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Regioselective Halogenation of Arenes and Heterocycles in Hexafluoroisopropanol

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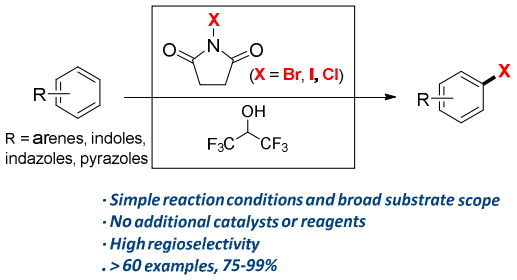


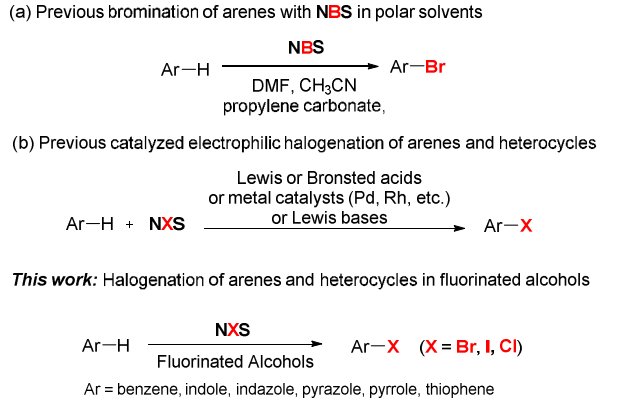
ABSTRACT: Regioselective halogenation of arenes and heterocycles with *N*-halosuccinimides in fluorinated alcohols is disclosed. Under mild condition reactions, a wide diversity of halogenated arenes are obtained in good yields with high regioselectivity. Additionally, the versatility of the method is demonstrated by the development of one-pot sequential halogenation and halogenation-Suzuki cross-coupling reactions.

INTRODUCTION

The importance and value of aryl halides stem from their versatile applications as key precursors for metal-catalyzed cross-couplings[1] and widely employed in natural products, pharmaceuticals, and materials science.[2] The development of efficient and mild halogenation of aromatic compounds is an intensively investigated area of great significance. By far the most prevalent strategies for preparing aromatic bromides and chlorides are rely on the use of hazardous and toxic X_2 (X = Br, Cl) which cause serious environmental issues. In order to replace the use of X_2, a large array of effective halogenating agents which are operationally safe have been successfully developed in the past decades.[3] Among them, *N*-halosuccinimides (NBS, NIS and NCS) have turn out to be practically useful halogenating reagents due to their low-cost, ease of handling, as well as the convenient recycling of the by-product succinimide. At first, the bromination of activated aromatic compounds with NBS in few polar solvents such as DMF, CH_3CN and propylene carbonate have been reported (Scheme 1a).[4] However, these reaction systems are only applicable to electron-rich arenes and require long reaction times and sometimes heating. Besides, these conditions could not be extended to iodination and chlorination due to the lower reactivity of NIS and NCS.[5] Therefore, in the last decades, numerous researchers have sought to activate NXS by using Lewis or Brønsted acids.[6]

Meanwhile, significant efforts have been devoted to the development of metal catalysts (Pd, Rh, etc.) in selective electrophilic halogenation of arenes with NXS.[7] More recently, a new class of Lewis base catalyzed systems have been developed for the electrophilic halogenation of aromatic compounds (Scheme 1b).[8] While remarkable progress has been achieved, the development of efficient and mild halogenation systems is still a sustained topic in synthetic chemistry.

Scheme 1. Halogenation of arenes or heterocycles with NXS

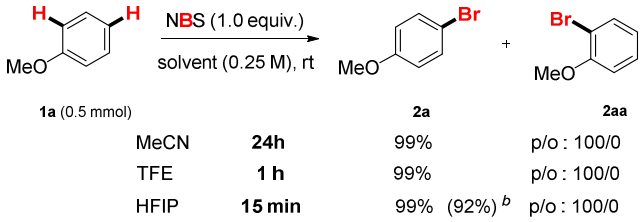


Over the last years, fluorinated alcohols such as trifluoroethanol (TFE) and hexafluoro-2-propanol (HFIP) have been shown to display unique features as solvents, co-solvents and additives in organic synthesis.[9] Indeed, the presence of the strong electron-withdrawing trifluoromethyl group generates several key parameters: high ionizing power, strong hydrogen-bond donation HBD (or H-bond acidity), mild acidity, and low nucleophilicity.[10] All these combined properties seem to be ideal media for the halogenation reaction without the need for any activator.[11] Therefore, we studied the halogenation of arenes with NXS in fluorinated alcohols.

RESULTS AND DISCUSSION

In our initial study, we first tested the bromination of anisole with 1.0 equiv. of NBS in TFE at room temperature (Scheme 2). To our delight, clean conversion of anisole was observed, and the mono-brominated product **2a** was obtained exclusively after 1h, which proved that NBS showed enhanced reactivity in fluorinated alcohols. The replacement of TFE with HFIP shortened the reaction time to 15 min. On the other hand in acetonitrile, the reaction required 24h for a complete conversion. These results could be explained by an electrophilic activation of NBS through hydrogen bonding. The ^{1}H NMR studies between HFIP and NBS showed strong hydrogen bonding interaction between NBS and HFIP with HFIP as the hydrogen bonding donor and NBS as the acceptor, reflecting in the significant changes in the chemical shift of protons (see SI).

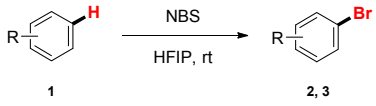
Scheme 2. Bromination of anisole [a]



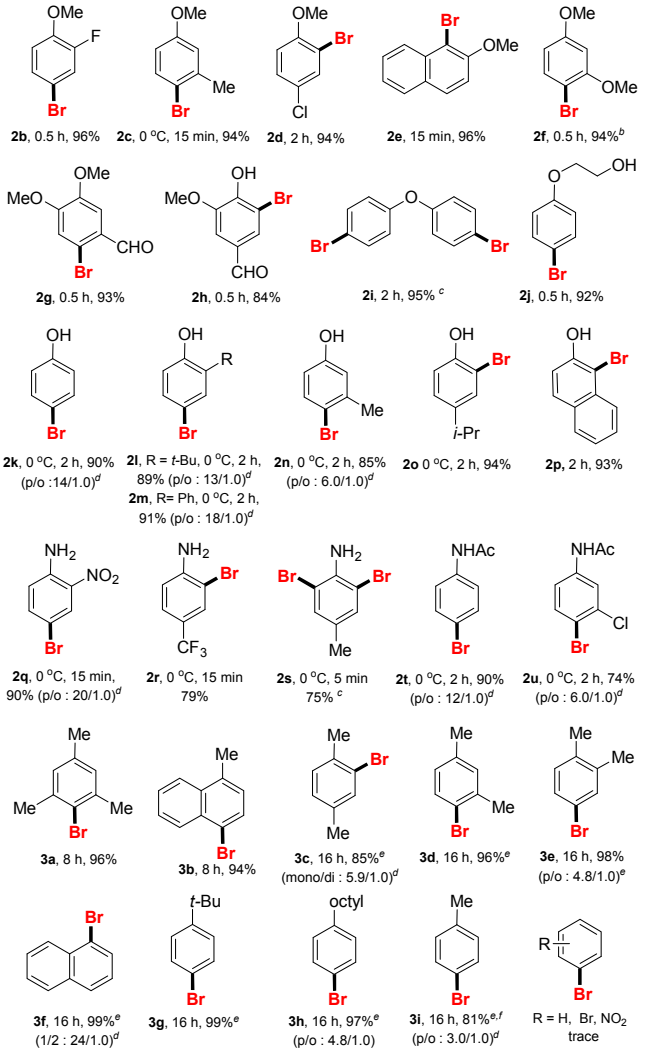
[a] NMR yields using nitromethane as internal standard. [b] Isolated yield.

