

Communication

Nucleophilic aromatic substitution of polyfluoroarene to access highly functionalized 10-phenylphenothiazine derivatives

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Abstract: Nucleophilic aromatic substitution (S_NAr) reactions can provide metal-free access to synthesize mono-substituted aromatic compounds. We have developed efficient S_NAr conditions for *p*-selective substitution of polyfluoroarenes with phenothiazine in the presence of a mild base to afford the corresponding 10-phenylphenothiazine (PTH) derivatives. The resulting polyfluoroarene-bearing PTH derivatives were subjected to a second S_NAr reaction to generate highly functionalized PTH derivatives with potential applicability as photocatalysts for the reduction of carbon–halogen bonds.

Keywords: polyfluoroarene; phenothiazine; nucleophilic aromatic substitution; amination; photocatalyst

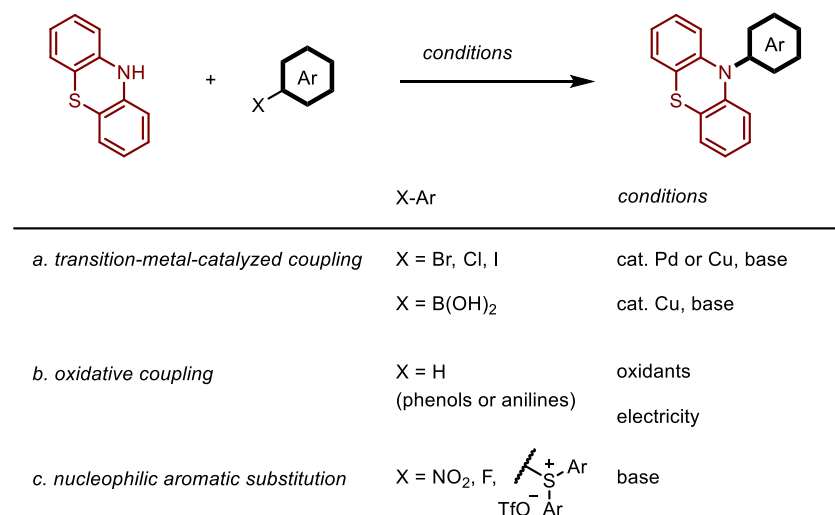
1. Introduction

Owing to the high electronegativity of fluorine atoms, polyfluoroarenes can undergo nucleophilic aromatic substitution (S_NAr) [1], wherein nucleophiles attack the low-electron-density arene core, and the fluoride anion is eliminated as a fluoride salt. Although transition-metal-catalyzed C-F and C-H bond functionalization of polyfluoroarenes has advanced considerably in recent years [2–6], S_NAr of polyfluoroarenes offers a transition-metal-free approach to substituted polyfluoroarenes. Polyfluoroarenes react with organometallic compounds, such as organolithium or organomagnesium reagents, to convert aromatic C-F bonds into C-C bonds without the use of transition metal catalysts [7,8]. The combination of a fluoride salt and organosilane compounds as nucleophiles has also been successful in the S_NAr of polyfluoroarenes, wherein the reaction proceeds with a catalytic amount of a fluoride anion [9–13]. The use of alcohols or amines as nucleophiles enables C-O and C-N bond formation to produce the corresponding aryl ether and aniline derivatives [8,14,15].

Functionalized arenes, such as arylamine derivatives, can be synthesized via transition-metal-catalyzed cross-coupling reactions [16–21]. However, the high cost of organometallic catalysts and contamination of the resulting products with metal traces represent major drawbacks of such methods. Alternative methods for transition-metal-free synthesis of arylamine derivatives have been achieved using hypervalent iodine reagents [22–27], sulfonium reagents [28], or electrochemical conditions [29]. The S_NAr reaction also offers an alternative method without the use of transition metals, which is therefore potentially applicable in the facile synthesis of organic functional materials containing substituted arenes. For instance, 1,2,3,5-tetrakis(carbazolyl)-4,6-dicyanobenzene (4CzIPN), an organic photocatalyst, has been produced by multiple S_NAr reactions using carbazole and 1,3-dicyano-2,4,5,6-tetrafluorobenzene with NaH as the base [30]. In this context, we focused on the application of a sequential and controllable S_NAr reaction for the synthesis of 10-phenylphenothiazine (PTH) derivatives, which serve as organic photocatalysts that

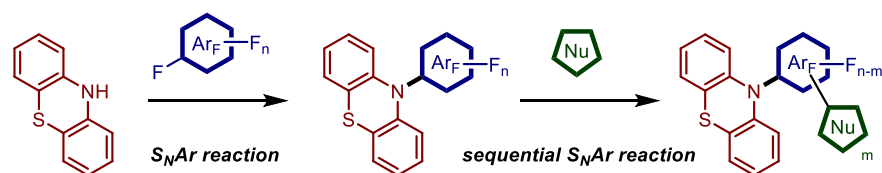
induce dehalogenative bond formation via processes such as atom transfer radical polymerization [31–41].

PTH derivatives are generally prepared via palladium- or copper-catalyzed coupling reactions of phenothiazine with aryl halides or arylboronic acids (Scheme 1a) [31–47]. Transition-metal-free methods for the synthesis of PTH derivatives include oxidative C-H amination in the presence of oxidants [48–52] or under electrolytic conditions [53,54], although starting materials are limited to phenols and anilines (Scheme 1b). In addition, S_NAr of triphenylsulfonium salts, nitroarenes, and fluoroarenes with phenothiazine have been demonstrated for the preparation of PTH derivatives (Scheme 1c) [28,55–62].



Scheme 1. Access to PTH derivatives under various conditions.

We envisioned that a reaction between phenothiazine and polyfluoroarenes would afford the corresponding polyfluoroarene-bearing PTH derivatives, which would then undergo a second S_NAr reaction for the introduction of other nucleophiles to afford highly functionalized PTH derivatives (Scheme 2). In addition to the synthetic utility of polyfluoroarenes, their introduction provides unique functionalities crucial in materials science, such as improvement of oxidation resistance, lowering of both HOMO and LUMO energy levels, and favorable stacking interactions with electron-rich aromatic rings [63–65]. However, S_NAr of polyfluoroarenes often suffers from uncontrollable substitution, resulting in a mixture of regioisomers and/or multi-substituted products. Therefore, it is necessary to establish appropriate conditions that suppress unselective substitution events and over-reactions, while being applicable to a wide range of polyfluoroarenes. Herein, we demonstrate S_NAr of various polyfluoroarenes resulting in mono-phenothiazination in the presence of an appropriate base to afford PTH derivatives bearing polyfluoroarenes, and further transformation of the resulting PTH derivatives to highly functionalized PTH derivatives via a second S_NAr reaction.

