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Note

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Aromatic Halogenation Using *N*-Halosuccinimide and $PhSSiMe_3$ or PhSSPh

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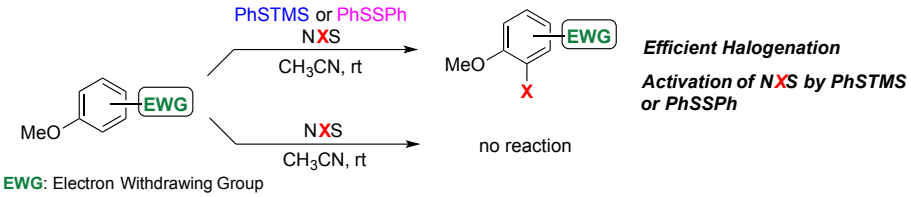
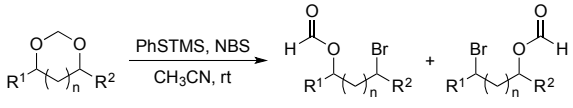


ABSTRACT: We developed a mild aromatic halogenation reaction using a combination of *N*-halosuccinimide and $PhSSiMe_3$ or PhSSPh. Less reactive aromatic compounds, such as methyl 4-methoxybenzoate, were brominated with $PhSSiMe_3$ or PhSSPh and *N*-bromosuccinimide in high yields. No reaction was observed in the absence of $PhSSiMe_3$ or PhSSPh. This method is also applicable to chlorination reactions using *N*-chlorosuccinimide and PhSSPh.

Sulfur-containing compounds are important in living organisms and in a wide variety of fields such as materials science and organic chemistry.[1] In living organisms, sulfur compounds such as cysteine act as redox substrates that can be reversibly oxidized to form disulfide (S-S) bonds. These can then be easily reduced back to thiols by glutathione.[2] Thiols are also well known as easily oxidized compounds in organic syntheses, being converted to their corresponding disulfides under oxidizing conditions.[3] Reactions of thiols with brominating reagent, 1,3-dibromo-5,5-dimethylhydantoin, naturally afford their corresponding disulfides.[4] Conversely, we have developed a novel series of reactions involving methylene acetals[5] and reported mild conversion method of methylene acetals using a combination of *N*-bromosuccinimide (NBS) and phenylthiotrimethylsilane (PhSTMS)[5d] (Scheme 1).



Scheme 1. Conversion of Methylene Acetal to Bromoformate Under Mild Conditions

Methylene acetal is a robust protective group for diols and requires harsh reaction conditions for deprotection. However, under mild conditions, a combination of NBS and PhSTMS is effective in the transformation of methylene acetal to its corresponding bromoformates. This reaction seems to involve the bromination of the methylene acetal moiety. We therefore hypothesized that the combination of these reagents would effectively brominate aromatic compounds under mild conditions. The combination of NBS and PhSTMS has not been previously reported but is expected to yield PhSBr as an intermediate. Although reactions involving PhSBr have been reported,[4,6] the bromination of aromatic rings by PhSBr has not been demonstrated. This study details the halogenation of aromatic compounds using a combination of *N*-halosuccinimide and PhSTMS or PhSSPh. Aryl bromides are known as some of the most efficient substrates for transition-metal catalyzed cross-coupling reaction.[7] A number of methods for aromatic bromination using NBS with activating reagents including Lewis acids and Lewis bases have been reported.[8] However, many of reported methods examined the bromination of reactive (electron-rich) arenes such as phenol and aniline derivatives. We then investigated the bromination of relatively less reactive arenes, anisole derivatives with electron-withdrawing groups. Some methods can brominate such arenes but they used acids for activation,[9] and only NH_4OAc was used for such a bromination of less reactive arenes as a mild activator.[10]

We first applied the optimized conditions from a previous method[5d] to the bromination of methyl 4-methoxybenzoate (**1a**) (Scheme 2). The reaction proceeded in CH_3CN at room temperature and afforded methyl 3-bromo-4-methoxybenzoate (**2a**) in 79% yield (Scheme 2, eq. 1). Surprisingly, no reaction was observed in the absence of PhSTMS (Scheme 2, eq. 2). Note, however, that sulfur

compounds activate NBS even under oxidative conditions. We then optimized the reagent ratios for maximum yield (Table 1).

