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# 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 monosubstituted aromatic compounds. We 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



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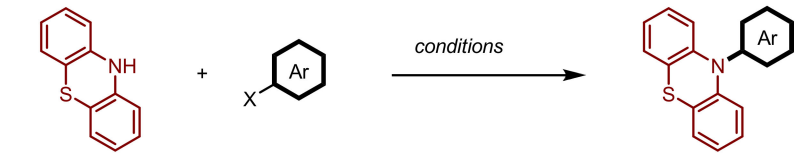
## 1. Introduction

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 have 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], nitrorarenes [29–33], or electrochemical conditions [34]. 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-terafluorobenzene with NaH as the base [35]. 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 [36–46].

PTH derivatives are generally prepared via palladium- or copper-catalyzed coupling reactions of phenothiazine with aryl halides or arylboronic acids (Scheme 1a) [36–52]. Transition-metal-free methods for the synthesis of PTH derivatives include oxidative C-H amination in the presence of oxidants [53–57] or under electrolytic conditions [58,59], 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) [28,60–67].

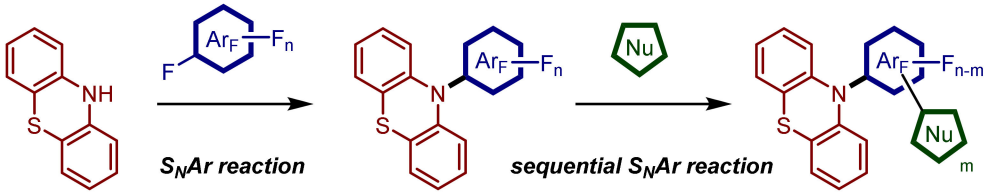



| | X-Ar | conditions |
|---|---|---|
| *a. transition-metal-catalyzed coupling* | X = Br, Cl, I | cat. Pd or Cu, base |
| | X = $B(OH)_2$ | cat. Cu, base |
| *b. oxidative coupling* | X = H (phenols or anilines) | oxidants<br>electricity |
| *c. nucleophilic aromatic substitution* | X = $NO_2$, F,  | base |



**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 [68–70]. However, $S_NAr$ of polyfluoroarenes often suffers from uncontrollable substitution, resulting in a mixture of regioisomers and/or multisubstituted 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.