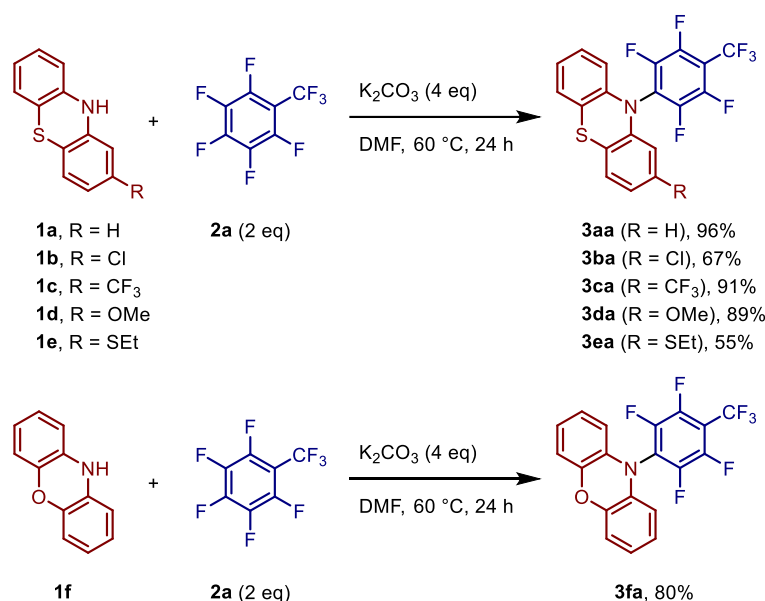


Scheme 2. Synthesis of highly functionalized PTH derivatives via sequential S_NAr reactions.

2. Results and Discussion

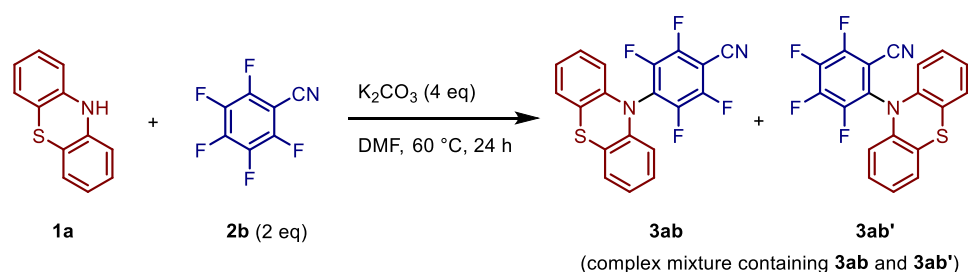
The reaction of phenothiazine with octafluorotoluene in the presence of K_2CO_3 in *N,N*-dimethylformamide (DMF) at 60 °C afforded the corresponding PTH derivative **3aa**

as the sole product in 96% yield (Scheme 3). The fluorine atom at the *p*-position of trifluoromethyl group of octafluorotoluene was substituted by phenothiazine, without the formation of regioisomers or multi-substituted products. The observed regioselectivity was in agreement with previously reported outcomes of octafluorotoluene S_NAr [11,13], and it is governed by the electron density at the reactive carbons (*ortho*- and *para*-positions) on the aromatic ring and the steric effect of the trifluoromethyl group. The K_2CO_3 /DMF system was found to be an efficient combination for mono S_NAr between various phenothiazines and octafluorotoluene (Scheme 3). For example, phenothiazine derivatives bearing electron-deficient and electron-donating groups (**1b–1e**) were employed in the present reaction to give the corresponding PTH derivatives (**3ba–3ea**). Moreover, phenoxazine derivative **3fa** was synthesized under similar conditions. Next, we examined various polyfluoroarenes for the S_NAr reaction with phenothiazine.



Scheme 3. S_NAr reaction of octafluorotoluene with phenothiazine derivatives or phenoxazine.

In contrast to octafluorotoluene, several other polyfluoroarenes exhibited decreased selectivities with the combination of K_2CO_3 and DMF, due to their inherently high reactivities, and the reaction of pentafluorobenzonitrile yielded complex mixtures including *p*- and *o*-substituted products, **3ab** and **3ab'**, respectively (Scheme 4). Pentafluoronitrobenzene provided similar results, undergoing uncontrollable S_NAr .

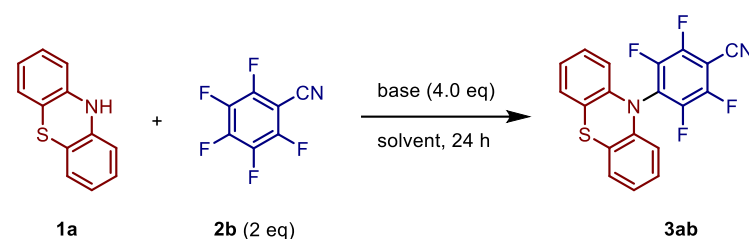


Scheme 4. Reaction of pentafluorobenzonitrile with phenothiazine using K_2CO_3 /DMF system.

Thus, optimization of the reaction conditions was performed for pentafluorobenzonitrile (**2b**) to suppress multiple substitution (Table 1). Using Li_2CO_3 or Na_2CO_3 instead of K_2CO_3 afforded the desired product **3ab** in low yield along with unreacted **2b** (entries 1 and 2). On the other hand, the use of Cs_2CO_3 led to high reactivity, and multiple substitutions occurred to give a complex mixture, which did not include **3ab** (entry 3). Inor-

ganic phosphate salts, such as Li_3PO_4 and Na_3PO_4 , exhibited comparable results to those of carbonate salts (entries 4 and 5). On the other hand, the use of K_3PO_4 improved the reaction yield of **3ab** to 48% (entry 6). The use of Na_3PO_4 or K_3PO_4 at an elevated reaction temperature of 80 °C resulted in lower yields compared to those attained under the conditions in entry 6 (entries 7 and 8). Next, we surveyed reaction solvents. In the case of acetonitrile (MeCN) at 60 °C, the reaction yield improved to 64% (entry 9). *N,N*-Dimethylacetamide (DMA) and dimethyl sulfoxide (DMSO) were also suitable, albeit providing slightly decreased yields (entries 10 and 11). Chloroform, tetrahydrofuran (THF), and 1,4-dioxane were found to be inappropriate solvents (entries 12–14).