Having identified HFIP as a suitable media, then we examined the scope of the process with a wide range of aryl compounds (Table 1). Substituted anisoles were mono-brominated rapidly to afford the corresponding products **2b-h** in excellent yields with single regioisomer. The bromination of aryl ether **1i** with 2.0 equiv. of NBS afforded dibrominated product **2i** in 95% yields. Phenoxyethanol was brominated smoothly in 92% yield (**2j**). We also explored the bromination of phenol derivatives (**2k-p**). For the phenol, the regioselectivity was observed in favour of the *para* position (*p*/*o* (**2k**/**2kk**) ratio 14/1) with **2k** was isolated in 92% yield. The bromination of ortho- and *meta*-substituted phenols proceeded predominantly in *para*-position (**2l-n**). For the *para*-substituted phenols, the bromination took place exclusively at the *ortho*-position (**2o**, **2p**). Furthermore, free aniline derivatives reacted in the same conditions to give the corresponding brominated products **2q-s** in excellent yields and with high selectivity. The bromination of acetanilides succeeded to afford the *para*-brominated **2t** and **2u** products in 90% and 74% yields respectively. Then, we evaluated the bromination of alkyl-substituted benzene derivatives. Under the standard conditions, mesitylene and 1-methylnaphthalene gave mono-brominated **3a**, **3b** in 96% and 94% yields respectively after 5h. It is noteworthy that the bromination of xylene derivatives performed successfully to afford brominated products **3c-e** in high yields and with excellent regioselectivities, except to the *p*-xylene where 14% of dibromide product was present. In addition, corresponding brominated derivatives **3f-h** of the naphthalene, tert-butylbenzene and 1-phenyloctane were obtained in good yields and *para* selectivity. Toluene was brominated in a moderate yield (**3i**). Less electron-rich than toluene such as benzene and the bromo, nitro benzenes did not react with NBS in HFIP. Additionally, it is important to note that the benzylic bromination did not occur on the alkyl-substituted benzene derivatives.

Table 1. Bromination of arenes in fluorinated alcohols[a]



1 2, 3



2b, 0.5 h, 96% **2c**, 0 °C, 15 min, 94% **2d**, 2 h, 94% **2e**, 15 min, 96% **2f**, 0.5 h, 94%[b]

2g, 0.5 h, 93% **2h**, 0.5 h, 84% **2i**, 2 h, 95% [c] **2j**, 0.5 h, 92%

2k, 0 °C, 2 h, 90% (p/o :14/1.0)[d] **2l**, R = *t*-Bu, 0 °C, 2 h, 89% (p/o : 13/1.0)[d] **2m**, R= Ph, 0 °C, 2 h, 91% (p/o : 18/1.0)[d] **2n**, 0 °C, 2 h, 85% (p/o : 6.0/1.0)[d] **2o** 0 °C, 2 h, 94% **2p,** 2 h, 93%

2q, 0 °C, 15 min, 90% (p/o : 20/1.0)[d] **2r**, 0 °C, 15 min 79% **2s**, 0 °C, 5 min 75% [c] **2t**, 0 °C, 2 h, 90% (p/o : 12/1.0)[d] **2u**, 0 °C, 2 h, 74% (p/o : 6.0/1.0)[d]

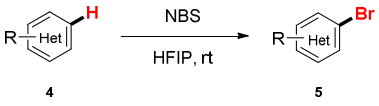
3a, 8 h, 96% **3b**, 8 h, 94% **3c**, 16 h, 85%[e] (mono/di : 5.9/1.0)[d] **3d**, 16 h, 96%[e] **3e**, 16 h, 98% (p/o : 4.8/1.0)[e]

3f, 16 h, 99%[e] (1/2 : 24/1.0)[d] **3g**, 16 h, 99%[e] **3h**, 16 h, 97%[e] (p/o : 4.8/1.0) **3i**, 16 h, 81%[e,f] (p/o : 3.0/1.0)[d] R = H, Br, NO_2 trace

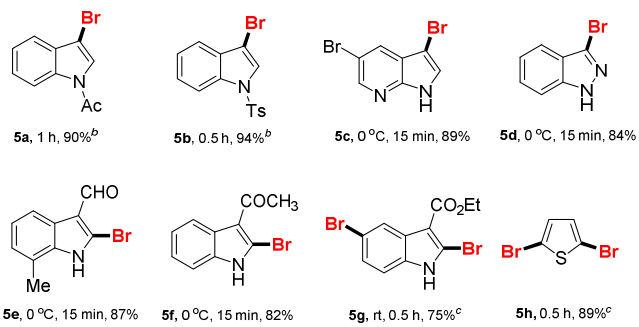
[a] Conditions: Arenes (0.5 mmol) and NBS (0.5 mmol, 1.0 equiv.) in HFIP (0.25 M) at r.t. for a specified period. [b] HFIP and DCM (1:1). [c] 2.0 equiv. NBS was used. [d] Major product is shown, isomeric ratios were determined by ^{1}H NMR. [e] Yield were determined by ^{1}H NMR using nitromethane as internal standard, combined yield of regioisomers. [f] Toluene (2.0 equiv.) was used.

We turned then our attention to the bromination of heteroaromatic derivatives. As illustrated in Table 2, electron-rich heteroarenes including indole, indazole, pyrazole, imidazole and thiophene were brominated to give corresponding products **5a-h** in good to excellent yields. For indoles, pyrazole and indazole, the halogenation worked with complete C-3 selectivity (**5a-d**). When the C-3 position was substituted, the bromination took place at the C-2 position (**5e-5f**). Besides, dibrominated indole and thiophene (**5g-5h**) were obtained in good yields when treated with 2.0 equiv of NBS.