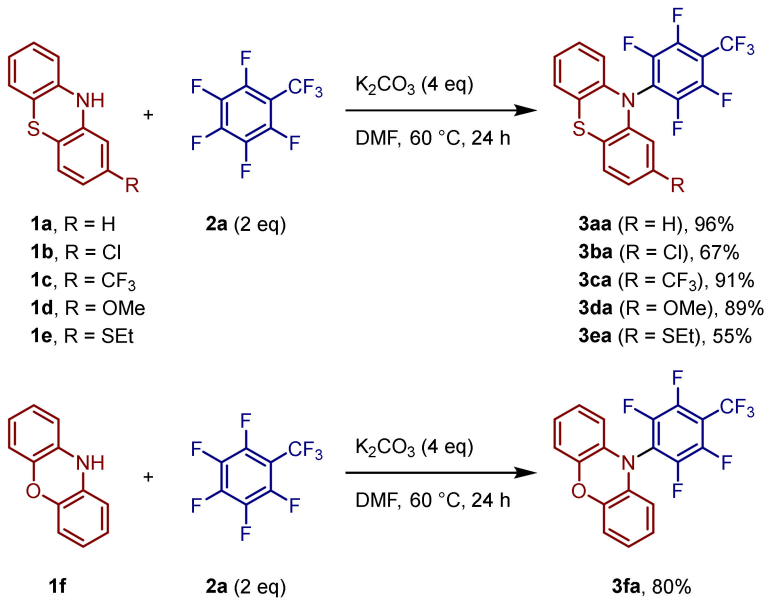



**Scheme 2.** Synthesis of highly functionalized PTH derivatives via sequential $S_NAr$ reactions.

## 2. Results and Discussion

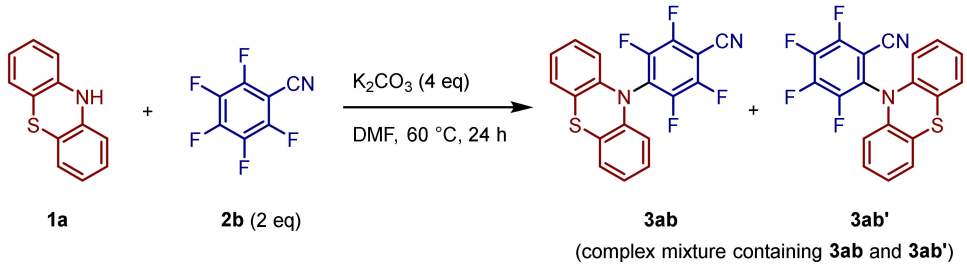
The reaction of phenothiazine with octafluorotoluene in the presence of $K_2CO_3$ in *N*,*N*-dimethylformamide (DMF) at 60 °C afforded the corresponding PTH derivative **3aa** as the sole product in 96% yield (Scheme 3). The fluorine atom at the *p*-position of the trifluoromethyl group of octafluorotoluene was substituted by phenothiazine, without the

formation of regioisomers or multisubstituted 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 repulsion between the trifluoromethyl group and bulky phenothiazine. 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 $S_NAr$.

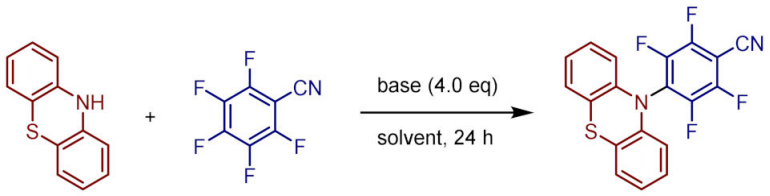



**Scheme 4.** Reaction of pentafluorobenzonitrile with phenothiazine using the $K_2CO_3$/DMF system.

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, containing **3ab** in 13% (entry 3). Inorganic 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 76% (entry 9). *N*,*N*-Dimethylacetoamide (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].