Table 1. Optimization of reaction conditions using pentafluorobenzonitrile. ^a

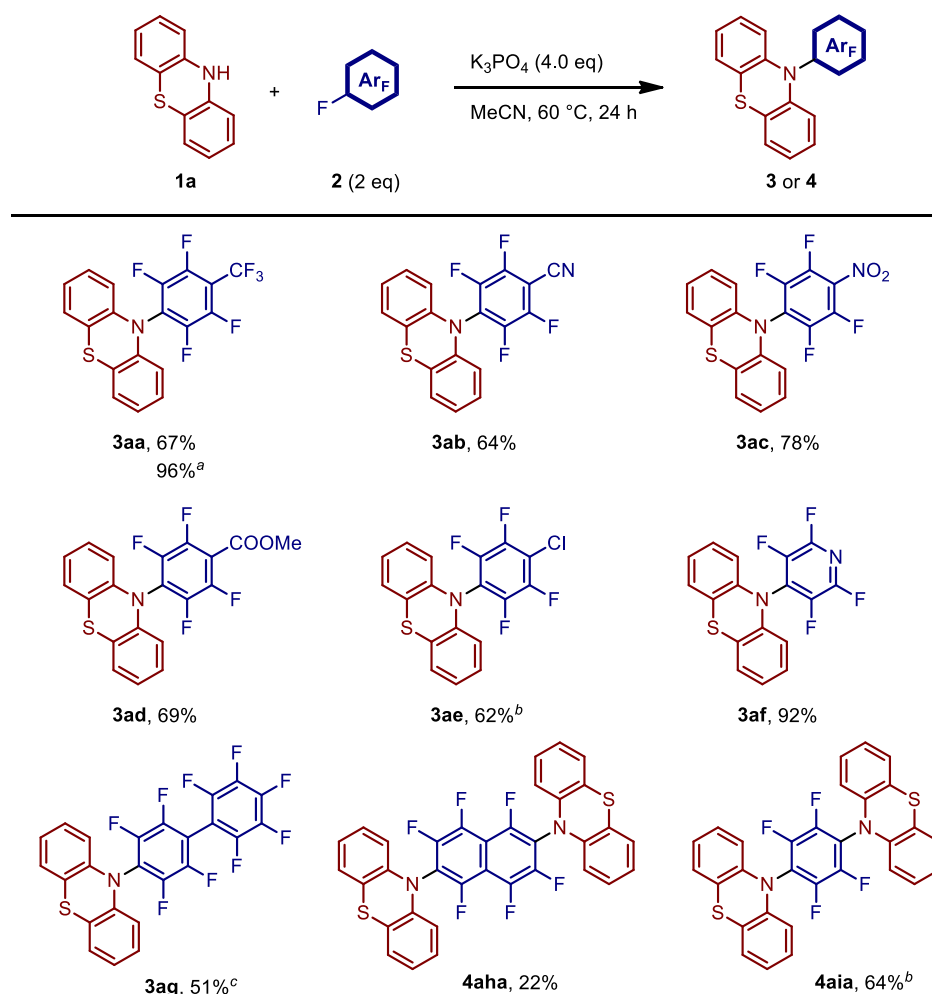


Entry	Base	Solvent	Temperature	Yield
1	Li_2CO_3	DMF	60 °C	0% ^b
2	Na_2CO_3	DMF	60 °C	7% ^b
3	Cs_2CO_3	DMF	60 °C	0% ^{b,c}
4	Li_3PO_4	DMF	60 °C	1% ^b
5	Na_3PO_4	DMF	60 °C	13% ^b
6	K_3PO_4	DMF	60 °C	48% ^d
7	Na_3PO_4	DMF	80 °C	32% ^d
8	K_3PO_4	DMF	80 °C	38% ^d
9	K_3PO_4	MeCN	60 °C	64% ^d
10	K_3PO_4	DMA	60 °C	43% ^d
11	K_3PO_4	DMSO	60 °C	38% ^d
12	K_3PO_4	CHCl_3	60 °C	0%
13	K_3PO_4	THF	60 °C	0%
14	K_3PO_4	1,4-dioxane	60 °C	0%

^a Reaction conditions: Phenothiazine **1a** (0.50 mmol), pentafluorobenzonitrile **2b** (1.0 mmol), and base (2.0 mmol) in solvent (5.0 mL, 0.1 M). ^b Determined by ^{19}F -NMR using 4-fluorotoluene as an internal standard. ^c Multiple substitutions were observed. ^d Isolated yield.

Next, various polyfluoroarenes were subjected to $\text{S}_\text{N}\text{Ar}$ with phenothiazine under the optimum conditions of K_3PO_4 in MeCN at 60 °C, as summarized in Scheme 5. Under these conditions, octafluorotoluene (**2a**) produced **3aa** in 67% yield, which was lower than that obtained with the use of K_2CO_3 and DMF. Pentafluoronitrobenzene (**2c**) also underwent $\text{S}_\text{N}\text{Ar}$ with high selectivity to afford *p*-substituted product **3ac** in 78% yield. Ester-bearing PTH derivative **3ad** was synthesized from methyl pentafluorobenzoate (**2d**) in 69% yield. Thus, the combination of K_3PO_4 and MeCN proved effective for achieving *p*-selective mono-substitution of a wide range of highly reactive polyfluoroarenes. Chloropentafluorobenzene (**2e**) underwent $\text{S}_\text{N}\text{Ar}$ using K_2CO_3 in DMSO at 85 °C to afford the corresponding product **3ae**, while the $\text{K}_3\text{PO}_4/\text{MeCN}$ system resulted in low reactivity. It should be noted that selective C–F bond functionalization occurred and the chlorine atom remained intact under these $\text{S}_\text{N}\text{Ar}$ conditions, allowing for further product transformation via transition-metal-catalyzed cross-coupling reactions. In contrast to results obtained with electron-deficient groups, methyl-substituted pentafluorobenzene did not furnish the desired product even under $\text{K}_2\text{CO}_3/\text{DMSO}$ con-

ditions. When pentafluoropyridine (**2f**) was employed as the substrate, the S_NAr reaction proceeded smoothly under K_3PO_4 /MeCN conditions to produce fluorinated pyridylphenothiazine **3af** in 92% yield. Simple polyfluoroarenes lacking other functional groups were also tested in the present S_NAr protocol. The reaction of decafluorobiphenyl (**2g**) afforded the corresponding mono-substituted product **3ag** in 51% yield, along with a trace amount of the di-substituted compound (**4aga**). On the other hand, octafluoronaphthalene (**2h**) underwent double substitution to give **4aha** in 22% yield, even with 2 equivalents of **2h**. Hexafluorobenzene (**2i**) exhibited low reactivity under the K_3PO_4 /MeCN system, as was the case with **2e**. The combination of K_2CO_3 and DMSO at 85 °C led to double substitution of **2i** affording **4aia** in 64% yield. In this case, **2i** exists in the vapor phase as a result of its low boiling point (bp: ca. 80 °C); therefore, once the first S_NAr reaction occurs, the second is favored due to the mono-substituted product being in solution while the bulk of **2i** remains in the vapor phase.