Table 2. Bromination of heterocycles in fluorinated alcohols[a]



4 5



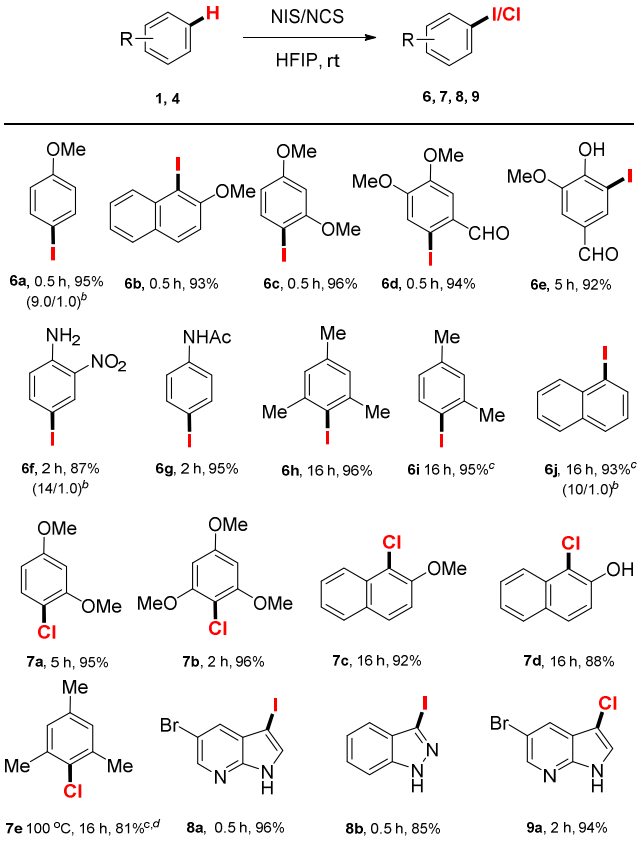
5a, 1 h, 90%[b] **5b**, 0.5 h, 94%[b] **5c**, 0 °C, 15 min, 89% **5d**, 0 °C, 15 min, 84%

5e, 0 °C, 15 min, 87% **5f**, 0 °C, 15 min, 82% **5g**, rt, 0.5 h, 75%[c] **5h**, 0.5 h, 89%[c]

[a] Conditions: Heterocycles (0.5 mmol) and NBS (0.5 mmol, 1.0 equiv.) in HFIP (0.25 M) at r.t. for a specified period.[b] HFIP and DCM (1:4). [c] 2.0 equiv. NBS were used.

Thereafter we were also interested in the reactivity of NIS and NCS in HFIP with a series of arenes and heterocycles (Table 3). From anisole derivatives, aniline, acetanilide, naphthalene and benzene derivatives, indoles and indazole, corresponding iodinated products **6a-j**, **8a-b** were obtained in high yields and regioselectivities. On the other hand, the chlorination with NCS worked solely on anisole, phenol and indole derivatives, affording monochlorinated products **7a-d** and **9a** in excellent yields and regioselectivities. The chlorination of mesitylene required high temperature, and the corresponding product **7e** was isolated in 81% yield.

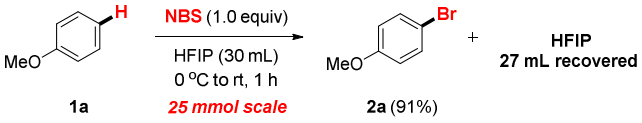
Table 3. Iodination and chlorination of Arenes and heterocycles



[a] Conditions: Arenes or heterocycles (0.5 mmol) and NIS (0.5 mmol, 1.0 equiv.) in HFIP (0.25 M) at r.t. for a specified period. [b] Major product is shown, isomeric ratios were determined by ^{1}H NMR. [c]Yield were determined by ^{1}H NMR using nitromethane as internal standard. [d] 1.2 equiv. NCS was used.

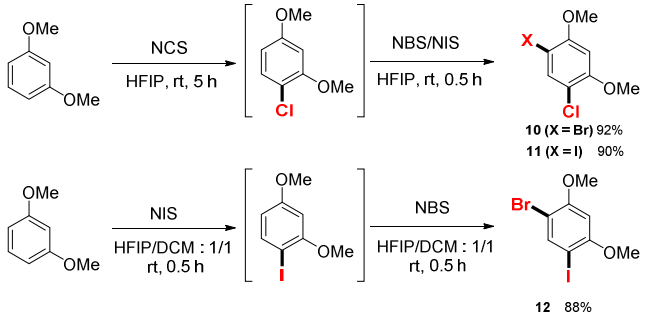
This halogenation could be easily scaled up and the solvent could be recycled due to its low boiling point (b.p. = 59°C) (Scheme 3).[9c] For example, when the bromination of anisole **1a** with NBS was performed on 25 mmol scale in 30 mL HFIP for 1 h. The desired product **2a** could be obtained smoothly in 91% yield, and 27 mL of HFIP was recovered after distillation directly from the reaction.

Scheme 3. Gram scale reaction.



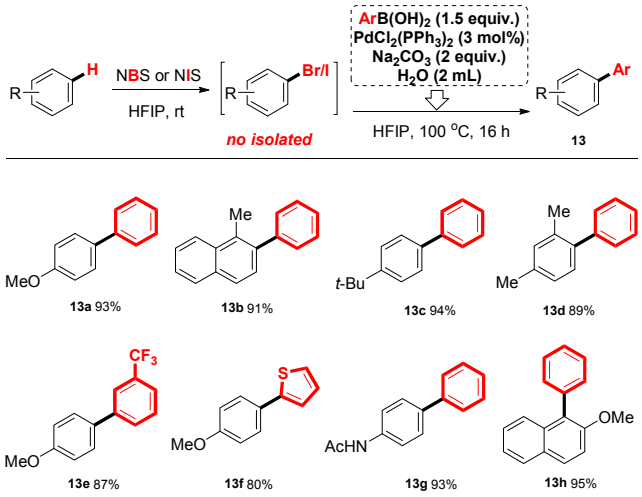
Face to the different reactivities of the *N*-halosuccinimides in HFIP, we undertook the sequential halogenation in one-pot (Scheme 4). For example, when 1,3-dimethoxybenzene was treated successively by NCS then NBS or NIS, corresponding compounds **10** and **11** were obtained in 92% and 90% yields respectively. Evenly the sequential treatment with NIS then NBS, the iodo-bromo-substituted compound **12** was isolated in 88% yield. For each step, the reactions are completely regioselective.

Scheme 4. One-pot sequential halogenation



In order to take advantage of these effective and mild conditions, we attempted the one-pot combination halogenation/Pd-catalyzed Suzuki cross-coupling reaction (Table 4).[12] After conversion of arenes into halo-arenes with NBS or NIS, the reaction medium was directly subjected to the Suzuki reaction in the presence of aryl boronic acids (1.5 equiv), $PdCl_2(PPh_3)_2$ (3 mol%), Na_2CO_3 (2 equiv) and water (2 mL) as co-solvent.[13] The reaction proceeded at 100°C during 16h. The corresponding coupling compounds **13a-h** could be isolated in good to excellent yields (80-95%) in two steps.

Table 4. One-pot halogenation/Suzuki cross-coupling reaction.



[a] Conditions: Arenes (0.5 mmol) and NBS (**13a-f**) or NIS(**13g-h**) (1.0 equiv.) in 2 mL HFIP for the first step. $ArB(OH)_2$ (1.5 equiv.), Na_2CO_3 (2 equiv.), $PdCl_2(PPh_3)_2$ (3 mol%) and 2 mL H_2O were added for the second step. Isolated yields.

CONCLUSIONS

In conclusion, due to its strong H-bond donation ability, hexafluoroisopropanol have proved to be a very efficient solvent for the regioselective halogenation of arenes and heterocycles with *N*-halosuccinimides. The aryl halides are obtained in short times at room temperature without any additional catalyst or reagent. Furthermore, the clean conditions allow the sequential halogenation of arenes and the combination of halogenation reaction followed by the Suzuki cross-coupling reaction without removal of the solvent or isolation of the brominated intermediate.

