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Iron(III)-Catalyzed Chlorination of Activated Arenes

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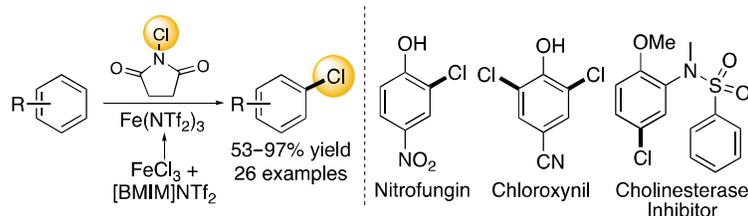
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Abstract: A general and regioselective method for the chlorination of activated arenes has been developed. The transformation uses iron(III) triflimide as a powerful Lewis acid for the activation of N -chlorosuccinimide and the subsequent chlorination of a wide range of anisole, aniline, acetanilide and phenol derivatives. The reaction was utilized for the late-stage mono- and di-chlorination of a range of target compounds such as the natural product nitrofungin, the antibacterial agent chloroxynol and the herbicide chloroxynil. The facile nature of this transformation was demonstrated with the development of one-pot tandem iron-catalyzed dihalogenation processes allowing highly regioselective formation of different carbon-halogen bonds. The synthetic utility of the resulting dihalogenated aryl compounds as building blocks was established with the synthesis of natural products and pharmaceutically relevant targets.

Keywords: Chlorination, iron catalysis, N -iodosuccinimide, nitrofungin, chloroxynil.

INTRODUCTION

Aromatic chlorides are an important class of compounds, widely used in organic chemistry as synthetic intermediates for coupling or substitution reactions, allowing the preparation of natural products and medicinally active compounds.¹ Due to the relative stability of the carbon-chlorine bond, aryl chlorides are also found as components in a vast array of natural products (e.g. phenols **1–3**, Figure 1)^{2–5} and used as structural motifs in pharmaceuticals, agrochemicals and other biologically active compounds. Examples include the fungicide nitrofungin (**1**),³ the broad spectrum antimicrobial agent chloroxylenol (**4**)⁶ and the pesticide chloroxynil (**5**).⁷

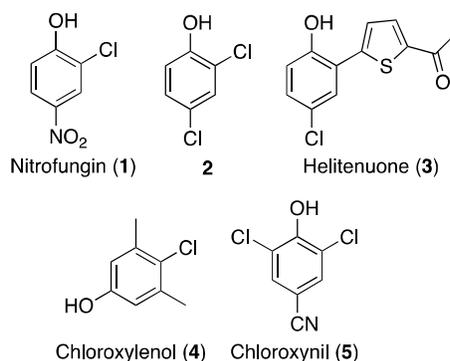


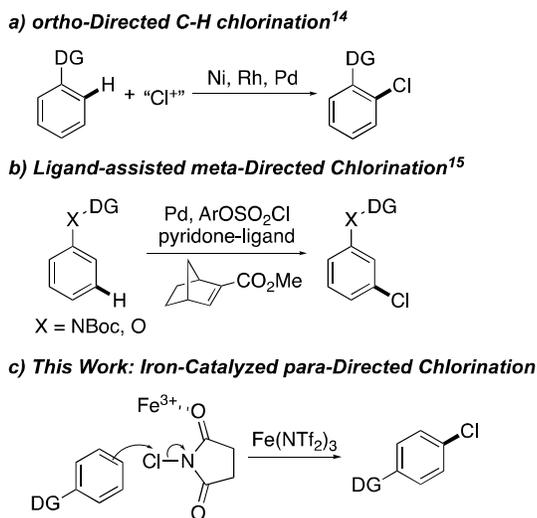
Figure 1. Structures of biologically active chlorobenzenes.