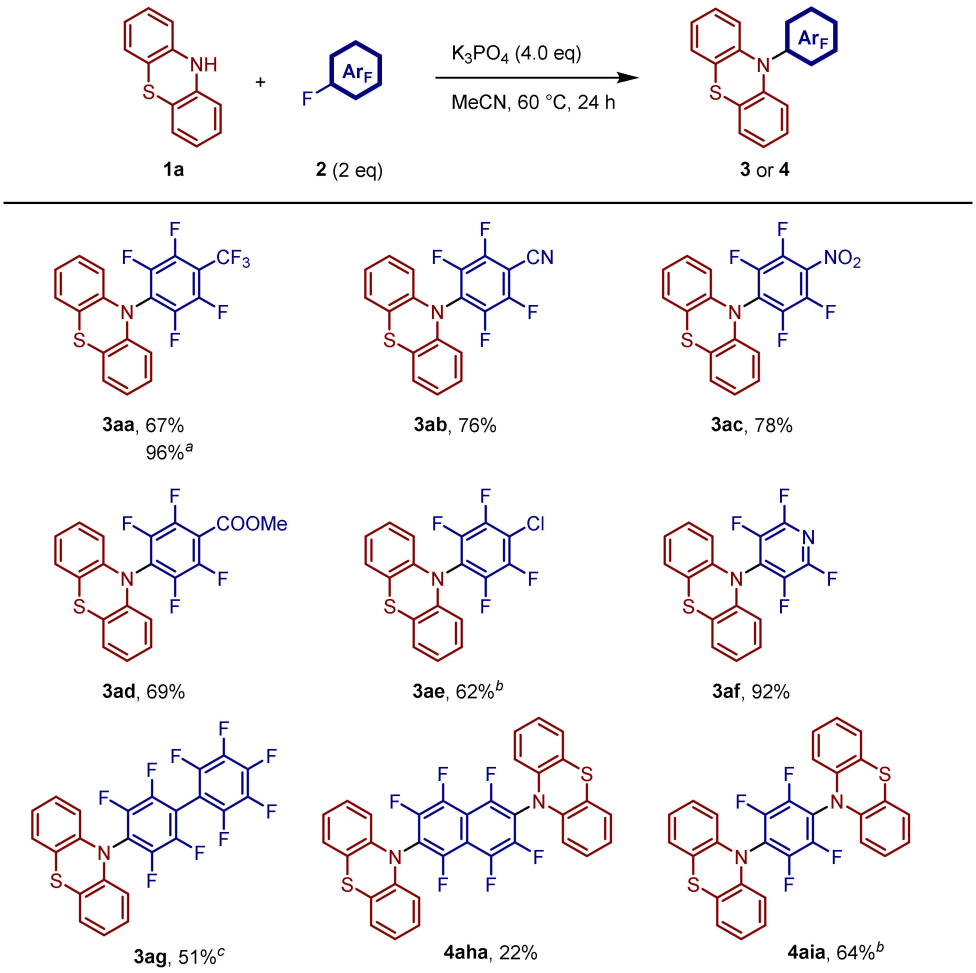

**1a** **2b** (2 eq) **3ab**

| Entry | Base | Solvent | Temperature | 3ab 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 | 13% [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 | 76% [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] With multi-substitution products [d] Isolated yield.

Next, various polyfluoroarenes were subjected to $S_NAr$ 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 $S_NAr$ 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 $S_NAr$ using $K_2CO_3$ in DMSO at 85 °C to afford the corresponding product **3ae**, while the $K_3PO_4$/MeCN system resulted in low yield. The use of DMSO improved the reactivity of substitution presumably due to the higher solubility of the base. It should be noted that selective C–F bond functionalization occurred and the chlorine atom remained intact under these $S_NAr$ 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 $K_2CO_3$/DMSO conditions. 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 disubstituted 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 monosubstituted product being in solution while the bulk of **2i** remains in the vapor phase.