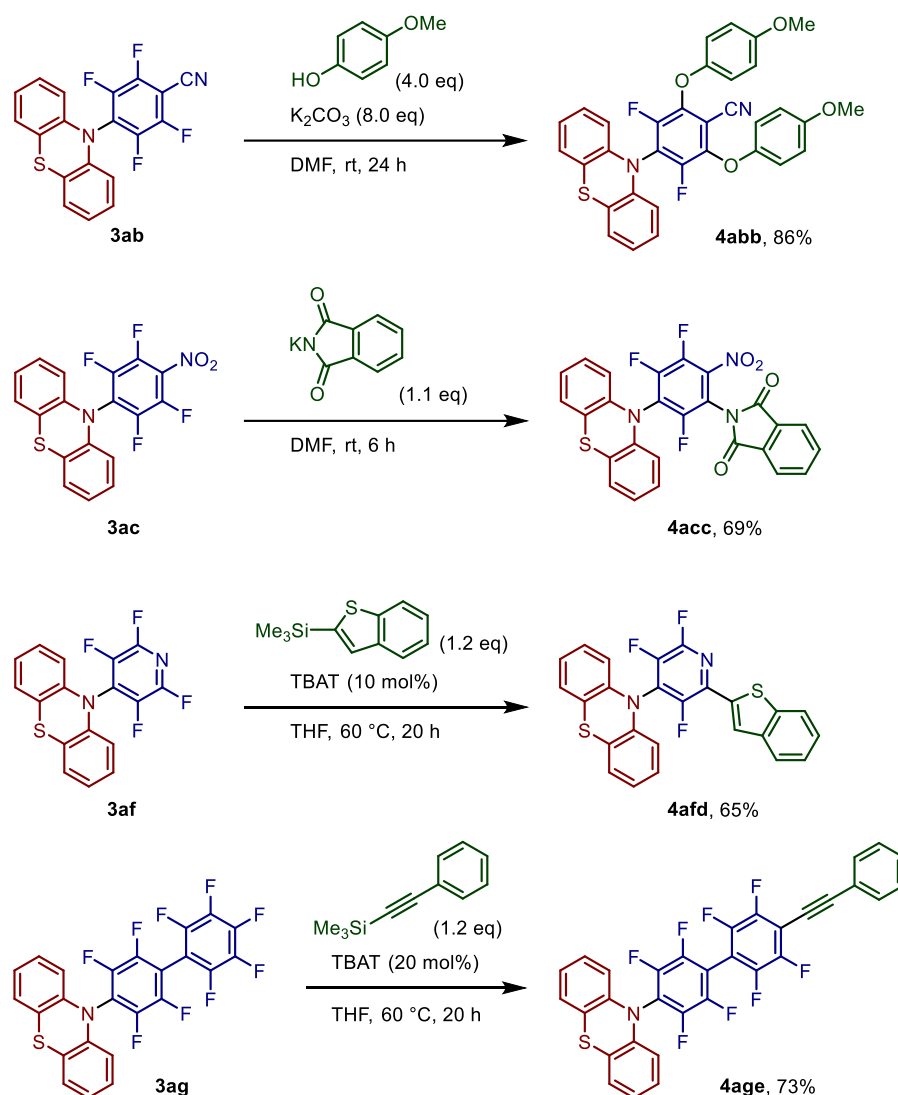


^a Conducted with K_2CO_3 in DMF at 60 °C. ^b Conducted with K_2CO_3 in DMSO at 85 °C. ^c Along with trace amounts of di-substituted product **4aga**.

Scheme 5. S_NAr reaction of phenothiazine with various polyfluoroarenes.

Next, further transformations of obtained PTH derivatives **3** were performed (Scheme 6). Thus, S_NAr of **3ab** with *p*-methoxyphenol proceeded in the presence of K_2CO_3 to afford PTH derivative **4abb**, bearing both cyano and phenoxy groups. Phthalimide, commonly used as a protecting group and photosensitizer, was also introduced onto **3ac** via further S_NAr to obtain multi-functionalized **4acc**. Transition-metal-free carbon-carbon bond formation was also examined using a combination of organosilanes and a catalytic amount of $Bu_4NSiF_2Ph_3$ (TBAT). Thiophene moieties, ubiquitous in functional organic

materials owing to their high electron density, can be introduced onto **3af** via the reaction with thienyl silane and TBAT to afford diheteroaromatic **4afd**. Similarly, ethynylsilane participated in the carbon–carbon bond forming reaction with **3ag** to produce linear analog **4age**. Hence, PTH derivatives bearing various functional groups, connected through C–O, C–N, and C–C bonds, were synthesized via sequential S_NAr of polyfluoroarenes under transition-metal-free conditions.



Scheme 6. Synthesis of highly functionalized PTH derivatives via S_NAr .

3. Materials and Methods

3.1. General Information

¹H, ¹³C, and ¹⁹F nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JMN-400 spectrometer at 25 °C unless otherwise noted. The data are reported as follows: chemical shift in part per million (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constant (Hz). The chemical shifts in the ¹H NMR spectra were recorded relative to the residual solvent peaks (CDCl₃: δ 7.26). The chemical shifts in the ¹³C NMR spectrum were also recorded relative to the residual solvent peaks (CDCl₃: δ 77.0). The chemical shifts in the ¹⁹F NMR spectrum were recorded relative to that of the internal standard (4-fluorotoluene: δ -121.0). High-resolution mass spectra (HRMS) were obtained using a Thermo Scientific Exactive Plus Orbitrap (Thermo

Fisher Scientific, Inc., Waltham, MA, USA). All commercially available reagents were used as received unless otherwise noted.