Scheme 2. Activation of NBS with PhSTMS for Aromatic Bromination

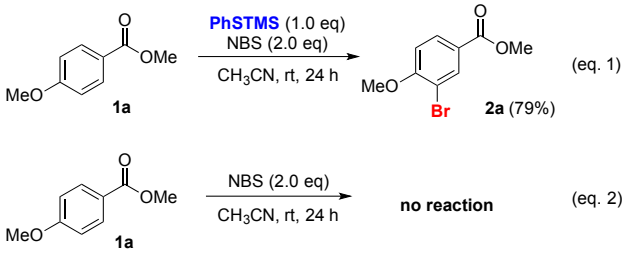
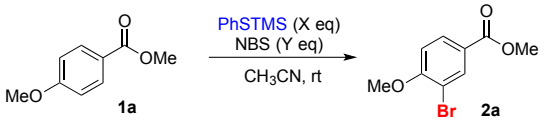


Table 1. Equivalent of Reagents



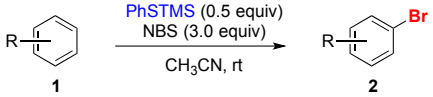
Entry	PhSTMS (equiv)	NBS (equiv)	Time (h)	Yield (%)
1	1.0	2.0	24	79 (10)[a]
2	1.0	3.0	2	quant.
3	0.5	3.0	3	95
4	0.3	3.0	24	96
5	0.1	3.0	24	56 (28)[a]

a) The yield of the parenthesis indicated the remained starting material.

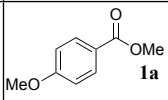
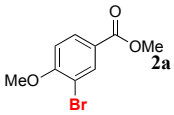
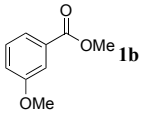
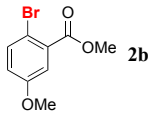
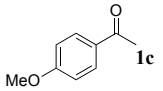
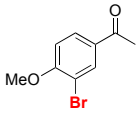
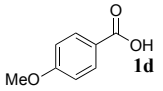
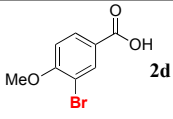
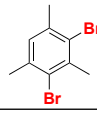
The use of one equivalent of PhSTMS and two equivalents of NBS afforded a 79% yield, but returned starting material (entry 1). Increasing the equivalent of NBS led to the complete consumption of starting material to give **2a** in quantitative yield (entry 2). Decreasing the equivalent of PhSTMS to 0.5 gave almost the same result as that of one equivalent (entry 3). Further decreasing the amount of PhSTMS increased the reaction time (entries 4 and 5) and the use of 0.1 equivalent of PhSTMS resulted in remaining starting material after 24 h (entry 5). Given the above results, 0.5 equivalents of PhSTMS and 3.0 equivalents of NBS in CH_3CN were selected as optimized conditions for the bromination of aromatic compounds (Table 2). Reactions

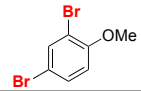
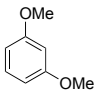
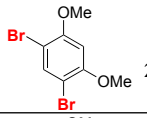
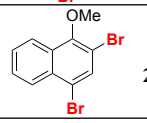
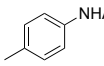
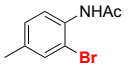
of anisole derivatives with electron-withdrawing groups such as esters, ketones, and carboxylic acids (**1a**–**1d**) afforded corresponding mono-brominated compounds (**2a**–**2d**) in high yields, whereas no reaction was observed in the absence of PhSTMS (entries 1–8). Electron-rich arenes (**1e**–**1h**) underwent dibromination, giving the corresponding products (**2e**–**2h**) in good to high yields (entries 9, 11, 13, and 15) except for 4-methylacetanilide (**1i**). In the absence of PhSTMS, the reaction of mesitylene (**1e**), anisole (**1f**) and 1-methoxynaphthalene (**1h**) afforded sole mono-brominated compounds (**3e**, **3f** and **3h**) (entries 10, 12, and 16). Similar result was obtained in the case of more electron-rich dimethoxybenzene (**1g**) even in the absence of PhSTMS (entries 13 and 14). The reaction of **1i** furnished the mono-brominated product **3i** in 85% yield, which decreased to 18% in the absence of PhSTMS with the same reaction time (entries 17 and 18). More electron-deficient aromatic compounds, such as bromobenzene or nitrobenzene, did not undergo bromination under these optimized reaction conditions (entries 19 and 20).