Due to the prevalence and importance of aryl chlorides, many general methods are known for the synthesis of these compounds. In fact, the halogenation of arenes is a fundamental reaction of organic synthesis. Traditionally, chlorination of aromatic compounds has involved electrophilic aromatic substitution,⁸ the Sandmeyer reaction of anilines⁹ or a directed *ortho*-lithiation-chlorination sequence.¹⁰ Despite the widespread use of these methods, they can involve harsh conditions, long reaction times and give poor regioselectivity and control. To overcome these limitations, recent efforts have focused on the development of new chlorination methods,¹¹ including transition metal-catalyzed reactions.^{12,13} In particular, the widespread developments in transition metal-catalyzed chelation-directed aryl C-H

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activation have led to a number of methods for *ortho*-chlorination (Scheme 1a).¹⁴ Recently, a chelation-directed aryl C-H activation process for *meta*-chlorination was developed by Yu and co-workers using a palladium-catalyzed pyridone ligand promoted protocol (Scheme 1b).¹⁵

Scheme 1. Strategies for Regioselective Aryl Chlorination

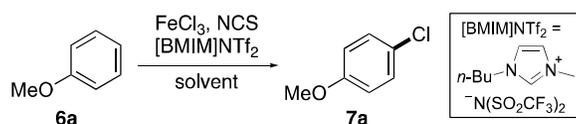


We recently reported the use of iron(III) triflimide or silver(I) triflimide as powerful Lewis acids for *N*-iodosuccinimide activation and the iodination of aryl compounds for application in radionuclide imaging.¹⁶ This type of transformation was also coupled with a copper-catalyzed Ullmann-type reaction resulting in a one-pot intermolecular aryl C-H amination process.¹⁷ We were interested in extending this Lewis acid catalyzed activation of *N*-halosuccinimides for the *para*-chlorination of arenes, resulting in a protocol that would be complementary to the many known *ortho*-directed chlorination methods. Furthermore, it was proposed that this type of Lewis acid catalyzed chlorination process could be coupled with other halogenation reactions for the regioselective, one-pot dihalogenation of aromatic compounds. We now report the development of a general chlorination protocol for *para*-substitution of activated arenes (Scheme 1c). As well as exploring the scope of this process for the preparation of a wide range of synthetic building blocks, natural products and pharmaceutically important compounds, we also describe the development of a tandem iron(III)-catalyzed chlorination-bromination process for

1 the regioselective dihalogenation of aromatic compounds. The synthetic utility of these compounds for
2 targeted synthesis is also reported.
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7 RESULTS AND DISCUSSION 8

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10 The study began with an investigation of the chlorination of anisole. We have previously shown
11 iron(III) triflimide catalyzed bromination and iodination of anisole.^{16a,17} During these transformations,
12 iron(III) triflimide was generated in situ using iron(III) chloride (5 mol %) and the ionic liquid, 1-butyl-
13 3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([BMIM]NTf₂), which was also used as the
14 reaction solvent.^{18,19} Under the same conditions, it was found that chlorination of anisole (**6a**) with *N*-
15 chlorosuccinimide (NCS) required more forcing conditions, with a higher temperature of 50 °C (versus
16 20 °C for iodination), to give 100% conversion after 5 h (Table 1, entry 1). The presence of iron(III)
17 chloride during this transformation is crucial for activation of NCS, as performing the reaction in the
18 absence of FeCl₃ under the same conditions (50 °C, [BMIM]NTf₂ as the solvent) showed no reaction
19 after 24 h (entry 2).²⁰ While [BMIM]NTf₂ is relatively inexpensive, recyclable and imparts high
20 cohesive pressure to the reaction resulting in fast halogenations, we were interested in developing for
21 the first time a halogenation reaction that was catalytic in both iron(III) chloride and [BMIM]NTf₂. It
22 was proposed that such a process would allow the chlorination of a wider substrate scope and simpler
23 work up and isolation protocols. Therefore, a solvent screen was performed using iron(III) chloride (2.5
24 mol %) and [BMIM]NTf₂ (7.5 mol %). Although no conversion was observed using *t*-butyl methyl ether
25 (entry 3), good reactivity was noted after 24 h in both toluene and THF (entries 4 and 5). Using THF as
26 the optimal solvent, an increase in temperature to 60 °C gave complete conversion, combined with a
27 shorter reaction time of 18 h (entry 6). It was also noted that a doubling of catalyst loading of both
28 iron(III) trichloride and [BMIM]NTf₂ at 60 °C gave a shorter reaction time of 8 h (entry 7). While the
29 conditions with low catalyst loadings (entry 6) were deemed suitable for most activated aryl
30 compounds, it was felt necessary to demonstrate the viability of procedures with higher catalyst
31 loadings (entries 1 and 7), that would likely be required for more challenging substrates.
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Table 1. Optimization of the Iron-Catalyzed Chlorination of Anisole