3.2. *S_NAr* Reaction of Phenothiazines with Polyfluoroarenes

3.2.1. General procedure A for the reaction of phenothiazines with polyfluoroarenes

Phenothiazine derivatives (1.0 mmol) and base (4.0 mmol, 4.0 eq) were placed in a screw-capped test tube and dried under vacuum for 1 h. After backfilling with N₂, solvent (10 mL) and polyfluoroarenes (2.1 mmol, 2.1 eq) were added in this order. The reaction mixture was stirred at 60 °C for 24 h. The reaction was quenched with water (50 mL), and the mixture was transferred to a separatory funnel containing diethyl ether (50 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic fractions were washed with brine (50 mL), dried over Na₂SO₄, and all volatiles were removed under vacuum. The residue was purified by flash column chromatography (SiO₂) to yield the corresponding 10-phenylphenothiazine (PTH) derivatives.

3.2.2. 10-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)-10H-phenothiazine (3aa)

The title compound was prepared according to General Procedure A with phenothiazine (**1a**, 200 mg, 1.0 mmol), octafluorotoluene (**2a**, 300 µL, 2.1 mmol, 2.1 eq), and K₂CO₃ (554 mg, 4.0 mmol, 4.0 eq) in DMF (10 mL). **3aa** was isolated by flash column chromatography (SiO₂, AcOEt/hexane = 1/100) in 96% yield (398 mg, 0.958 mmol) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃, rt, δ/ppm): 7.12 (dd, *J* = 7.3, 2.0 Hz, 2H), 6.93–7.02 (m, 4H), 6.26 (dd, *J* = 7.8, 1.5 Hz, 2H). ¹⁹F NMR (376 MHz, CDCl₃, rt, δ/ppm): -58.5 (t, *J* = 22.0 Hz, 3F), -140.5– -140.6 (m, 2F), -142.0– -142.1 (m, 2F). HRMS (DART) *m/z*: ([M+H]⁺) Calcd for C₁₉H₉F₇NS 416.0338; Found 416.0342.

3.2.3. 2-Chloro-10-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-10H-phenothiazine (3ba)

The title compound was prepared according to General Procedure A with 2-chloro-10H-phenothiazine (**1b**, 66.9 mg, 0.50 mmol), octafluorotoluene (**2a**, 150 µL, 1.05 mmol, 2.1 eq), and K₂CO₃ (277 mg, 2.0 mmol, 4.0 eq) in DMF (5 mL). **3ba** was isolated by flash column chromatography (SiO₂, AcOEt/hexane = 1/200) in 67% yield (150 mg, 0.334 mmol) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃, rt, δ/ppm): 7.11 (dd, *J* = 7.3, 2.0 Hz, 1H), 7.04–6.93 (m, 4H), 6.27–6.23 (m, 2H). ¹⁹F NMR (376 MHz, CDCl₃, rt, δ/ppm): -58.5 (t, *J* = 22.0 Hz, 3F), -140.4– -140.6 (m, 2F), -142.1– -142.2 (m, 2F). HRMS (DART) *m/z*: ([M+H]⁺) Calcd for C₁₉H₈ClF₇NS⁺ 449.9949; Found 449.9946.

3.2.4. 10-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)-2-(trifluoromethyl)-10H-phenothiazine (3ca)

The title compound was prepared according to General Procedure A with 2-(trifluoromethyl)-10H-phenothiazine (**1c**, 133.6 mg, 0.50 mmol), octafluorotoluene (**2a**, 150 µL, 1.05 mmol, 2.1 eq), and K₂CO₃ (277 mg, 2.0 mmol, 4.0 eq) in DMF (5 mL). **3ca** was isolated by flash column chromatography (SiO₂, AcOEt/hexane = 1/200) in 91% yield (220 mg, 0.455 mmol) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃, rt, δ/ppm): 7.21 (s, 2H), 7.13–7.10 (m, 1H), 7.06–6.98 (m, 2H), 6.43 (s, 1H), 6.27 (d, *J* = 7.3 Hz, 1H). ¹⁹F NMR (376 MHz, CDCl₃, rt, δ/ppm): -58.5 (t, *J* = 22.0 Hz, 3F), -65.1 (s, 3F), -139.6– -139.7 (m, 2F), -142.1– -142.2 (m, 2F). HRMS (DART) *m/z*: ([M+H]⁺) Calcd for C₂₀H₈F₁₀NS⁺ 484.0212; Found 484.0210.

3.2.5. 2-Methoxy-10-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-10H-phenothiazine (3da)

The title compound was prepared according to General Procedure A with 2-methoxy-10H-phenothiazine (**1d**, 114.6 mg, 0.50 mmol), octafluorotoluene (**2a**, 150 µL, 1.05 mmol, 2.1 eq), and K₂CO₃ (277 mg, 2.0 mmol, 4.0 eq) in DMF (5 mL). **3da** was isolated

by flash column chromatography (SiO₂, AcOEt/hexane = 1/150) in 89% yield (200 mg, 0.449 mmol) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃, rt, δ/ppm): 7.05 (dd, *J* = 7.8, 2.0 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.93–6.87 (m, 2H), 6.46 (d, *J* = 7.3 Hz, 1H), 6.20–6.17 (m, 1H), 5.79–5.77 (m, 1H), 3.64 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃, rt, δ/ppm): -58.5 (t, *J* = 22.0 Hz, 3F), -139.7– -140.0 (m, 2F), -142.1– -142.2 (m, 2F). HRMS (DART) *m/z*: ([M+H]⁺) Calcd for C₂₀H₁₁F₇NS⁺ 446.0444; Found 446.0447.

3.2.6. 2-(Ethylthio)-10-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-10H-phenothiazine (3ea)

The title compound was prepared according to General Procedure A with 2-ethylthio-10H-phenothiazine (**1e**, 129.7 mg, 0.50 mmol), octafluorotoluene (**2a**, 150 μL, 1.05 mmol, 2.1 eq), and K₂CO₃ (277 mg, 2.0 mmol, 4.0 eq) in DMF (5 mL). **3ea** was isolated by flash column chromatography (SiO₂, AcOEt/hexane = 1/100) in 55% yield (130 mg, 0.273 mmol) as a yellow oil. ¹H NMR (400 MHz, CDCl₃, rt, δ/ppm): 7.10–7.08 (m, 1H), 7.03–6.91 (m, 4H), 6.25–6.21 (m, 2H), 2.81 (q, *J* = 7.3 Hz, 2H), 1.23 (t, *J* = 7.3 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃, rt, δ/ppm): -58.5 (t, *J* = 19.5 Hz, 3F), -140.2– -140.4 (m, 2F), -142.1– -142.2 (m, 2F). HRMS (DART) *m/z*: ([M+H]⁺) Calcd for C₂₁H₁₃F₇NS₂⁺ 476.0372; Found 476.0371.