Table 2. **Aromatic Bromination with the Combination of PhSTMS and NBS**



1 **2**

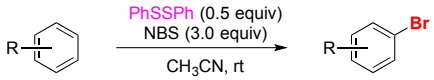
Entry	Substrate	Time (h)	Product	Yield (%)
1	 **1a**	3	 **2a**	95
2[a]		24		no reaction
3	 **1b**	1	 **2b**	92
4[a]		24		no reaction
5	 **1c**	2	 **2c**	93
6[a]		24		no reaction
7	 **1d**	24	 **2d**	82
8[a]		24		no reaction
9	 **1e**	1	 **2e**	92
10[a]		1		31 (**3e**)[b]

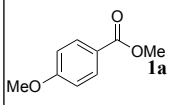
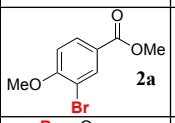
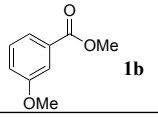
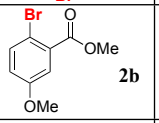
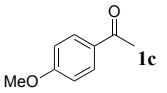
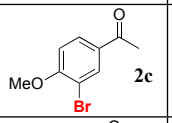
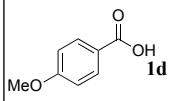
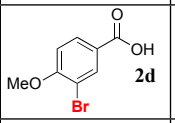
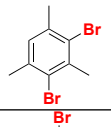
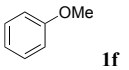
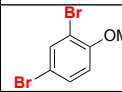
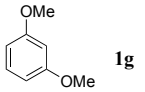
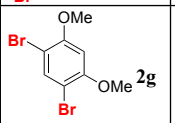
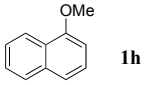
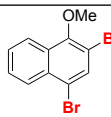
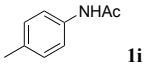
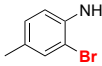
11 12[a]	 **1f**	2 2	 **2f**	96 90 (**3f**)[c]
13 14[a]	 **1g**	1 1	 **2g**	97 quant.
15 16[a]	 **1h**	1 1	 **2h**	94 79 (**3h**)[d]
17 18[a]	 **1i**	1 1	 **3i**	85 18
19	 **1j**	12		no reaction
20	 **1k**	12		no reaction

a) Without PhSTMS. b) The yield of 2-bromomesitylene (**3e**). c) The yield of 4-bromoanisole (**3f**). d) The yield of 4-bromo-1-methoxynaphthalene (**3h**).

In these reactions, PhSSPh was observed as a byproduct and the reactions proceeded with only a catalytic amount of PhSTMS (Table 1, entries 3–5). This suggests that PhSSPh also acts as an activator for NBS. PhSSPh is less expensive than PhSTMS and, being a solid, is easier to handle. PhSSPh also exhibits less of the malodor associated with sulfur. We next examined the bromination of aromatic compounds using a combination of PhSSPh and NBS. With 0.5 equivalent of PhSSPh and 3.0 equivalents of NBS, **1a** was successfully converted to the corresponding brominated product **2a** in quantitative yield. Note that a longer reaction time was needed relative to that required for the combination of PhSTMS and NBS (Table 3, entry 1 vs. Table 2, entry 1). Reactions of anisole derivatives bearing electron-withdrawing groups (**1b**–**1d**) afforded the corresponding bromides (**2b**–**2d**) in high yields with similar or longer reaction time than those with PhSTMS (entries 2 and 3). The activation of NBS with PhSSPh seems to be weaker than that with PhSTMS. The bromination of electron-rich arenes **1g** and **1i** with PhSSPh also yielded high yields, however **1f** and **1h** resulted in mono-brominated products as inseparable mixture.

