). Electron deficient borane-mediated hydride abstraction in amines: stoichiometric and catalytic processes. Chem. Soc. Rev. *50*, 3720–3737. https://doi.org/10.1039/D0CS00531B.

11. Köring, L., Stepen, A., Birenheide, B., Barth, S., Leskov, M., Schoch, R., Krämer, F., Breher, F., and Paradies, J. (2023). Boron-Centered Lewis Superacid through Redox-Active Ligands: Application in C−F and S−F Bond Activation. Angew. Chem. Int. Ed. Engl. *62*, e202216959. https://doi.org/10.1002/anie.202216959.

12. Mancinelli, J.P., Kong, W.-Y., Guo, W., Tantillo, D.J., and Wilkerson-Hill, S.M. (2023). Borane-Catalyzed C–F Bond Functionalization of gem-Difluorocyclopropenes Enables the Synthesis of Orphaned Cyclopropanes. J. Am. Chem. Soc. *145*, 17389–17397. https://doi.org/10.1021/jacs.3c05278.

13. Kiyokawa, K., Ishizuka, M., and Minakata, S. (2023). Stereospecific Oxycyanation of Alkenes with Sulfonyl Cyanide. Angew. Chem. Int. Ed. Engl. *62*, e202218743. https://doi.org/10.1002/anie.202218743.

14. Yu, Z., Li, Y., Shi, J., Ma, B., Liu, L., and Zhang, J. (2016). $(C_6F_5)_3B$ Catalyzed Chemoselective and ortho-Selective Substitution of Phenols with α-Aryl α-Diazoesters. Angew. Chem. Int. Ed. Engl. *55*, 14807–14811. https://doi.org/10.1002/anie.201608937.

15. Wang, G., Gao, L., Chen, H., Liu, X., Cao, J., Chen, S., Cheng, X., and Li, S. (2019). Chemoselective Borane-Catalyzed Hydroarylation of 1,3-Dienes with Phenols. Angew. Chem. Int. Ed. Engl. *58*, 1694–1699. https://doi.org/10.1002/anie.201811729.

16. Meng, S.-S., Tang, X., Luo, X., Wu, R., Zhao, J.-L., and Chan, A.S.C. (2019). Borane-Catalyzed Chemoselectivity-Controllable N-Alkylation and ortho C-Alkylation of Unprotected Arylamines Using Benzylic Alcohols. ACS Catal. *9*, 8397–8403. https://doi.org/10.1021/acscatal.9b03038.

17. Soltani, Y., Dasgupta, A., Gazis, T.A., Ould, D.M.C., Richards, E., Slater, B., Stefkova, K., Vladimirov, V.Y., Wilkins, L.C., Willcox, D., and Melen, R.L. (2020). Radical Reactivity of Frustrated Lewis Pairs with Diaryl Esters. Cell Reports Physical Science *1*, 100016. https://doi.org/10.1016/j.xcrp.2020.100016.

18. Dasgupta, A., Stefkova, K., Babaahmadi, R., Yates, B.F., Buurma, N.J., Ariafard, A., Richards, E., and Melen, R.L. (2021). Site-Selective C_{sp3}–C_{sp}/C_{sp3}–C_{sp2} Cross-Coupling Reactions Using Frustrated Lewis Pairs. J. Am. Chem. Soc. *143*, 4451–4464. https://doi.org/10.1021/jacs.1c01622.

19. Engman, L., Stern, D., Frisell, H., Vessman, K., Berglund, M., Ek, B., and Andersson, C.M. (1995). Synthesis, antioxidant properties, biological activity and molecular modelling of a series of chalcogen analogues of the 5-lipoxygenase inhibitor DuP 654. Bioorg. Med. Chem. *3*, 1255–1262. https://doi.org/10.1016/0968-0896(95)00111-S.

20. G.K. Ahluwalia, ed. (2017). Applications of Chalcogenides: S, Se, and Te (Springer International Publishing). https://doi.org/10.1007/978-3-319-41190-3.

21. Li, Q., Zhang, Y., Chen, Z., Pan, X., Zhang, Z., Zhu, J., and Zhu, X. (2020). Organoselenium chemistry-based polymer synthesis. Org. Chem. Front. *7*, 2815–2841. https://doi.org/10.1039/D0QO00640H.