3.2.7. 10-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)-10H-phenoxazine (3fa)

The title compound was prepared according to General Procedure A with 10H-phenoxazine (**1f**, 91.6 mg, 0.50 mmol), octafluorotoluene (**2a**, 150 μL, 1.05 mmol, 2.1 eq), and K₂CO₃ (277 mg, 2.0 mmol, 4.0 eq) in DMF (5 mL). **3fa** was isolated by flash column chromatography (SiO₂, AcOEt/hexane = 1/100) in 80% yield (160 mg, 0.400 mmol) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃, rt, δ/ppm): 6.82–6.78 (m, 4H), 6.75–6.69 (m, 2H), 6.00 (dd, *J* = 7.3, 1.5 Hz, 2H). ¹⁹F NMR (376 MHz, CDCl₃, rt, δ/ppm): -58.5 (t, *J* = 22.0 Hz, 3F), -140.3– -140.5 (m, 2F), -142.0– -142.1 (m, 2F). HRMS (DART) *m/z*: ([M+H]⁺) Calcd for C₁₉H₉F₇ON⁺ 400.0567; Found 400.0565.

3.2.8. 2,3,5,6-Tetrafluoro-4-(10H-phenothiazin-10-yl)benzonitrile (3ab)

The title compound was prepared according to General Procedure A with phenothiazine (**1a**, 100 mg, 0.50 mmol), pentafluorobenzonitrile (**2b**, 128 μL, 1.0 mmol, 2.0 eq), and K₃PO₄ (424.5 mg, 2.0 mmol, 4.0 eq) in MeCN (5 mL). **3ab** was isolated by flash column chromatography (SiO₂, AcOEt/hexane = 1/40) in 64% yield (120 mg, 0.322 mmol) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃, rt, δ/ppm): 7.13 (dd, *J* = 7.3, 2.0 Hz, 2H), 7.08–6.95 (m, 4H), 6.27 (dd, *J* = 7.8, 1.5 Hz, 2H). ¹⁹F NMR (376 MHz, CDCl₃, rt, δ/ppm): -132.4– -132.5 (m, 2F), -140.6– -140.7 (m, 2F). HRMS (DART) *m/z*: ([M+H]⁺) Calcd for C₁₉H₉F₄N₂S 373.0417; Found 373.0415.

3.2.9. 10-(2,3,5,6-Tetrafluoro-4-nitrophenyl)-10H-phenothiazine (3ac)

The title compound was prepared according to General Procedure A with phenothiazine (**1a**, 399 mg, 2.0 mmol), pentafluoronitrobenzene (**2c**, 496 μL, 4.0 mmol, 2.0 eq), and K₃PO₄ (1.70 g, 8.0 mmol, 4.0 eq) in MeCN (20 mL). **3ac** was isolated by flash column chromatography (SiO₂, hexane) in 78% yield (613 mg, 1.56 mmol) as an orange solid. ¹H NMR (400 MHz, CDCl₃, rt, δ/ppm): 7.11 (dd, *J* = 7.3, 1.5 Hz, 2H), 7.02–6.94 (m, 4H), 6.26 (dd, *J* = 7.3, 1.5 Hz, 2H). ¹⁹F NMR (376 MHz, CDCl₃, rt, δ/ppm): -140.1– -140.1 (m, 2F), -146.9– -146.9 (m, 2F). HRMS (DART) *m/z*: ([M+H]⁺) Calcd for C₁₈H₉F₄N₂O₂S⁺ 393.0315; Found 393.0317.

3.2.10. Methyl 2,3,5,6-tetrafluoro-4-(10H-phenothiazin-10-yl)benzoate (3ad)

The title compound was prepared according to General Procedure A with phenothiazine (**1a**, 100 mg, 0.50 mmol), methyl pentafluorobenzoate (**2d**, 146 μL, 1.0 mmol, 2.0 eq), and K₃PO₄ (424.5 mg, 2.0 mmol, 4.0 eq) in MeCN (5 mL). **3ad** was isolated by flash column chromatography (SiO₂, AcOEt/hexane = 1/200) in 69% yield (140 mg, 0.345 mmol)

as a pale yellow solid. ^1H NMR (400 MHz, CDCl_3 , rt, δ/ppm): 7.10 (dd, $J = 7.3, 1.5$ Hz, 2H), 7.00–6.91 (m, 4H), 6.25 (dd, $J = 7.8, 1.0$ Hz, 2H), 4.05 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3 , rt, δ/ppm): -140.2– -140.3 (m, 2F), -139.7– -139.8 (m, 2F). HRMS (DART) m/z : ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{20}\text{H}_{12}\text{F}_4\text{NO}_2\text{S}^+$ 406.0519; Found 406.0520.

3.2.11. 10-(4-Chloro-2,3,5,6-tetrafluorophenyl)-10H-phenothiazine (3ae)

The title compound was prepared according to General Procedure A with phenothiazine (**1a**, 100 mg, 0.50 mmol), chloropentafluorobenzene (**2e**, 129 μL , 1.0 mmol, 2.0 eq), and K_2CO_3 (277 mg, 2.0 mmol, 4.0 eq) in DMSO (5 mL) at 80 $^\circ\text{C}$. **3ae** was isolated by flash column chromatography (SiO_2 , AcOEt/hexane = 1/200) in 62% yield (118 mg, 0.309 mmol) as a pale yellow solid. ^1H NMR (400 MHz, CDCl_3 , rt, δ/ppm): 7.09 (dd, $J = 7.3, 1.5$ Hz, 2H), 7.00–6.91 (m, 4H), 6.26 (dd, $J = 7.8, 1.5$ Hz, 2H). ^{19}F NMR (376 MHz, CDCl_3 , rt, δ/ppm): -141.0– -141.0 (m, 2F), -143.8– -143.8 (m, 2F). HRMS (DART) m/z : ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{18}\text{H}_9\text{ClF}_4\text{NS}^+$ 382.0075; Found 382.0075.