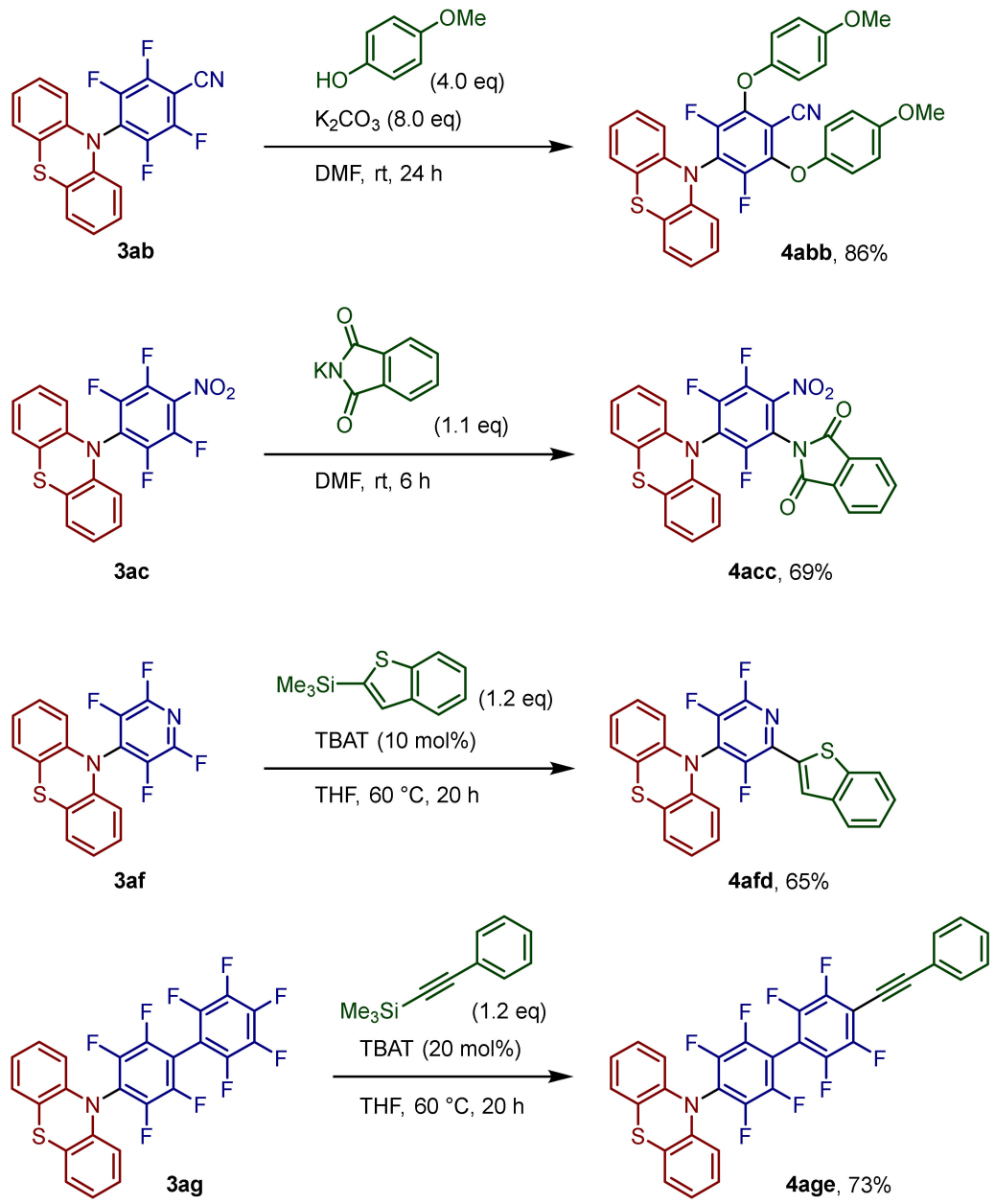



[a] Conducted with $K_2CO_3$ in DMF at 60 °C. [b] Conducted with $K_2CO_3$ in DMSO at 85 °C.
[c] Along with trace amounts of di-substituted product **4aga**.

**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 multifunctionalized **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*

$^1H$, $^{13}C$, and $^{19}F$ 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, and m = multiplet), integration, and coupling constant (Hz). The chemical shifts in the $^1H$ NMR spectra were recorded relative to the residual solvent peaks ($CDCl_3$: δ 7.26). The chemical shifts in the $^{13}C$ NMR spectrum were also recorded relative to the residual solvent peaks ($CDCl_3$: δ 77.0). The chemical shifts in the $^{19}F$ 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 $N_2$, 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 $Na_2SO_4$, and all volatiles were removed under vacuum. The residue was purified by flash column chromatography ($SiO_2$) to yield the corresponding 10-phenylphenothiazine (PTH) derivatives.

#### 3.2.2. 10-(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)-10*H*-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 $K_2CO_3$ (554 mg, 4.0 mmol, 4.0 eq) in DMF (10 mL). **3aa** was isolated by flash column chromatography ($SiO_2$, AcOEt/hexane = 1/100) in 96% yield (398 mg, 0.958 mmol) as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$, 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). $^{19}$F NMR (376 MHz, $CDCl_3$, 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 $C_{19}H_9F_7NS$ 416.0338; Found 416.0342.

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

The title compound was prepared according to General Procedure A with 2-chloro-10*H*-phenothiazine (**1b**, 66.9 mg, 0.50 mmol), octafluorotoluene (**2a**, 150 μL, 1.05 mmol, 2.1 eq), and $K_2CO_3$ (277 mg, 2.0 mmol, 4.0 eq) in DMF (5 mL). **3ba** was isolated by flash column chromatography ($SiO_2$, AcOEt/hexane = 1/200) in 67% yield (150 mg, 0.334 mmol) as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$, 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). $^{19}$F NMR (376 MHz, $CDCl_3$, 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 $C_{19}H_8ClF_7NS^+$ 449.9949; Found 449.9946.