22. Lenardão, E.J., Santi, C., Perin, G., and Alves, D. (2022). Organochalcogen Compounds, First Edition (Elsevier). https://shop.elsevier.com/books/organochalcogen-compounds/lenardao/978-0-12-819449-2.

23. Sinha, S.K., Panja, S., Grover, J., Hazra, P.S., Pandit, S., Bairagi, Y., Zhang, X., and Maiti, D. (2022). Dual Ligand Enabled Nondirected C–H Chalcogenation of Arenes and Heteroarenes. J. Am. Chem. Soc. *144*, 12032–12042. https://doi.org/10.1021/jacs.2c02126.

24. Xu, W., Wang, W., Liu, T., Xie, J., and Zhu, C. (2019). Late-stage trifluoromethylthiolation of benzylic C-H bonds. Nat. Commun. *10*, 4867. https://doi.org/10.1038/s41467-019-12844-9.

25. Feng, M., Tang, B., Liang, S.H., and Jiang, X. (2016). Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistry. Curr. Top. Med. Chem. *16*, 1200–1216. https://doi.org/10.2174/1568026615666150915111741.

26. Dykstra, K.D., Ichiishi, N., Krska, S.W., and Richardson, P.F. (2019). Emerging Fluorination Methods in Organic Chemistry Relevant for Life Science Application. In Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals Progress in Fluorine Science, *1*, G. Haufe and F.R. Leroux, eds. (Academic Press), pp. 1–90. https://doi.org/10.1016/B978-0-12-812733-9.00001-5.

27. (2014). Appendix - Vaccination Schedules for Dogs and Cats. In Canine and Feline Infectious Diseases, J.E. Sykes, ed. (W.B. Saunders), pp. 893–900. https://doi.org/10.1016/B978-1-4377-0795-3.15001-X.

28. Landelle, G., Panossian, A., and Leroux, F.R. (2014). Trifluoromethyl ethers and -thioethers as tools for medicinal chemistry and drug discovery. Curr. Top. Med. Chem. *14*, 941–951. https://doi.org/10.2174/1568026614666140202210016.

29. Eichman, C.C., and Stambuli, J.P. (2011). Transition Metal Catalyzed Synthesis of Aryl Sulfides. Molecules *16*, 590–608. https://doi.org/10.3390/molecules16010590.

30. Abedinifar, F., Bahadorikhalili, S., Larijani, B., Mahdavi, M., and Verpoort, F. (2022). A review on the latest progress of C-S cross-coupling in diaryl sulfide synthesis: Update from 2012 to 2021. Applied Organom. Chem. *36*, e6482. https://doi.org/10.1002/aoc.6482.

31. Sandfort, F., Knecht, T., Pinkert, T., Daniliuc, C.G., and Glorius, F. (2020). Site-Selective Thiolation of (Multi)halogenated Heteroarenes. J. Am. Chem. Soc. *142*, 6913–6919. https://doi.org/10.1021/jacs.0c01630.

32. Oderinde, M.S., Frenette, M., Robbins, D.W., Aquila, B., and Johannes, J.W. (2016). Photoredox Mediated Nickel Catalyzed Cross-Coupling of Thiols With Aryl and Heteroaryl Iodides via Thiyl Radicals. J. Am. Chem. Soc. *138*, 1760–1763. https://doi.org/10.1021/jacs.5b11244.

33. Liu, B., Lim, C.-H., and Miyake, G.M. (2017). Visible-Light-Promoted C–S Cross-Coupling via Intermolecular Charge Transfer. J. Am. Chem. Soc. *139*, 13616–13619. https://doi.org/10.1021/jacs.7b07390.

34. Zhong, S., Zhou, Z., Zhao, F., Mao, G., Deng, G.-J., and Huang, H. (2022). Deoxygenative C–S Bond Coupling with Sulfinates via Nickel/Photoredox Dual Catalysis. Org. Lett. *24*, 1865–1870. https://doi.org/10.1021/acs.orglett.2c00478.

35. Kibriya, G., Mondal, S., and Hajra, A. (2018). Visible-Light-Mediated Synthesis of Unsymmetrical Diaryl Sulfides via Oxidative Coupling of Arylhydrazine with Thiol. Org. Lett. *20*, 7740–7743. https://doi.org/10.1021/acs.orglett.8b03549.