3.2.12. 10-(Perfluoropyridin-4-yl)-10H-phenothiazine (3af)

The title compound was prepared according to General Procedure A with phenothiazine (**1a**, 399 mg, 2.0 mmol), pentafluoropyridine (**2f**, 430 μL , 4.0 mmol, 2.0 eq), and K_3PO_4 (1.70 g, 8.0 mmol, 4.0 eq) in MeCN (20 mL). **3af** was isolated by flash column chromatography (SiO_2 , AcOEt/hexane = 1/50) in 92% yield (640 mg, 1.84 mmol) as a pale yellow solid. ^1H NMR (400 MHz, CDCl_3 , rt, δ/ppm): 7.06 (dd, $J = 6.8, 1.5$ Hz, 2H), 7.04–6.94 (m, 4H), 6.34 (d, $J = 7.8$ Hz, 2H). ^{19}F NMR (376 MHz, CDCl_3 , rt, δ/ppm): -88.9– -89.0 (m, 2F), -144.5– -144.7 (m, 2F). HRMS (DART) m/z : ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{17}\text{H}_9\text{F}_4\text{N}_2\text{S}^+$ 349.0417; Found 349.0420.

3.2.13. 10-(Perfluoro-[1,1'-biphenyl]-4-yl)-10H-phenothiazine (3ag)

The title compound was prepared according to General Procedure A with phenothiazine (**1a**, 100 mg, 0.50 mmol), decafluorobiphenyl (**2g**, 334 mg, 1.0 mmol, 2.0 eq), and K_3PO_4 (424.5 mg, 2.0 mmol, 4.0 eq) in MeCN (5 mL). **3ag** was isolated by flash column chromatography (SiO_2 , AcOEt/hexane = 1/100) in 51% yield (130 mg, 0.253 mmol) as a pale yellow solid. ^1H NMR (400 MHz, CDCl_3 , rt, δ/ppm): 7.10 (dd, $J = 7.8, 1.5$ Hz, 2H), 7.03–6.92 (m, 4H), 6.33 (d, $J = 7.8$ Hz, 2H). ^{19}F NMR (376 MHz, CDCl_3 , rt, δ/ppm): -138.4– -138.4 (m, 2F), -139.1– -139.2 (m, 2F), -143.4– -143.5 (m, 1F), -151.4– -151.6 (m, 2F), -162.2– -162.3 (m, 2F). HRMS (DART) m/z : ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{24}\text{H}_9\text{F}_9\text{NS}^+$ 514.0307; Found 514.0303.

3.2.14. 10,10'-(Perfluoronaphthalene-2,6-diyl)bis(10H-phenothiazine) (4aha)

The title compound was prepared according to General Procedure A with phenothiazine (**1a**, 100 mg, 0.50 mmol), octafluoronaphthalene (**2h**, 270 mg, 1.0 mmol, 2.0 eq), and K_3PO_4 (424.5 mg, 2.0 mmol, 4.0 eq) in MeCN (5 mL). **4aha** was isolated by flash column chromatography (SiO_2 , AcOEt/hexane = 1/10) in 22% yield (70 mg, 0.111 mmol) as a pale yellow solid. ^1H NMR (400 MHz, CDCl_3 , rt, δ/ppm): 7.12 (dd, $J = 7.8, 1.5$ Hz, 2H), 6.99–6.96 (m, 4H), 6.32 (d, $J = 7.8$ Hz, 2H). ^{19}F NMR (376 MHz, CDCl_3 , rt, δ/ppm): -123.5– -123.8 (m, 2F), -140.9– -140.9 (m, 2F), -144.5– -144.8 (m, 2F). HRMS (DART) m/z : ($[\text{M}+\text{H}]^+$) Calcd for $\text{C}_{34}\text{H}_{17}\text{F}_8\text{N}_2\text{S}_2^+$ 631.0732; Found 631.0733.

3.2.15. 10,10'-(Perfluoro-1,4-phenylene)bis(10H-phenothiazine) (4aia)

The title compound was prepared according to General Procedure A with phenothiazine (**1a**, 100 mg, 0.50 mmol), hexafluorobenzene (**2i**, 177 μL , 1.0 mmol, 2.0 eq), and K_2CO_3 (277 mg, 2.0 mmol, 4.0 eq) in DMSO (5 mL) at 80 $^\circ\text{C}$. **4aia** was isolated by flash column chromatography (SiO_2 , AcOEt/hexane = 1/50) in 64% yield (174 mg, 0.320 mmol) as a pale yellow solid. ^1H NMR (400 MHz, CDCl_3 , rt, δ/ppm): 7.14 (dd, $J = 7.3, 1.5$ Hz, 2H), 7.06–6.98 (m, 4H), 6.39 (d, $J = 8.3$ Hz, 2H). ^{19}F NMR (376 MHz, CDCl_3 , rt, δ/ppm):

-143.0 (s, 2F). HRMS (DART) m/z : $([M+H]^+)$ Calcd for $C_{30}H_{17}F_4N_2S_2^+$ 545.0764; Found 545.0766.

3.3. Sequential S_NAr reaction with **3ab**, **3ac**, **3af**, and **3ag**

3.3.1.3,5-Difluoro-2,6-bis(4-methoxyphenoxy)-4-(10H-phenothiazin-10-yl)benzonitrile (**4abb**)

Phenothiazine derivative **3ab** (0.10 mmol), 4-methoxyphenol (0.40 mmol, 4.0 eq), and K_2CO_3 (0.80 mmol, 8.0 eq) were placed in a screw-capped test tube and dried under vacuum for 1 h. After backfilling with N_2 , DMF (1.5 mL) was added to the test tube. The reaction mixture was stored at room temperature for 24 h. The reaction was quenched with water (20 mL) and the mixture was transferred to a separatory funnel containing diethyl ether (20 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2×20 mL). The combined organic fractions were washed with brine (20 mL), dried over Na_2SO_4 , and all volatiles were removed under vacuum. **4abb** was isolated by flash column chromatography (SiO_2 , AcOEt/hexane = 1/10) in 86% yield (50 mg, 0.0862 mmol) as a pale yellow solid. 1H NMR (400 MHz, $CDCl_3$, rt, δ /ppm): 7.06–7.03 (m, 2H), 6.99–6.83 (m, 12H), 6.20 (d, J = 6.8 Hz, 2H), 3.77 (s, 6H). ^{19}F NMR (376 MHz, $CDCl_3$, rt, δ /ppm): -132.2 (s, 2F). HRMS (DART) m/z : $([M+H]^+)$ Calcd for $C_{33}H_{23}F_2N_2S^+$ 581.1341; Found 581.1342.