Table 3. Aromatic Bromination with the Combination of PhSSPh and NBS



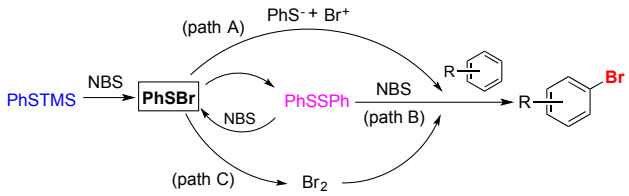
Entry	Substrate	Time (h)	Product	Yield (%)
1	 **1a**	12	 **2a**	quant.
2	 **1b**	6.5	 **2b**	95
3	 **1c**	3	 **2c**	88
4	 **1d**	24	 **2d**	93
5	 **1e**	2	 **2e**	64 (35)[a]
6	 **1f**	3	 **3f**	-[b]
7	 **1g**	1	 **2g**	quant.
8	 **1h**	1	 **3h**	-[b]
9	 **1i**	2.5	 **3i**	quant.

a) The yield of 2-bromomesitylene (**3e**) was indicated in the parenthesis. b) Mono-brominated product was obtained as inseparable mixture.

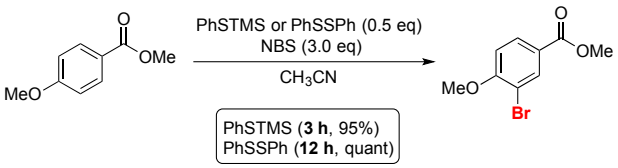
A plausible reaction mechanism is as follows (Scheme 3). First, PhSTMS reacts with NBS to generate PhSBr as a reactive species. The resulting Br^+ ion is then able to brominate the aromatic compound, converting the sulfur moiety to a disulfide. The reaction of PhSSPh and NBS also affords the same reactive species, PhSBr,[6c] which acts as a Br^+ source for aromatic bromination[6d]

(Scheme 3, path A). However, PhSBr is also reported as acting as a PhS^+ ion,[6c] indicating that Br should act as an anion. Another reaction mechanism involves the *in situ* conversion of PhSTMS to PhSSPh, which then acts as a Lewis base to activate Br (Scheme 3, path B).[11] However, the reaction using PhSTMS is much faster than that using PhSSPh although PhSTMS should be converted to PhSSPh (Scheme 4). Therefore, disulfide is unlikely to work as Lewis base for activation. Another possible reactive intermediate is Br_2, which may be generated from the disproportionation of PhSBr (Scheme 3, path C).[4,12] The reaction of olefin with a combination of PhSTMS and NBS did not yield a dibrominated product, but bromothiophenylation was observed. Although this result does not rule out the generation of Br_2, the true active species has not been elucidated. We also examined the addition of a radical scavenger, *tert*-dibutylhydroxytoluene (BHT), to the reaction mixture. Surprisingly, this significantly suppressed the reaction (Scheme 5). Although the exact radical pathway remains unclear, disproportionation may occur via a radical intermediate in the generation of Br_2.