36. Rahaman, R., Das, S., and Barman, P. (2018). Visible-light-induced regioselective sulfenylation of imidazopyridines with thiols under transition metal-free conditions. Green Chem. *20*, 141–147. https://doi.org/10.1039/C7GC02906C.

37. Mondal, S., Di Tommaso, E.M., and Olofsson, B. (2023). Transition-Metal-Free Difunctionalization of Sulfur Nucleophiles. Angew. Chem. Int. Ed. Engl. *62*, e202216296. https://doi.org/10.1002/anie.202216296.

38. Fernández-Salas, J.A., Pulis, A.P., and Procter, D.J. (2016). Metal-free C–H thioarylation of arenes using sulfoxides: a direct, general diaryl sulfide synthesis. Chem. Commun. (Camb) *52*, 12364–12367. https://doi.org/10.1039/C6CC07627K.

39. Zhao, F., Tan, Q., Wang, D., and Deng, G.-J. (2020). Metal- and solvent-free direct C–H thiolation of aromatic compounds with sulfonyl chlorides. Green Chem. *22*, 427–432. https://doi.org/10.1039/C9GC03384J.

40. Choudhuri, K., Maiti, S., and Mal, P. (2019). Iodine(III) Enabled Dehydrogenative Aryl C−S Coupling by in situ Generated Sulfenium. Adv. Synth. Catal. *361*, 1092–1101. https://doi.org/10.1002/adsc.201801510.

41. Yonova, I.M., Osborne, C.A., Morrissette, N.S., and Jarvo, E.R. (2014). Diaryl and Heteroaryl Sulfides: Synthesis via Sulfenyl Chlorides and Evaluation as Selective Anti-Breast-Cancer Agents. J. Org. Chem. *79*, 1947–1953. https://doi.org/10.1021/jo402586v.

42. Martins, G.M., Meirinho, A.G., Ahmed, N., Braga, A.L., and Mendes, S.R. (2019). Recent Advances in Electrochemical Chalcogen (S/Se)-Functionalization of Organic Molecules. ChemElectroChem *6*, 5928–5940. https://doi.org/10.1002/celc.201901525.

43. Prasad, Ch.D., Balkrishna, S.J., Kumar, A., Bhakuni, B.S., Shrimali, K., Biswas, S., and Kumar, S. (2013). Transition-Metal-Free Synthesis of Unsymmetrical Diaryl Chalcogenides from Arenes and Diaryl Dichalcogenides. J. Org. Chem. *78*, 1434–1443. https://doi.org/10.1021/jo302480j.

44. Wang, Y., Deng, J., Chen, J., Cao, F., Hou, Y., Yang, Y., Deng, X., Yang, J., Wu, L., Shao, X., et al. (2020). Dechalcogenization of Aryl Dichalcogenides to Synthesize Aryl Chalcogenides via Copper Catalysis. ACS Catal. *10*, 2707–2712. https://doi.org/10.1021/acscatal.9b04931.

45. Aramaki, Y., Imaizumi, N., Hotta, M., Kumagai, J., and Ooi, T. (2020). Exploiting single-electron transfer in Lewis pairs for catalytic bond-forming reactions. Chem. Sci. *11*, 4305–4311. https://doi.org/10.1039/D0SC01159B.

46. Chen, G.-Q., Kehr, G., Daniliuc, C.G., Bursch, M., Grimme, S., and Erker, G. (2017). Intermolecular Redox-Neutral Amine C−H Functionalization Induced by the Strong Boron Lewis Acid $B(C_6F_5)_3$ in the Frustrated Lewis Pair Regime. Chemistry *23*, 4723–4729. https://doi.org/10.1002/chem.201700477.

47. Nori, V., Dasgupta, A., Babaahmadi, R., Carlone, A., Ariafard, A., and Melen, R.L. (2020). Triarylborane catalysed N-alkylation of amines with aryl esters. Catal. Sci. Technol. *10*, 7523–7530. https://doi.org/10.1039/D0CY01339K.

48. Neto, J.S.S., Granja, I.J.A., Scheide, M.R., Franco, M.S., Moraes, C.A.O., Beatriz, A., de Lima, D.P., Botteselle, G.V., Frizon, T.E.A., Saba, S., et al. (2023). Catalyst- and metal-free C_{sp2}-H bond selenylation of (n-hetero)-arenes using diselenides and trichloroisocyanuric acid at room temperature. Sci. Rep. *13*, 14251. https://doi.org/10.1038/s41598-023-41430-9.