EXPERIMENTAL SECTION

General information. Thin-layer chromatography (TLC) was performed on silica gel, 60F-250 (0.26mm thickness) plates. The plates were visualized with UV light (254 nm) or with a 3.5% solution of phosphomolybdic acid in ethanol or with a solution of $KMnO_4$ in water. High-resolution mass spectra (HRMS) were obtained from waters LCT Premier (ESI/TOF). Flash chromatography (FC) was performed on Merck 60 silica gel (230 - 400 mesh). Melting points were determined on a Kofler melting point apparatus. NMR spectra were mesured on an Ultrafield AVANCE300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) spectrometer. Unless otherwise stated, NMR data were obtained under ambient temperature conditions. Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard (dimethyl sulfoxide: δ 2.50 ppm, chloroform: δ 7.26 ppm, methanol: δ 3.31 ppm). Chemical shifts for ^{13}C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent as the internal standard (dimethyl sulfoxide: δ 39.52 ppm, chloroform: δ 77.16 ppm, methanol: δ 49.00 ppm). Data are reported as following: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, appt = apparent triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration.

Reagents. Unless otherwise noted, commercially available arenes, N-halosuccinimide (NBS, NIS, and NCS), heterocycles, and benzeneboronic acid were purchased from various commercial sources (Acros, Aldrich) and used without further purification. NCS, NBS were purified by recrystallization from water.

General procedure for bromination of arenes with NBS. To a stirred solution of arenes 1 (0.5 mmol) in HFIP (2 mL) was added NBS (0.5 mmol) under air. The reaction mixture was stirred at rt for 0.25-16 h. After, the reaction mixture was evaporated under reduce pressure and the crude product was purified by column chromatography on silica gel using cyclohexane: ethyl acetate as the eluent to give the brominated products **2**, **3**.

Characterization Data of 2a – 2u, 3a – 3b.

1-bromo-4-methoxybenzene (2a).[8a] The title compound was prepared between anisole (54.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 15 min, and purified by using 5 % EtOAc in cyclohexane as a colorless oil (86 mg, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 8.9 Hz, 2H), 6.79 (d, J = 8.9 Hz, 2H), 3.78 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.8, 132.4, 115.8, 112.9, 55.6.

4-bromo-2-fluoro-1-methoxybenzene (2b).[14] The title compound was prepared between 2-fluoroanisole (63.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 30 min, and purified by using 5 % EtOAc in cyclohexane as a colorless oil (98 mg, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 – 7.09 (m, 2H), 6.75 (t, J = 8.9 Hz, 1H), 3.79 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 152.4 (d, J = 249.0 Hz), 147.2 (d, J = 9.8 Hz), 127.3 (d, J = 4.5 Hz), 119.7 (d, J = 21.0 Hz), 114.7, 112.0 (d, J = 8.3 Hz), 56.5.

1-bromo-4-methoxy-2-methylbenzene (2c).[8a] The title compound was prepared between 3-methylanisole (61.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 °C for 15 min, and purified by using 5 % EtOAc in cyclohexane as a colorless oil (94 mg, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 8.7 Hz, 1H), 6.79 (d, J = 2.9 Hz, 1H), 6.62 (dd, J = 8.7, 3.0 Hz, 1H), 3.77 (s, 3H), 2.37 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.9, 138.9, 132.9, 116.6, 115.5, 113.5, 55.5, 23.2.

2-bromo-4-chloro-1-methoxybenzene (2d).[15] The title compound was prepared between 4-chloroanisole (72.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h, and purified by using 5 % EtOAc in cyclohexane as a colorless oil (103 mg, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 2.5 Hz, 1H), 7.24 (dd, J = 9.3, 2.6 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 3.88 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.9, 132.9, 128.4, 126.1, 112.6, 112.3, 56.6.

1-bromo-2-methoxynaphthalene (2e).[8a] The title compound was prepared between 2-methoxynaphthalene (79.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 15 min, and purified by using 5 % EtOAc in cyclohexane as a white solid (113 mg, 96%): mp 86–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 8.6 Hz, 1H), 7.82 (d, J = 9.2, 1H), 7.78 (d, J = 9.0, 1H), 7.57 (appt, J = 6.9 Hz, 1H), 7.40 (appt, J = 6.9 Hz, 1H), 7.27 (d, J = 8.9 Hz, 1H), 4.03 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 153.9, 133.3, 129.9, 129.1, 128.2, 127.9, 126.3, 124.4, 113.8, 108.8, 57.2.

1-bromo-2,4-dimethoxybenzene (2f).[8a] The title compound was prepared between 1,3-dimethoxybenzene (69.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP/DCM (1/1, 2 ml) at rt for 30 min, and purified by using 5 % EtOAc in cyclohexane as a colorless oil (102 mg, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 8.7 Hz, 1H), 6.48 (d, J = 2.6 Hz, 1H), 6.39 (dd, J = 8.7, 2.7 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 160.3, 156.6, 133.2, 106.0, 102.5, 100.1, 56.2, 55.7.

2-bromo-4,5-dimethoxybenzaldehyde (2g).[16] The title compound was prepared between 3,4-dimethoxybenzaldehyde (83.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 30 min, and purified by using 20 % EtOAc in cyclohexane as a white solid (114 mg, 93%): mp 134–136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.96 (s, 1H), 6.42 (s, 1H), 3.96 (s, 1H), 3.93 (s, 1H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 187.2, 163.1, 161.8, 132.9, 119.5, 103.6, 95.7, 56.6, 56.1.

3-bromo-4-hydroxy-5-methoxybenzaldehyde (2h).[3c] The title compound was prepared between 3-methoxy-4-hydroxybenzaldehyde (76.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 30 min, and purified by using 30 % EtOAc in cyclohexane as a white solid (97 mg, 84%): mp 166–168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.64 (s, 1H), 7.36 (s, 1H), 6.53 (s, 1H), 3.98 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 189.8, 149.0, 147.8, 130.2, 130.2, 108.3, 108.2, 56.8.

4,4'-oxybis(bromobenzene) (2i).[17] The title compound was prepared between diphenyl oxide (85.0 mg, 0.5 mmol) and NBS (178.0 mg, 1.0 mmol) in HFIP (2 ml) at rt for 2 h, and purified by using pure cyclohexane as a white

solid (155 mg, 95%): mp 60–62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 8.6 Hz, 4H), 6.88 (d, J = 8.6 Hz, 4H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 156.1, 133.0, 120.7, 116.3.

2-(4-bromophenyl)ethanol (2j).[18] The title compound was prepared between 2-phenylethanol (69.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 0.5 h, and purified by using 20 % EtOAc in cyclohexane as a white solid (99 mg, 92%): mp 56–58 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 4.03 (t, J = 4.2 Hz, 2H), 3.94 (t, J = 4.2 Hz, 2H), 2.22 (s, 1H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 157.8, 132.4, 116.4, 113.4, 69.5, 61.4.

4-bromophenol (2k).[19] The title compound was prepared between phenol (47.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 °C for 2 h, and purified by using 10 % EtOAc in cyclohexane as a white solid (77 mg, 90%): mp 66–68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J = 8.9 Hz, 2H), 6.72 (d, J = 8.9 Hz, 2H), 4.85 (s, 1H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.7, 132.6, 117.3, 113.0.