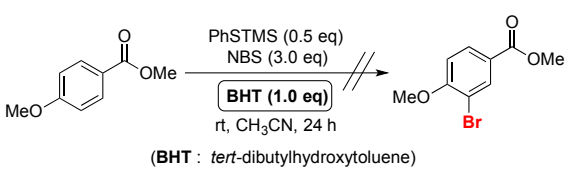
Scheme 3. Plausible Reaction Mechanism



Scheme 4. Differences of Reactivity between PhSTMS and PhSSPh



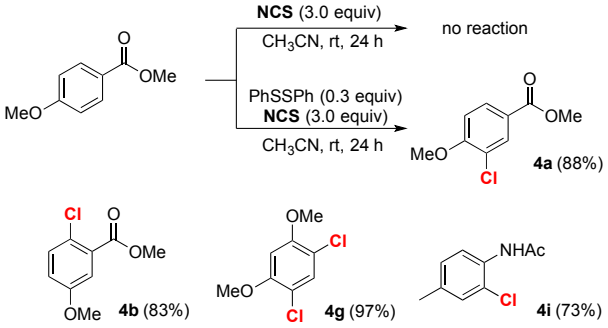
Scheme 5. Addition of Radical Scavenger



(**BHT** : *tert*-dibutylhydroxytoluene)

Finally, we applied our method to the chlorination of aromatic compounds using PhSTMS-*N*-chlorosuccinimide (NCS). Most general methods for the chlorination of aromatic rings with NCS require activation with an acid.[9d,13] We performed a chlorination of methyl 4-methoxybenzoate (**1a**) using 0.3 equivalents of PhSSPh and 3.0 equivalents of NCS, affording methyl 3-chloro-4-methoxybenzoate **4a** in 88% yield after 24 h whereas no reaction proceeded without PhSSPh. Other arenes (**1b**, **1g**, and **1i**) underwent the same chlorination reaction to give the corresponding products **4b, 4g,** and **4i** in good to high yields (Scheme 6).

Scheme 6. Aromatic Chlorination with the Combination of PhSSPh and NCS



In conclusion, we have developed a novel halogenation method using a combination of *N*-halosuccinimides and PhSTMS or PhSSPh under mild reaction conditions. This method was shown to be applicable to less reactive aromatic compounds that do not react with *N*-halosuccinimide alone. *N*-Halosuccinimides could be activated in the presence of sulfur-containing compounds such as PhSTMS or PhSSPh through the generation of a reactive species, PhSX, although the true reactive intermediate has not been fully elucidated. Furthermore, this reaction proceeds under mild conditions and employs solid reagents that are relatively low-odor and easy to handle. Further elucidation of the reaction mechanism and broadening of the application space to similar reactions are currently underway.

Experimental Section

General Information

Column chromatography and TLC were performed on Merck Silica gel 60 (230–400 mesh) and Merck Silica gel F254 plates (0.25 mm), respectively. ^{1}H and ^{13}C NMR spectra were recorded on the JEOL JMN-400 spectrometer in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as an internal standard. Data are reported as follows: chemical shift in ppm (δ), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant (Hz). High-resolution mass spectra were obtained on the SHIMAZU IRAffinity-1 instrument with ionization voltages of 70 eV.

General Procedure for bromination with PhSTMS and NBS (Table 2)

Typical procedure from 1a to 2a: PhSTMS (0.023 mL, 0.12 mmol) was added to a solution of **1a** (40 mg, 0.24 mmol) in CH_3CN (1.2 mL), then NBS (128 mg, 0.72 mmol) was added and stirred for 3 h. Saturated $NaHCO_3$ and $Na_2S_2O_3$ (1:1) aqueous solution was added to the resultant solution and the mixture was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography on a silica gel (*n*-Hex/AcOEt = 10/1) to give **2a** (56.1 mg, 95%).

Methyl 3-bromo-4-methoxybenzoate (2a)[14]

White solid, mp 95-96 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ : 8.21 (d, J = 2.0 Hz, 1H), 7.94 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H).