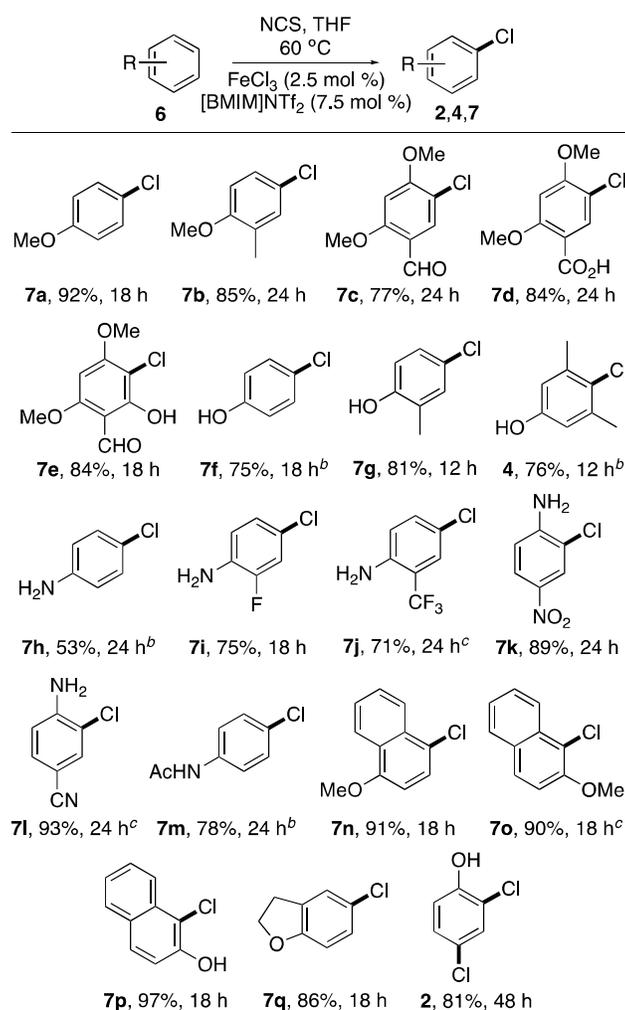
entry	FeCl ₃ (mol %)	[BMIM]NTf ₂ (mol %)	solvent	time (h)	temp (°C)	conversion (%) ^a
1	5	---	[BMIM]NTf ₂	5	50	100
2	---	---	[BMIM]NTf ₂	24	50	---
3	2.5	7.5	<i>t</i> -BuOMe	24	50	---
4	2.5	7.5	toluene	24	50	60
5	2.5	7.5	THF	24	50	75
6	2.5	7.5	THF	18	60	100
7	5	15	THF	8	60	100

^aConversions were measured using ¹H NMR spectroscopy.

The optimized procedure (Table 1, entry 6) was then used to explore the chlorination of activated arenes (Scheme 2). In general, the transformation was found to be compatible with a wide range of functional groups and could be used for the efficient mono-chlorination of anisole, phenol, aniline and acetanilide compounds (**7a–7q**). In contrast to iodination using iron(III) triflimide where only *para*-products were formed,^{16a} chlorination of several mono-substituted substrates [e.g. phenol (**6f**), aniline (**6h**) and acetanilide (**6m**)] yielded the *ortho*-isomer as a byproduct. This is likely due to a combination of the relatively small size of the chlorinating agent and the more forcing conditions required for this transformation. Nevertheless, the major *para*-isomers were easily separated and isolated in good yields (53–78%). For di-, tri- and tetra-substituted substrates, only the *para*-chlorinated products were formed, as observed by NMR spectroscopy of the crude reaction mixture. Similarly, for compounds with the *para*-positioned blocked, *ortho*-chlorinated compounds were cleanly formed in high yield and as single regioisomers. While the optimized procedure (2.5 mol % of FeCl₃) was effective for most substrates, including **6k** bearing the deactivating *para*-nitro group, several other aryl compounds containing

strongly electron withdrawing groups (e.g. **6j** and **6l**) required higher catalyst loading of both FeCl₃ (5 mol %) and [BMIM]NTf₂ (15 mol %) and a higher reaction temperature (70 °C) for efficient chlorination. Other arenes, such as naphthalenes **6n–6p** and 2,3-dihydrobenzofuran (**6q**) were also chlorinated, yielding single regioisomers in high yields. As well as using this method for the preparation of antiseptic agent chloroxylenol (**4**),⁶ reaction of phenol (**6f**) with two equivalents of NCS allowed efficient dichlorination and the synthesis of 2,4-dichlorophenol (**2**), a compound isolated from soil *Penicillium*, that is used as a growth hormone and as an intermediate for the preparation of herbicides.⁴