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

The title compound was prepared according to General Procedure A with 2-(trifluoromethyl)-10*H*-phenothiazine (**1c**, 133.6 mg, 0.50 mmol), octafluorotoluene (**2a**, 150 μL, 1.05 mmol, 2.1 eq), and $K_2CO_3$ (277 mg, 2.0 mmol, 4.0 eq) in DMF (5 mL). **3ca** was isolated by flash column chromatography ($SiO_2$, AcOEt/hexane = 1/200) in 91% yield (220 mg, 0.455 mmol) as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$, 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). $^{19}$F NMR (376 MHz, $CDCl_3$, rt, δ/ppm): −58.5 (t, *J* = 22.0 Hz, 3F), −65.1 (s, 3F), −139.3–(−139.7) (m, 2F), −142.1–(−142.2) (m, 2F). HRMS (DART) *m/z*: ([M + H]$^+$) Calcd for $C_{20}H_8F_{10}NS^+$ 484.0212; Found 484.0210.

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

The title compound was prepared according to General Procedure A with 2-methoxy-10*H*-phenothiazine (**1d**, 114.6 mg, 0.50 mmol), octafluorotoluene (**2a**, 150 μL, 1.05 mmol, 2.1 eq), and $K_2CO_3$ (277 mg, 2.0 mmol, 4.0 eq) in DMF (5 mL). **3da** was isolated by flash column chromatography ($SiO_2$, AcOEt/hexane = 1/150) in 89% yield (200 mg, 0.449 mmol) as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$, 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). $^{19}$F NMR (376 MHz, $CDCl_3$, 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 $C_{20}H_{11}F_7NS^+$ 446.0444; Found 446.0447.

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

The title compound was prepared according to General Procedure A with 2-ethylthio-10*H*-phenothiazine (**1e**, 129.7 mg, 0.50 mmol), octafluorotoluene (**2a**, 150 μL, 1.05 mmol, 2.1 eq), and $K_2CO_3$ (277 mg, 2.0 mmol, 4.0 eq) in DMF (5 mL). **3ea** was isolated by flash column chromatography ($SiO_2$, AcOEt/hexane = 1/100) in 55% yield (130 mg, 0.273 mmol) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 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). $^{19}$F NMR (376 MHz, $CDCl_3$, 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 $C_{21}H_{13}F_7NS_2^+$ 476.0372; Found 476.0371.

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

The title compound was prepared according to General Procedure A with 10*H*-phenoxazine (**1f**, 91.6 mg, 0.50 mmol), octafluorotoluene (**2a**, 150 μL, 1.05 mmol, 2.1 eq), and $K_2CO_3$ (277 mg, 2.0 mmol, 4.0 eq) in DMF (5 mL). **3fa** was isolated by flash column chromatography ($SiO_2$, AcOEt/hexane = 1/100) in 80% yield (160 mg, 0.400 mmol) as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$, 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). $^{19}$F NMR (376 MHz, $CDCl_3$, 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 $C_{19}H_9F_7ON^+$ 400.0567; Found 400.0565.

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

The title compound was prepared according to General Procedure A with phenothiazine (**1a**, 399 mg, 2.0 mmol), pentafluorobenzonitrile (**2b**, 512 μL, 4.0 mmol, 2.0 eq), and $K_3PO_4$ (1.70 g, 8.0 mmol, 4.0 eq) in MeCN (20 mL). **3ab** was isolated by flash column chromatography ($SiO_2$, AcOEt/hexane = 1/40) in 76% yield (568 mg, 1.53 mmol) as a pale yellow solid. $^1$H NMR (400 MHz, $CDCl_3$, 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). $^{19}$F NMR (376 MHz, $CDCl_3$, rt, δ/ppm): −132.4–(−132.5) (m, 2F), −140.6–(−140.7) (m, 2F). HRMS (DART) *m/z*: ([M + H]$^+$) Calcd for $C_{19}H_9F_4N_2S$ 373.0417; Found 373.0415.