Methyl 2-bromo-5-methoxybenzoate (2b)[15]

According to the general procedure, the reaction of **1b** (0.035 mL, 0.24 mmol) with PhSTMS (0.023 mL, 0.12 mmol) and NBS (128 mg, 0.72 mmol) in CH_3CN (1.2 mL) gave **2b** (53.9 mg, 92%) after purification by SiO_2 column chromatography (*n*-Hex/AcOEt = 10/1).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.50 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 3.0 Hz, 1H), 6.87 (dd, J = 3.0 Hz, 8.8 Hz, 1H), 3.91 (s, 3H), 3.80 (s, 3H)

3-Bromo-4-methoxyacetophenone (2c)[16]

According to the general procedure, the reaction of **1c** (36 mg, 0.24 mmol) with PhSTMS (0.023 mL, 0.12 mmol) and NBS (128 mg, 0.72 mmol) in CH_3CN (1.2 mL) gave **2c** (51.1 mg, 93%) after purification by SiO_2 column chromatography (*n*-Hex/AcOEt = 5/1).

White solid, mp 87-88 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ : 8.16 (s, 1H), 7.91 (d, *J* = 8.8 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 3.96 (s, 3H), 2.55 (s, 3H)

3-Bromo-4-methoxybenzoic acid (2d)[17]

According to the general procedure, the reaction of **1d** (36 mg, 0.24 mmol) with PhSTMS (0.023 mL, 0.12 mmol) and NBS (128 mg, 0.72 mmol) in CH_3CN (1.2 mL) gave **2d** (43.5 mg, 82%) after back extraction.

Yellow solid, mp 216-217 ºC, ^{1}H NMR (400 MHz, DMSO-d_6) δ : 12.98 (brs, 1H), 8.06 (s, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 3.93 (s, 3H), 3.34 (s, 3H)

2,4-Dibromo-1,3,5-trimethylbenzene (2e)[18]

According to the general procedure, the reaction of **1e** (0.1 mL, 0.72 mmol) with PhSTMS (0.068 mL, 0.36 mmol) and NBS (384 mg, 2.16 mmol) in CH_3CN (3.6 mL) gave **2e** (184.1 mg, 92%) after purification by SiO_2 column chromatography (*n*-Hex only).

White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ : 6.87 (s, 1H), 2.35 (s, 6H), 2.22 (s, 3H)

2,4-Dibromo-1-methoxybenzene (2f)[16]

According to the general procedure, the reaction of **1f** (0.1 mL, 0.93 mmol) with PhSTMS (0.088 mL, 0.47 mmol) and NBS (497 mg, 2.79 mmol) in CH_3CN (4.7 mL) gave **2f** (243.6 mg, 96%) after purification by SiO_2 column chromatography (*n*-Hex only).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.67 (d, *J* = 2.4 Hz, 1H), 7.38 (dd, *J* = 2.4 Hz, 8.8 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 3.88 (s, 3H)

1,5-Dibromo-2,4-dimethoxybenzene (2g)[18]

According to the general procedure, the reaction of **1g** (0.1 mL, 0.76 mmol) with PhSTMS (0.072 mL, 0.38 mmol) and NBS (408 mg, 2.29 mmol) in CH_3CN (3.8 mL) gave **2g** (218.4 mg, 97%) after purification by SiO_2 column chromatography (*n*-Hex only).

White solid, mp 144 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.59 (s, 1H), 6.42 (s, 1H), 3.84 (s, 6H)

2,4-Dibromo-1-methoxynaphthalene (2h)[19]

According to the general procedure, the reaction of **1h** (0.035 mL, 0.24 mmol) with PhSTMS (0.023 mL, 0.12 mmol) and NBS (128 mg, 0.72 mmol) in CH_3CN (1.2 mL) gave **2h** (71.4 mg, 94%) after purification by SiO_2 column chromatography (*n*-Hex only).

Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ : 8.17-8.11 (m, 2H), 7.90 (s, 1H), 7.63-7.56 (m, 2H), 3.98 (s, 3H)

***N*-Acetyl-2-bromo-*p*-toluidine (3i)**[20]

According to the general procedure, the reaction of **1i** (36 mg, 0.24 mmol) with PhSTMS (0.023 mL, 0.12 mmol) and NBS (128 mg, 0.72 mmol) in CH_3CN (1.2 mL) gave **3i** (46.3 mg, 85%) after purification by SiO_2 column chromatography (*n*-Hex /AcOEt = 2/1).