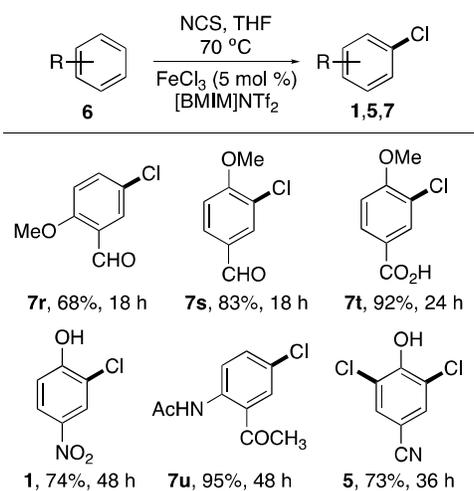
Scheme 2. Scope of Iron(III) Triflimide Catalyzed Chlorination^a



^aIsolated yields are shown. ^b*Ortho*-chlorinated products were observed (20% for **6f**, *m*-xylenol and **6m**; 30% for **6h**). ^cReaction was performed at 70 °C, using iron(III) trichloride (5 mol %) and [BMIM]NTf₂ (15 mol %).

A number of aryl compounds with deactivating groups gave poor or modest conversion when using the procedures involving catalytic [BMIM]NTf₂. Therefore, an alternative procedure was utilized for the chlorination of these compounds. It was found that using FeCl₃ (5 mol %) and [BMIM]NTf₂ as the solvent, at 70 °C, gave complete conversion to the mono-chlorinated products (**1**, **5** and **7r–7u**, Scheme 3). While the reactions required relatively long reaction times, the products were cleanly isolated in high yields. This allowed the efficient synthesis of 3-chloro-4-methoxybenzaldehyde (**7s**),²¹ a major metabolite from soil *Lepista nuda*, as well as nitrofungin (**1**), a compound isolated from *Stephanospora caroticolor*, which was previously used as a fungicide.³ These conditions were also effective for the dichlorination of 4-hydroxybenzoxynil, producing the pesticide chloroxynil (**5**) in 73% yield.⁷

Scheme 3. Iron(III) Triflimide Catalyzed Chlorination in [BMIM]NTf₂^a

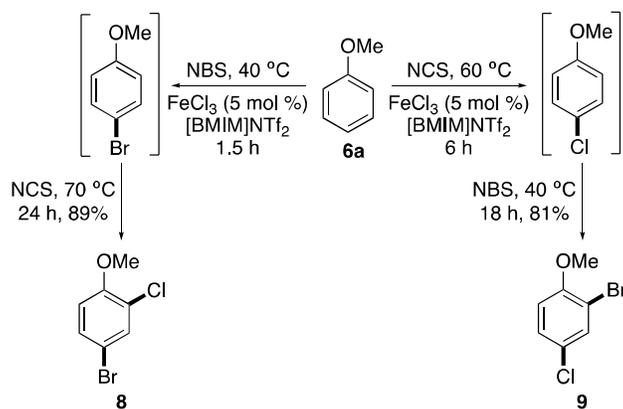


^aIsolated yields are shown.

The examination of the scope of this protocol clearly demonstrated that iron(III) triflimide catalyzed chlorination, compared to bromination or iodination, required higher temperatures and longer reaction

times. This was expected due to the stronger N-Cl bond of NCS. It was decided to take advantage of the reactivity difference and the clean production of halogenated products, to use this protocol for the design of one-pot multistep halogenation processes. It was proposed that a single loading of iron(III)-triflimide could be used to catalyze multiple halogenation reactions, allowing the selective preparation of carbon-halogen bonds with high regiocontrol. It was believed that the products of such a process could be exploited by using the differences in reactivity of the carbon-halogen bonds to introduce further functionality. As a proof of concept, anisole (**6a**) was subjected to a bromination reaction, followed by chlorination (Scheme 4). Using iron(III) chloride (5 mol %) in [BMIM]NTf₂ as the solvent, at 40 °C gave the *para*-brominated product after 1.5 h. Addition of NCS to the reaction mixture and an increase in temperature to 70 °C, allowed complete *ortho*-chlorination after 24 h and the isolation of **8** in 89% yield. The order of halogenation could also be reversed. Chlorination at higher temperature (60 °C), followed by bromination at 40 °C gave 2-bromo-4-chloroanisole (**9**) in 81% yield. The highly regioselective, clean generation of both the intermediate and the final product allowed the scale up of this process and the multigram synthesis of **9**.