3.3.2. 2-(2,4,5-Trifluoro-6-nitro-3-(10H-phenothiazin-10-yl)phenyl)isoindoline-1,3-dione (**4acc**)

In a well-dried screw-capped test tube, **3ac** (78.5 mg, 0.20 mmol) was dissolved in DMF. Phthalimide (40.7 mg, 0.22 mmol, 1.1 eq) was added to the mixture and the test tube was sealed with a cap, and the reaction mixture was stirred at 60 °C for 20 h. The reaction was quenched with water (20 mL) and the mixture was then transferred to a separatory funnel with diethyl ether (20 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2×10 mL). The combined organic fractions were washed with brine (20 mL) and then dried over Na_2SO_4 , and all the volatiles were removed under vacuum. **4acc** was isolated by flash column chromatography (SiO_2 , AcOEt/hexane = 1/10) in 69% yield (72.3 mg, 0.139 mmol) as a white solid. 1H NMR (400 MHz, $CDCl_3$, rt, δ /ppm): 8.00 (dd, J = 5.4, 2.9 Hz, 2H), 7.87 (dd, 5.9, 2.9 Hz, 2H), 7.12 (dd, J = 7.3, 1.5 Hz, 2H), 7.06 (dt, J = 7.8, 1.5 Hz, 2H), 6.98 (t, J = 7.6 Hz, 2H), 6.39 (d, J = 7.3 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, rt, δ /ppm): -120.6– -120.7 (m, 1F), -131.0– -131.1 (m, 1F), -144.8– -144.9 (m, 1F). HRMS (DART) m/z : $([M+H]^+)$ Calcd for $C_{26}H_{13}F_3O_4N_3S^+$ 520.0573; Found 520.0572.

3.2.3. 10-(2-(Benzo[b]thiophen-2-yl)-3,5,6-trifluoropyridin-4-yl)-10H-phenothiazine (**4afd**)

In a well-dried screw-capped test tube, tetrabutylammonium difluorotriphenylsilicate (TBAT, 5.4 mg, 0.01 mmol, 20 mol%) and **3af** (34.8 mg, 0.10 mmol) were added and dried under vacuum for 1 h. After backfilling with N_2 , THF (1.0 mL) and benzo[b]thiophen-2-yltrimethylsilane (24.8 mg, 0.12 mmol, 1.2 eq) were added to the mixture in this order. The test tube was sealed with a cap, and the reaction mixture was stirred at 60 °C for 20 h. The reaction was quenched with water (20 mL) and the mixture was then transferred to a separatory funnel with AcOEt (20 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt (2×10 mL). The combined organic fractions were washed with brine (20 mL) and then dried over Na_2SO_4 , and all the volatiles were removed under vacuum. **4afd** was isolated by flash column chromatography (SiO_2 , AcOEt/hexane = 1/30) in 65% yield (30.0 mg, 0.0649 mmol) as a white solid. 1H NMR (400 MHz, $CDCl_3$, rt, δ /ppm): 8.07 (s, 1H), 7.95–7.82 (m, 2H), 7.43–7.37 (m, 2H), 7.14 (dd, J = 7.3, 1.5 Hz, 2H), 7.03–6.95 (m, 4H), 6.39 (d, J = 7.8 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, rt, δ /ppm): -85.5– -85.6 (m, 1F), -126.9– -126.9 (m, 1F), -141.8– -141.9 (m, 1F). HRMS (DART) m/z : $([M+H]^+)$ Calcd for $C_{25}H_{14}F_3N_2S_2^+$ 463.0545; Found 463.0544.

3.2.4. 10-(2,2',3,3',5,5',6,6'-octafluoro-4'-(phenylethynyl)-[1,1'-biphenyl]-4-yl)-10H-phenothiazine (4age)

In a well-dried screw-capped test tube, tetrabutylammonium difluorotriphenylsilicate (TBAT, 10.8 mg, 0.02 mmol, 20 mol%) and **3ag** (51.3 mg, 0.10 mmol) were added and dried under vacuum for 1 h. After backfilling with N₂, THF (1.0 mL) and 1-phenyl-2-(trimethylsilyl)acetylene (24 μ L, 0.12 mmol, 1.2 eq) were added to the mixture in this order. The test tube was sealed with a cap, and the reaction mixture was stirred at 60 °C for 20 h. The reaction was quenched with water (20 mL) and the mixture was then transferred to a separatory funnel with AcOEt (20 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt (2 \times 10 mL). The combined organic fractions were washed with brine (20 mL) and then dried over Na₂SO₄, and all the volatiles were removed under vacuum. **4age** was isolated by flash column chromatography (SiO₂, AcOEt/hexane = 1/19) in 73% yield (43.3 mg, 0.0727 mmol) as a white solid. ¹H NMR (400 MHz, CDCl₃, rt, δ /ppm): 7.64 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.47–7.42 (m, 3H), 7.12 (dd, *J* = 7.3, 1.5 Hz, 2H), 7.04 (dt, *J* = 7.8, 1.4 Hz, 2H), 6.96 (dt, *J* = 7.3, 1.5 Hz, 2H), 6.35 (d, *J* = 7.8 Hz, 2H). ¹⁹F NMR (376 MHz, CDCl₃, rt, δ /ppm): -137.7– -137.8 (m, 2F), -138.0– -138.1 (m, 2F), -140.4– -140.5 (m, 2F), -143.6– -143.7 (m, 2F). HRMS (DART) *m/z*: ([M+H]⁺) Calcd for C₃₂H₁₄F₈NS⁺ 596.0714; Found 596.0715.

4. Conclusions

In conclusion, we have demonstrated a controllable S_NAr reaction of polyfluoroarenes with phenothiazine for the transition-metal-free synthesis of PTH derivatives. The combination of K₃PO₄ as the base and MeCN as the solvent was found to be widely applicable for the regioselective mono-substitution of highly reactive polyfluoroarenes, whereas the combination of K₂CO₃ and DMF resulted in multi-substitution. Various functional groups, including cyano, nitro, ester, and chlorine atoms, tolerated to the present conditions, thus enabling further transformations of the S_NAr products. The obtained fluorine-containing PTH derivatives were employed in a sequential S_NAr reaction to afford highly functionalized PTH derivatives. Further investigation of the optical characteristics of these compounds and their photocatalytic capabilities is currently underway.

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