White solid, mp 120-122 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ : 8.14 (d, J = 8.4 Hz, 1H), 7.49 (brs, 1H), 7.33 (s, 1H), 7.09 (d, J = 8.4 Hz, 1H), 2.27 (s, 3H), 2.20 (s, 3H)

2-Bromo-1,3,5-trimethylbenzene (3e)[21]

Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ : 6.87(s, 2H), 2.35(s, 6H), 2.22(s, 3H)

4-Bromo-1-methoxybenzene (3f)[22]

Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.36(dd, J = 2.4 Hz, 6.8 Hz, 2H), 6.76 (dd, J = 2.4 Hz, 6.8 Hz, 2H), 3.77(s, 3H)

1-Bromo-4-methoxynaphthalene (3h)[19]

Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ : 8.27 (d, *J* = 8.8 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.65-7.50 (m, 3H), 6.66 (d, *J* = 8.0 Hz, 1H), 3.97 (s, 3H)

General Procedure for chlorination with PhSSPh and NCS (Scheme 6)

Typical procedure from 1a to 4a: PhSSPh (16.4 mg, 0.075 mmol) was added to a solution of **1a** (41.5 mg, 0.25 mmol) in CH_3CN (1.25 mL), then NCS (100 mg, 0.75 mmol) was added and stirred for 3 h. Saturated $NaHCO_3$ and $Na_2S_2O_3$ (1:1) aqueous solution was added to the resultant solution and the mixture was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography on a silica gel (*n*-Hex only to *n*-Hex /AcOEt = 10/1 to 4/1) to give **4a** (44.2, 88%).

Methyl 3-chloro-4-methoxybenzoate (4a)[23]

White solid, mp 90-92 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ : 8.04 (d, *J* = 1.8 Hz, 1H), 7.92 (dd, *J* = 1.8 Hz, 8.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H).

Methyl 2-chloro-5-methoxybenzoate (4b)[24]

According to the general procedure, the reaction of **1b** (41.5 mg, 0.25 mmol) with PhSSPh (16.4 mg, 0.075 mmol) and NCS (100 mg, 0.75 mmol) in CH_3CN (1.25 mL) gave **4b** (41.4 mg, 83%) after purification by SiO_2 column chromatography (*n*-Hex only to *n*-Hex/AcOEt = 10/1 to 4/1). Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.31 (d, *J* = 8.8 Hz, 1H), 7.30 (d, *J* = 3.0 Hz, 1H), 6.93 (dd, *J* = 3.0 Hz, 8.8 Hz, 1H), 3.90 (s, 3H), 3.79 (s, 3H).

2,4-Dichloro-1,5-dimethoxybenzene (4g)[25]

According to the general procedure, the reaction of **1g** (0.065 mL, 0.5 mmol) with PhSSPh (32.7 mg, 0.15 mmol) and NCS (200 mg, 1.50 mmol) in CH_3CN (2.5 mL) gave **4g** (100 mg, 97%) after

purification by SiO_2 column chromatography (*n*-Hex only).

White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ : 6.95 (s, 1H), 2.47 (s, 3H), 2.23 (s, 3H)

***N*-Acetyl-2-chloro-*p*-toluidine (4i)**[26]

According to the general procedure, the reaction of **1i** (37.3 mg, 0.25 mmol) with PhSSPh (16.4 mg, 0.075 mmol) and NCS (100 mg, 0.75 mmol) in CH_3CN (1.25 mL) gave **4i** (33.7 mg, 73%) after purification by SiO_2 column chromatography (*n*-Hex/AcOEt = 2/1).

Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ : 8.18 (d, J = 7.8 Hz, 1H), 7.50 (brs, 1H), 7.16 (s, 1H), 7.05 (d, J = 7.8 Hz, 1H), 2.28 (s, 3H), 2.20 (s, 3H).

ASSOCIATED CONTENT

Supporting information

The Supporting Information is available free of charge on the ACS Publication website at DOI:

^{1}H NMR spectra.

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Notes

The authors declare no competing financial interest.

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