4-bromo-2-(tert-butyl)phenol (2l).[20] The title compound was prepared between 2-tert-butylphenol (75.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 °C for 2 h, and purified by using 10 % EtOAc in cyclohexane as a colorless oil (101 mg, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 2.2 Hz, 1H), 7.17 (dd, J = 8.4, 2.4 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 4.82 (s, 1H), 1.39 (s, 9H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 153.4, 138.7, 130.3, 129.7, 118.2, 113.0, 34.9, 29.5.

5-bromo-[1,1'-biphenyl]-2-ol (2m).[19] The title compound was prepared between 2-phenylphenol (85.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 °C for 2 h, and purified by using 15 % EtOAc in cyclohexane as a colorless oil (114 mg, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.48 (m, 2H), 7.45 – 7.42 (m, 3H), 7.37 – 7.34 (m, 2H), 6.88 (d, J = 8.6 Hz, 1H), 5.21 (s, 1H); ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 151.7, 132.7, 131.9, 129.6, 129.0, 128.6, 117.8, 112.9.

4-bromo-3-methylphenol (2n).[3c] The title compound was prepared between 3-methylphenol (54.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 °C for 2 h, and purified by using 10 % EtOAc in cyclohexane as a colorless oil (79 mg, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.6 Hz, 1H), 6.73 (d, J = 2.7 Hz, 1H), 6.55 (dd, J = 8.6, 2.9 Hz, 1H), 5.00 (s, 1H), 2.33 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.7, 139.3, 133.2, 117.9, 115.6, 114.6, 23.1.

2-bromo-4-isopropylphenol (2o).[21] The title compound was prepared between 4-isopropylphenol (68.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 °C for 2 h, and purified by using 10 % EtOAc in cyclohexane as a colorless oil (101 mg, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 1.9 Hz, 1H), 7.08 (dd, J = 8.3, 1.7 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 5.37 (s, 1H), 2.90 – 2.76 (m, 1H), 1.22 (d, J = 6.9 Hz, 6H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 150.3, 142.8, 129.8, 127.4, 115.9, 110.11, 33.3, 24.2.

1-bromonaphthalen-2-ol (2p).[8a] The title compound was prepared between β-naphthol (72.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h, and purified by using 15 % EtOAc in cyclohexane as a white solid (103 mg, 93%): mp 82–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 8.9 Hz, 1H), 7.58 (appt, J = 7.3 Hz, 1H), 7.40 (appt, J = 7.5 Hz, 1H), 7.27 (d, J = 8.7 Hz, 1H), 5.93 (s, 1H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 150.7, 132.4, 129.8, 129.5, 128.3, 128.0, 125.5, 124.3, 117.3, 106.3.

4-bromo-2-nitroaniline (2q).[22] The title compound was prepared between 2-nitroaniline (69.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 °C for 15 min, and purified by using 20 % EtOAc in cyclohexane as a yellow solid (97 mg, 90%): mp 114–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J = 2.0 Hz, 1H), 7.42 (dd, J = 8.9, 2.0 Hz, 1H), 6.73 (d, J = 8.9 Hz, 1H), 6.11 (s, 2H); ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 143.7, 138.6, 128.4, 120.4, 108.0.

2-bromo-4-(trifluoromethyl)aniline (2r).[23] The title compound was prepared between 4-trifluoromethylaniline (80.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 °C for 15 min, and purified by using 10 % EtOAc in cyclohexane as a colorless oil (94 mg, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.34 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 4.37 (s, 2H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 147.1, 130.0 (d, J = 3.0 Hz), 125.7 (d, J = 3.8 Hz), 122.2, 121.1 (d, J = 33.0 Hz), 114.8, 108.2.

2,6-dibromo-4-methylaniline (2s).[22] The title compound was prepared between 4-methylaniline (53.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 °C for 5 min, and purified by using 10 % EtOAc in cyclohexane as a yellow solid (99 mg, 75%): mp 74–76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (s, 2H), 4.23 (s, 2H), 2.21 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 139.6, 132.3, 129.4, 108.8, 19.9.

N-(4-bromophenyl)acetamide (2t).[8a] The title compound was prepared between N-phenylacetamide (67.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 °C for 2 h, and purified by using 30 % EtOAc in cyclohexane as a white solid (96 mg, 90%): mp 168–170 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.05 (s, 1H), 7.54 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), 2.03 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6) δ 168.5, 138.7, 131.5, 120.9, 114.5, 24.0.

N-(4-bromo-3-chlorophenyl)acetamide (2u).[3a] The title compound was prepared between N-(3-chlorophenyl)acetamide (84.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 °C for 2 h, and purified by using 30 % EtOAc in cyclohexane as a white solid (92 mg, 74%): mp 122–124 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.21 (s, 1H), 7.96 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.38 (dd, J = 8.8, 2.0 Hz, 1H), 2.05 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6) δ 168.8, 139.9, 133.7, 132.9, 120.0, 119.1, 114.0, 24.0.

2-bromo-1,3,5-trimethylbenzene (3a).[23] The title compound was prepared between mesitylene (60.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 5 h, and purified by using pure cyclohexane as a colorless oil (95 mg, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (s, 2H), 2.40 (s, 6H), 2.26 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 138.0, 136.4, 129.1, 124.3, 23.8, 20.8.

2-bromo-1-methylnaphthalene (3b).[23] The title compound was prepared between 1-methylnaphthalene (71.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 5 h, and purified by using pure cyclohexane as a colorless oil (104 mg, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 9.2 Hz, 1H), 8.00 (d, J = 7.4 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.17 (d, J = 7.5 Hz, 1H), 2.67 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 134.5, 134.0, 131.9, 129.7, 127.8, 127.1, 127.1, 126.6, 124.7, 120.8, 19.4.

General procedure for bromination of heterocycles with NBS. To a stirred solution of heterocycles **4** (0.5 mmol) in HFIP (2 mL) was added NBS (0.5 mmol) under air. The reaction mixture was stirred at rt for 0.25–1 h. After, the reaction mixture was evaporated under reduce pressure and the crude product was purified by column chromatography on silica gel using cyclohexane: ethyl acetate as the eluent to give the brominated products **5**.

Physical data of 5a – 5h.

1-(3-bromo-1H-indol-1-yl)ethan-1-one (5a). [8c] The title compound was prepared between N-acetylindole (79.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP/DCM (1/4) at rt for 15 min, and purified by using 10 % EtOAc in cyclohexane as a white solid (107 mg, 90%): mp 114–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.49 (s, 1H), 7.44 – 7.33 (m, 2H), 2.62 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.9, 135.0, 129.5, 126.5, 124.4, 124.3, 119.6, 116.6, 100.2, 24.0.

3-bromo-1-tosyl-1H-indole (5b).[24] The title compound was prepared between N-tosylindole (135.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP/DCM (1/4) at rt for 15 min, and purified by using 5 % EtOAc in cyclohexane as a white solid (164 mg, 94%): mp 124–126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.63 (s, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.41 – 7.28 (m, 2H), 7.23 (d, J = 8.3 Hz, 2H), 2.34 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 145.5, 135.0, 134.4, 130.1, 129.9, 127.0, 125.9, 124.9, 124.0, 120.2, 113.7, 99.7, 21.7.