3.2.9. 10-(2,3,5,6-Tetrafluoro-4-nitrophenyl)-10*H*-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 $K_3PO_4$ (1.70 g, 8.0 mmol, 4.0 eq) in MeCN (20 mL). **3ac** was isolated by flash column chromatography ($SiO_2$, hexane) in 78% yield (613 mg, 1.56 mmol) as an orange solid. $^1$H NMR (400 MHz, $CDCl_3$, 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). $^{19}$F NMR (376 MHz, $CDCl_3$, rt, δ/ppm): −140.1–(−140.1) (m, 2F), −146.9–(−146.9) (m, 2F). HRMS (DART) *m/z*: ([M + H]$^+$) Calcd for $C_{18}H_9F_4N_2O_2S^+$ 393.0315; Found 393.0317.

3.2.10. Methyl 2,3,5,6-tetrafluoro-4-(10*H*-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 $K_3PO_4$ (424.5 mg, 2.0 mmol, 4.0 eq) in MeCN (5 mL). **3ad** was isolated by flash column chromatography ($SiO_2$, AcOEt/hexane = 1/200) in 69% yield (140 mg, 0.345 mmol) as a pale yellow solid. $^1$H 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): −143.2–(−143.3) (m, 2F), −139.7–(−139.8) (m, 2F). HRMS (DART) *m/z*: ([M + H]$^+$) Calcd for $C_{20}H_{12}F_4NO_2S^+$ 406.0519; Found 406.0520.

3.2.11. 10-(4-Chloro-2,3,5,6-tetrafluorophenyl)-10*H*-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 °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. $^1$H 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*: ([M + H]$^+$) Calcd for $C_{18}H_9ClF_4NS^+$ 382.0075; Found 382.0075.

3.2.12. 10-(Perfluoropyridin-4-yl)-10*H*-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. $^1$H 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*: ([M + H]$^+$) Calcd for $C_{17}H_9F_4N_2S^+$ 349.0417; Found 349.0420.

3.2.13. 10-(Perfluoro-[1,1′-biphenyl]-4-yl)-10*H*-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. $^1$H 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*: ([M + H]$^+$) Calcd for $C_{24}H_9F_9NS^+$ 514.0307; Found 514.0303.

3.2.14. 10,10′-(Perfluoronaphthalene-2,6-diyl)bis(10*H*-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. $^1$H 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*: ([M + H]$^+$) Calcd for $C_{34}H_{17}F_6N_2S_2^+$ 631.0732; Found 631.0733.

3.2.15. 10,10′-(Perfluoro-1,4-phenylene)bis(10*H*-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 °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. $^1$H 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-(10*H*-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. $^1$H 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. $^1$H 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.

#### 3.3.3. 10-(2-(Benzo[*b*]thiophen-2-yl)-3,5,6-trifluoropyridin-4-yl)-10*H*-phenothiazine (**4afd**)

In a well-dried screw-capped test tube, tetrabutylammonium difluorotriphenylsilicate (TBAT, 5.4 mg, 0.01 mmol, 10 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. $^1$H 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.

#### 3.3.4. 10-(2,2′,3,3′,5,5′,6,6′-octafluoro-4′-(phenylethynyl)-[1,1′-biphenyl]-4-yl)-10*H*-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 $N_2$, THF (1.0 mL) and 1-phenyl-2-(trimethylsilyl)acetylene (24 μL, 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. **4age** was isolated by flash column chromatography ($SiO_2$, AcOEt/hexane = 1/19) in 73% yield (43.3 mg, 0.0727 mmol) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$, 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). $^{19}$F NMR (376 MHz, $CDCl_3$, 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 $C_{32}H_{14}F_8NS^+$ 596.0714; Found 596.0715.

## 4. Conclusions

In conclusion, we demonstrated a controllable $S_NAr$ reaction of polyfluoroaenes with phenothiazine for the transition-metal-free synthesis of PTH derivatives. The combination of $K_3PO_4$ as the base and MeCN as the solvent was found to be widely applicable for the regioselective monosubstitution of highly reactive polyfluoroarenes, whereas the combination of $K_2CO_3$ and DMF resulted in multisubstitution. 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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