49. Zhao, Y., Mandal, D., Guo, J., Wu, Y., and Stephan, D.W. (2021). $B(C_6F_5)_3$-Catalyzed site-selective N1-alkylation of benzotriazoles with diazoalkanes. Chem. Commun. (Camb) *57*, 7758–7761. https://doi.org/10.1039/D1CC03048E.

50. Dos Santos, D.C., Rafique, J., Saba, S., Grinevicius, V.M.A.S., Filho, D.W., Zamoner, A., Braga, A.L., Pedrosa, R.C., and Ourique, F. (2022). IP-Se-06, a Selenylated Imidazo[1,2-a] pyridine, Modulates Intracellular Redox State and Causes Akt/mTOR/HIF-1α and MAPK Signaling Inhibition, Promoting Antiproliferative Effect and Apoptosis in Glioblastoma Cells. Oxid. Med. Cell. Longev. *2022*, 3710449. https://doi.org/10.1155/2022/3710449.

51. Veloso, I.C., Delanogare, E., Machado, A.E., Braga, S.P., Rosa, G.K., De Bem, A.F., Rafique, J., Saba, S., da Trindade, R.N., Galetto, F.Z., and Moreira, E.L.G. (2021). A selanylimidazopyridine (3-SePh-IP) reverses the prodepressant- and anxiogenic-like effects of a high-fat/high-fructose diet in mice. J. Pharm. Pharmacol. *73*, 673–681. https://doi.org/10.1093/jpp/rgaa070.

52. He, F., and Koenigs, R.M. (2021). Borane-Catalyzed Carbazolation Reactions of Aryldiazoacetates. Org. Lett. *23*, 5831–5835. https://doi.org/10.1021/acs.orglett.1c01982.

53. Wang, D., Carlton, C.G., Tayu, M., McDouall, J.J.W., Perry, G.J.P., and Procter, D.J. (2020). Trifluoromethyl Sulfoxides: Reagents for Metal-Free C−H Trifluoromethylthiolation. Angew. Chem. Int. Ed. Engl. *59*, 15918–15922. https://doi.org/10.1002/anie.202005531.

54. Pramanik, M., Guerzoni, M.G., Richards, E., and Melen, R.L. (2024). Recent Advances in Asymmetric Catalysis Using p-Block Elements. Angew. Chem. Int. Ed. Engl. *63*, e202316461. https://doi.org/10.1002/anie.202316461.

55. Mile, B., Rowlands, C.C., Sillman, P.D., and Fildes, M. (1992). The EPR spectra of thiyl radical spin adducts produced by photolysis of disulfides in the presence of 2,4,6-tri-tert-butylnitrosobenzene and 5,5-dimethyl-1-pyrroline N-oxide. J. Chem. Soc. Perkin Trans *2*, 1431–1437. https://doi.org/10.1039/P29920001431.

56. Symons, M.C.R. (1974). On the electron spin resonance detection of RS radicals in irradiated solids: radicals of type $RSSR^-$, $RS–SR_2$, and $R_2SSR_2^+$. J. Chem. Soc. Perkin Trans *2*, 1618–1620. https://doi.org/10.1039/P29740001618.

57. Türkyilmaz, F., Kehr, G., Li, J., Daniliuc, C.G., Tesch, M., Studer, A., and Erker, G. (2016). Selective N,O-Addition of the TEMPO Radical to Conjugated Boryldienes. Angew. Chem. Int. Ed. Engl. *55*, 1470–1473. https://doi.org/10.1002/anie.201509114.

58. Qu, Z.-W., Zhu, H., and Grimme, S. (2024). Reactivity of Frustrated Lewis Pair: Carbocation versus Radical Intermediates. Chemistry *30*, e202303901. https://doi.org/10.1002/chem.202303901.

59. Saravanan, P., and Anbarasan, P. (2014). Palladium Catalyzed Aryl(alkyl)thiolation of Unactivated Arenes. Org. Lett. *16*, 848–851. https://doi.org/10.1021/ol4036209.

60. Andresini, M., Tota, A., Degennaro, L., Bull, J.A., and Luisi, R. (2021). Synthesis and Transformations of NH-Sulfoximines. Chemistry *27*, 17293–17321. https://doi.org/10.1002/chem.202102619.