3,5-dibromo-1H-pyrrolo[2,3-b]pyridine (5c). The title compound was prepared between 5-bromo-1H-pyrrolo[2,3-b]pyridine (98.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at o °C for 15 min, and purified by using 30 % EtOAc in cyclohexane as a light yellow solid (122 mg, 89%): mp 230–232 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.33 (s, 1H), 8.35 (s, 1H), 8.02 (s, 1H), 7.80 (s, 1H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6) δ 145.63, 144.0, 128.3, 127.6, 120.4, 111.5, 86.4; HRMS calcd. for $C_7H_5N_2Br_2$[M+H]$^+$ m/z 276.8799, found 276.8804.

3-bromo-1H-indazole (5d).[24] The title compound was prepared between indazole (59.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at o °C for 15 min, and purified by using 20 % EtOAc in cyclohexane as a white solid (83 mg, 84%): mp 120–122 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.27 (s, 1H), 8.06 (s, 1H), 8.00 (s, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6) δ 138.5, 133.0, 128.6, 124.5, 122.9, 112.5, 112.2.

2-bromo-7-methyl-1H-indole-3-carbaldehyde (5e). The title compound was prepared between 7-methyl-1H-indole-3-carbaldehyde (72.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at o °C for 15 min, and purified by using 20 % EtOAc in cyclohexane as a yellow solid (97 mg, 87%): mp 236–238 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.33 (s, 1H), 9.93 (s, 1H), 8.33 (d, J = 2.7 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 2.55 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6) δ 185.1, 138.7, 126.1, 123.2, 121.7, 119.7, 118.5, 118.5, 16.9; HRMS calcd. for $C_{10}H_9NOBr$[M+H]$^+$ m/z 237.9868, found 237.9878.

1-(2-bromo-1H-indol-3-yl)ethan-1-one (5f). The title compound was prepared between 1-(1H-indol-3-yl)ethan-1-one (79.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at o °C for 15 min, and purified by using 20 % EtOAc in cyclohexane as a white solid (97 mg, 82%): mp 228–230 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.09 (s, 1H), 8.33 (d, J = 14.0 Hz, 2H), 7.44 (d, J = 8.6 Hz, 1H), 7.33 (dd, J = 8.6, 1.5 Hz, 1H), 2.45 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6) δ 192.7, 135.5, 135.4, 127.0, 125.3, 123.4, 116.2, 114.4, 114.1, 27.2; HRMS calcd. for $C_{10}H_9NOBr$ [M+H]$^+$ m/z 237.9868, found 237.9872.

Ethyl 2-bromo-1H-indole-3-carboxylate (5g). The title compound was prepared between ethyl-1H-indole-3-carboxylate (94.5 mg, 0.5 mmol) and NBS (178.0 mg, 1.0 mmol) in HFIP (2 ml) at rt for 30 min, and purified by using 30 % EtOAc in cyclohexane as a yellow solid (130 mg, 75%): mp 226–228 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.15 (s, 1H), 8.27 (s, 1H), 8.15 (d, J = 2.9 Hz, 1H), 7.87 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1, 3H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6) δ 163.7, 136.1, 134.6, 126.5, 124.4, 117.2, 116.5, 115.9, 106.3, 59.4, 14.4; HRMS calcd. for $C_{11}H_{10}NO_2{}^{79}Br{}^{81}Br$ [M+H]$^+$ m/z 347.9058, found 347.9055.

2,5-dibromothiophene (5h).[25] The title compound was prepared between thiophene (42.0 mg, 0.5 mmol) and NBS (178.0 mg, 1.0 mmol) in HFIP (2 ml) at rt for 30 min, and purified by using 5 % EtOAc in cyclohexane as a colorless oil (107 mg, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 2H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 130.5, 111.7.

General procedure for iodination and chlorination of arenes or heterocycles. To a stirred solution of arenes **1** or heterocycles **4** (0.5 mmol) in HFIP (2 mL) was added NIS or NCS (0.5 mmol) under air. The reaction mixture was stirred at rt for 0.5–16 h. After, the reaction mixture was evaporated under reduce pressure and the crude product was purified by column chromatography on silica gel using cyclohexane: ethyl acetate as the eluent to give the brominated products **6**, **7**, **8**, **9**.

Physical data of 6a – 6h, 7a – 7d, 8a – 8b, 9a.

1-iodo-2-methoxybenzene and 1-iodo-4-methoxybenzene (6a/6aa: 9/1).[21] The title compound was prepared between anisole (54.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 30 min, and purified by using 5 % EtOAc in cyclohexane as a colorless oil (111 mg, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 7.7 Hz, 0.1 ×1 H), 7.56 (d, J = 8.8 Hz, 0.9 × 2H), 7.31 (t, J = 7.8 Hz, 0.1 ×1 H), 6.83 (d, J = 8.2 Hz, 0.1 × 1H), 6.68 (d, J = 8.8 Hz, 0.9 × 2H), 3.88 (s, 0.1 × 3H), 3.78 (s, 0.9 × 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.5, 158.2, 139.6, 138.3, 129.6, 122.6, 116.5, 111.1, 86.1, 82.8, 56.4, 55.4.

1-iodo-2-methoxynaphthalene (6b).[3c] The title compound was prepared between 2-methoxynaphthalene (79.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 30 min, and purified by using 5 % EtOAc in cyclohexane as a white solid (132 mg, 93%): mp 88–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 8.6 Hz, 1H), 7.82 (d, J = 8.9 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.55 (appt, J = 7.5 Hz, 1H), 7.39 (appt, J = 7.5 Hz, 1H), 7.20 (d, J = 8.9 Hz, 1H), 4.02 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 156.7, 135.7, 131.3, 130.5, 130.0, 128.3, 128.2, 124.4, 113.02, 87.8, 57.3.

1-iodo-2,4-dimethoxybenzene (6c).[3c] The title compound was prepared between 1,3-dimethoxybenzene (69.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 30 min, and purified by using 5 % EtOAc in cyclohexane as a white solid (127 mg, 96%): mp 38–40 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 8.7 Hz, 1H), 6.48 (s, 1H), 6.39 (d, J = 8.7 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 160.3, 133.2, 106.0, 102.5, 100.1, 56.2, 55.7.

2-iodo-4,5-dimethoxybenzaldehyde (6d).[26] The title compound was prepared between 3,4-dimethoxybenzaldehyde (83.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 30 min, and purified by using 20 % EtOAc in cyclohexane as a white solid (127 mg, 96%): mp 174–176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.18 (s, 1H), 6.37 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 187.1, 164.2, 139.3, 120.5, 94.9, 75.7, 56.8, 56.0.

4-hydroxy-3-iodo-5-methoxybenzaldehyde (6e).[21] The title compound was prepared between 3-methoxy-4-hydroxybenzaldehyde (76.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 30 min, and purified by using 30 % EtOAc in cyclohexane as a white solid (128 mg, 92%): mp 180–182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.79 (s, 1H), 9.74 (s, 1H), 7.87 (s, 1H), 7.40 (s, 1H), 3.89 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6) δ 190.3, 152.2, 147.4, 134.8, 130.1, 110.2, 84.1, 56.3.

4-iodo-2-nitroaniline (6f).[28] The title compound was prepared between 2-nitroaniline (69.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h, and purified by using 20 % EtOAc in cyclohexane as a yellow solid (117 mg, 87%): mp 124–126 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.59 (d, J = 8.9 Hz, 1H), 7.53 (s, 2H), 6.85 (d, J = 8.9 Hz, 1H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6) δ 145.5, 143.2, 132.8, 131.4, 121.5, 74.8.

N-(4-iodophenyl)acetamide (6g).[6a] The title compound was prepared between N-phenylacetamide (67.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h, and purified by using 30 % EtOAc in cyclohexane as a white solid (124 mg, 95%): mp 170–172 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.01 (s, 1H), 7.61 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 2.03 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6) δ 168.4, 139.1, 137.2, 121.1, 86.2, 24.0.

2-iodo-1,3,5-trimethylbenzene (6h).[26] The title compound was prepared between 1,3,5-trimethylbenzene (54.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 16 h, and purified by pure cyclohexane as a colorless oil (118 mg, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (s, 2H), 2.47 (d, J = 4.1 Hz, 6H), 2.27 (d, J = 4.0 Hz, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 141.8, 137.4, 128.1, 104.4, 29.6, 20.8.

1-chloro-2,4-dimethoxybenzene (7a).[5b] The title compound was prepared between 1,3-dimethoxybenzene (69.0 mg, 0.5 mmol) and NCS (66.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 5 h, and purified by using 5 % EtOAc in cyclohexane as a colorless oil (82 mg, 95%): mp 36–38 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 9.0 Hz, 1H), 6.51 (d, J = 2.6 Hz, 1H), 6.43 (dd, J = 8.7, 2.6 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.6, 155.7, 130.2, 114.3, 105.3, 100.2, 56.2, 55.7.

2-chloro-1,3,5-trimethoxybenzene (7b).[5b] The title compound was prepared between 1,3,5-trimethoxybenzene (84.0 mg, 0.5 mmol) and NCS (66.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h, and purified by using 5 % EtOAc in cyclohexane as a white solid (97 mg, 96%). mp 92–94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (s, 2H), 3.87 (s, 6H), 3.80 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.5, 156.7, 102.8, 91.7, 56.4, 55.6.

1-chloro-2-methoxynaphthalene (7c).[15] The title compound was prepared between 2-methoxynaphthalene (79.0 mg, 0.5 mmol) and NCS (66.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 16 h, and purified by using 5 % EtOAc in cyclohexane as a white solid (88 mg, 92%): mp 68–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 8.6 Hz, 1H), 7.80 (d, J = 6.5 Hz, 1H), 7.77 (d, J = 6.7 Hz, 1H), 7.58 (appt, J = 7.5 Hz, 1H), 7.41 (appt, J = 7.5 Hz, 1H), 7.30 (d, J = 9.0 Hz, 1H), 4.04 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 132.0, 129.6, 128.1, 128.1, 127.6, 124.4, 123.6, 113.8, 57.1.

1-chloronaphthalen-2-ol (7d).[15] The title compound was prepared between naphthalen-2-ol (64.0 mg, 0.5 mmol) and NCS (66.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 16 h, and purified by using 10 % EtOAc in cyclohexane as a white solid (72 mg, 88%): mp 66–68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 8.9 Hz, 1H), 7.58 (appt, J = 7.7 Hz, 1H), 7.41 (appt, J = 7.5 Hz, 1H), 7.27 (d, J = 8.7 Hz, 1H), 5.90 (s, 1H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 149.5, 131.2, 129.6, 128.6, 128.3, 127.7, 124.3, 122.9, 117.3, 113.4.

5-bromo-3-iodo-1H-pyrrolo[2,3-b]pyridine (8a). The title compound was prepared between 5-bromo-1H-pyrrolo[2,3-b]pyridine (98.5 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 0.5 h, and purified by using 30 % EtOAc in cyclohexane as a white solid (155 mg, 96%): mp 240–242 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.34 (s, 1H), 8.31 (s, 1H), 7.86 (s, 1H), 7.80 (s, 1H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6) δ 146.5, 143.8, 132.5, 129.9, 123.8, 111.5, 53.5; HRMS calcd. for $C_7H_5N_2IBr$ $[M+H]^+$ m/z 322.8681, found 322.8675.

3-iodo-1H-indazole (8b). The title compound was prepared between 1H-indazole (59.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 0.5 h, and purified by using 20 % EtOAc in cyclohexane as a yellow solid (104 mg, 85%): mp 134–136 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.51 (s, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.19 (appt, J = 13.5 Hz, 1H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6) δ 140.4, 127.2, 126.8, 121.2, 120.4, 110.5, 93.5; HRMS calcd. for $C_7H_6N_2I$ $[M+H]^+$ m/z 244.9576, found 244.9572.

5-bromo-3-chloro-1H-pyrrolo[2,3-b]pyridine (9a). The title compound was prepared between 5-bromo-1H-pyrrolo[2,3-b]pyridine (98.5 mg, 0.5 mmol) and NCS (66.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h, and purified by using 30 % EtOAc in cyclohexane as a white solid (108 mg, 94%): mp 206–208 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.35 (s, 1H), 8.11 (s, 1H), 7.76 (s, 1H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6) δ 145.1, 144.0, 127.7, 125.2, 118.7, 111.4, 101.3; HRMS calcd. for $C_7H_5N_2BrCl$ $[M+H]^+$ m/z 232.9304, found 232.9306.

One-pot sequential halogenation. To a stirred solution of 1,3-dimethoxybenzene (69.0 mg, 0.5 mmol) in HFIP (2 mL) was added NCS (66.5 mg, 0.5 mmol). The reaction mixture was stirred at rt for 5 h. Then added NBS (89.0 mg, 0.5 mmol) or NIS (112.0 mg, 0.5 mmol) and the mixture was stirred at rt for another 0.5 h. After, the reaction mixture was evaporated under reduce pressure to get crude product. Then the crude product was purified by column chromatography on silica gel using cyclohexane: ethyl acetate (20: 1) as the eluent to give the sequential halogenated products **10-Cl-Br** and **11-Cl-I**.

1-bromo-5-chloro-2,4-dimethoxybenzene (10-Cl-Br).[8c] White solid (115 mg, 92%): mp 116–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1H), 6.50 (s, 1H), 3.90 (s, 3H), (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 155.6, 155.3, 133.3, 114.6, 102.0, 97.7, 56.7, 56.6.

1-chloro-5-iodo-2,4-dimethoxybenzene (11-Cl-I). White solid (134 mg, 90%): mp 128–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 6.43 (s, 1H), 3.90 (s, 3H), (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.1, 156.3, 138.8, 115.2, 96.8, 73.9, 56.8, 56.4.

1-bromo-5-iodo-2,4-dimethoxybenzene (12-I-Br). To a stirred solution of 1,3-dimethoxybenzene (69.0 mg, 0.5 mmol) in HFIP/DCM (1/1, 2 mL) was added NIS (112.0 mg, 0.5 mmol). The reaction mixture was stirred at rt for 0.5 h. Then added NBS (89.0 mg, 0.5 mmol) and the mixture was stirred at rt for another 0.5 h. After, the reaction mixture was evaporated under reduce pressure to get crude product. Then the crude product was purified by column chromatography on silica gel using cyclohexane: ethyl acetate as the eluent (20: 1) to give the sequential halogenated product **12-I-Br** as a white solid (151 mg, 88%): mp 168–170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 6.41 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.7, 157.3, 141.5, 103.2, 96.7, 74.6, 56.8, 56.5.

One-pot of halogenation with Suzuki cross-coupling reaction. To a stirred solution of arenes **1** (0.5 mmol) in HFIP (2 mL) was added NBS or NIS (0.5 mmol) under air. The reaction mixture was stirred at rt for 0.25–16 h. Afterward added boronic acid derivatives (0.75 mmol), sodium carbonate (1.0 mmol), $PdCl_2(PPh_3)_2$ (0.015 mmol), and H_2O (2.0 mL) under N_2 atmosphere. The mixture was placed in an oil bath and stirred at 100 °C for 16 h. Subsequently the mixture was cooled down to room temperature and treated with DCM (10 mL) and water (20 mL) and then extracted by CH_2Cl_2 (20 mL × 3). The combined extraction was washed by brine, dried over anhydrous $NaSO_4$ and concentrated in vacuum. The residue was purified by silica-gel column chromatography using cyclohexane: ethyl acetate as eluant to give desired products **13**.

4-methoxy-1,1'-biphenyl (13a).[28] The title compound was prepared as described in the general procedure using anisol (54.0 mg, 0.5 mmol), NBS (89.0 mg, 0.5 mmol) and phenylboronic acid (91.5 mg, 0.75 mmol), and purified by using 5 % EtOAc in cyclohexane as a white solid (86 mg, 93%)**:** mp 92–94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.54 (m, 4H), 7.44 (t, J = 7.5 Hz, 2H), 7.34 (d, J = 7.3 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 3.87 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.3, 141.0, 133.9, 128.8, 128.3, 126.8, 126.8, 114.3, 55.5.

1-methyl-2-phenylnaphthalene (13b).[29] The title compound was prepared as described in the general procedure using 1-methylnaphthalene (71.0 mg, 0.5 mmol), NBS (89.0 mg, 0.5 mmol) and phenylboronic acid (91.5 mg, 0.75 mmol), and purified by using pure cyclohexane as a colorless oil (99 mg, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.59 – 7.34 (m, 9H), 2.78 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 141.1, 138.8, 133.9, 132.9, 131.8, 130.3, 128.9, 128.3, 127.2, 126.8, 126.7, 126.3, 125.7, 124.5, 19.7.

4-(tert-butyl)-1,1'-biphenyl (13c).[30] The title compound was prepared as described in the general procedure using tert-butylbenzene (67.0 mg, 0.5 mmol), NBS (89.0 mg, 0.5 mmol) and phenylboronic acid (91.5 mg, 0.75 mmol), and purified by using pure cyclohexane as a colorless oil (99 mg, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61–7.54 (m, 4H), 7.49–7.41 (m, 4H), 7.38 – 7.31 (m, 1H), 1.38 (s, 9H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 150.4, 141.2, 138.5, 128.8, 127.2, 127.1, 126.9, 125.8, 34.7, 31.5.

2,4-dimethyl-1,1'-biphenyl (13d).[30] The title compound was prepared as described in the general procedure using m-xylene (53.0 mg, 0.5 mmol), NBS (89.0 mg, 0.5 mmol) and phenylboronic acid (91.5 mg, 0.75 mmol), and purified by using pure cyclohexane as a colorless oil (81 mg, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J = 7.2 Hz, 0.14 × 4H), 7.50 – 7.34 (m, 5H + 0.14 × 4H), 7.19 – 7.08 (m, 3H + 0.14 × 2H), 2.40 (s, 3H), 2.29 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 142.1, 141.4, 139.2, 137.0, 135.3, 131.2, 129.9, 129.4, 128.9, 128.2, 127.4, 127.3, 126.7, 126.6, 21.2, 20.5.

4'-methoxy-3-(trifluoromethyl)-1,1'-biphenyl (13e).[28] The title compound was prepared as described in the general procedure using anisol (54.0 mg, 0.5 mmol), NBS (89.0 mg, 0.5 mmol) and 3-(trifluoromethyl)phenylboronic acid (142.5 mg, 0.75 mmol), and purified by using 5 % EtOAc in cyclohexane as a white solid (86 mg, 93%): mp 78–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.73 (d, J = 7.0 Hz, 1H), 7.56 – 7.50 (m, 4H), 7.01 (d, J = 8.7 Hz, 2H), 3.87 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.9, 141.7, 132.3, 131.2 (q, J = 31.9 Hz), 130.1, 129.3, 128.4, 124.4 (q, J = 270.7 Hz), 123.5 (q, J = 4.8Hz), 123.4 (q, J = 4.1 Hz), 114.6, 55.5.

2-(4-methoxyphenyl)thiophene (13f).[31] The title compound was prepared as described in the general procedure using anisol (54.0 mg, 0.5 mmol), NBS (89.0 mg, 0.5 mmol) and 2-thienylboronic acid (87.0 mg, 0.75 mmol), and purified by using 10 % EtOAc in cyclohexane as a

white solid (71 mg, 80%): mp 104–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.7 Hz, 2H), 7.23 – 7.20 (m, 2H), 7.06 (t, J = 4.8 Hz, 1H), 6.92 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.3, 144.5, 128.0, 127.4, 127.3, 124.0, 122.2, 114.4, 55.5.

N-([1,1'-biphenyl]-4-yl)acetamide (13g).[32] The title compound was prepared as described in the general procedure using acetanilide (67.5 mg, 0.5 mmol), NIS (112.0 mg, 0.5 mmol) and phenylboronic acid (91.5 mg, 0.75 mmol), and purified by using 30 % EtOAc in cyclohexane as a white solid (98 mg, 93%): mp 170–172 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.02 (s, 1H), 7.70 – 7.59 (m, 6H), 7.43 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 2.07 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6) δ 168.3, 139.7, 138.8, 134.6, 128.8, 126.9, 126.8, 126.2, 119.3, 24.0.

2-methoxy-1-phenylnaphthalene (13h).[33] The title compound was prepared as described in the general procedure using 2-methoxynaphthalene (79.0 mg, 0.5 mmol), NIS (112.0 mg, 0.5 mmol) and phenylboronic acid (91.5 mg, 0.75 mmol), and purified by using 5 % EtOAc in cyclohexane as a white solid (111 mg, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.63 – 7.34 (m, 10H), 2.77 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 141.1, 138.8, 133.9, 132.9, 131.8, 130.3, 128.9, 128.3, 127.2, 126.8, 126.7, 126.3, 125.7, 124.5, 19.7.

Gram scale reaction. To a stirred solution of anisol **1a** (25 mmol, 2.70 g) in HFIP (30 mL) was added NBS (25 mmol, 4.45 g, 1.0 equiv.) under ice bath. Then remove the ice bath and the reaction mixture was stirred at rt for 1 h. After, HFIP solvent was recovered directly by atmospheric distillation from the reaction pot (27 mL, 90%). The residue was purified under reduced pressure distillation to afforded **3a** as a colorless oil (91%, 4.21 g).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Copies of the ^{1}H and ^{13}C NMR spectra (PDF).

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Notes

Any additional relevant notes should be placed here.

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