Scheme 4. Tandem Iron(III)-Catalyzed Regioselective Dihalogenation^a

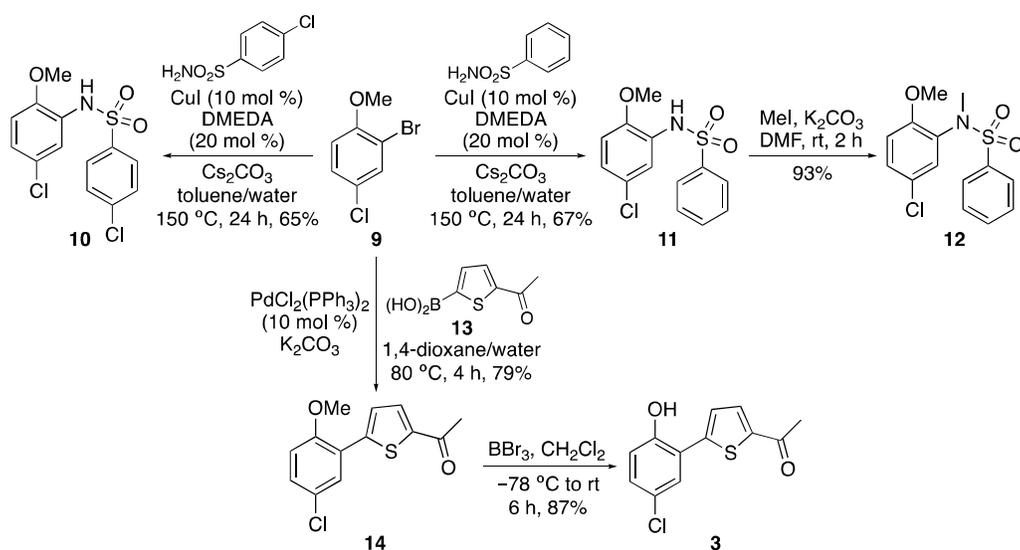


^aIsolated yields are shown.

Having used the tandem iron(III)-catalyzed halogenation process for the one-pot synthesis of **9**, we wanted to demonstrate the synthetic utility of such compounds, in particular, for the selective

functionalization of the C–Br bond and the preparation of biologically relevant chlorobenzene targets. 2-Bromo-4-chloroanisole (**9**) was found to be a good substrate for copper(I)-catalyzed *N*-arylation reactions (Scheme 5). Using 4-chlorobenzenesulfonamide as the nucleophile gave **10**, a compound with antibacterial activity, in 65% yield.²² A similar copper(I)-catalyzed *N*-arylation reaction with benzenesulfonamide, followed by *N*-methylation gave cholinesterase inhibitor **12** in good overall yield.²³ 2-Bromo-4-chloroanisole (**9**) was also used for a novel synthesis of helitenuone (**3**), a thiophene-derived chlorophenol isolated from *Helichrysum* species.⁵ The only other synthesis of this natural product involved a six-step sequence from a chlorinated benzaldehyde derivative, which gave helitenuone (**3**) in 7% overall yield.^{5b} In this current study, 2-bromo-4-chloroanisole (**9**) was subjected to a Suzuki-Miyaura reaction with commercially available thiophene-derived boronic acid **13**, under standard conditions. This gave coupled product **14** in 79% yield. Deprotection of the phenol moiety using boron tribromide completed the three-pot synthesis of helitenuone (**3**) in 56% overall yield from anisole (**6a**).

Scheme 5. Synthetic Applications of 2-Bromo-4-chloroanisole (9**)^a**



^aIsolated yields are shown.

CONCLUSIONS

In summary, methods for the chlorination of arenes using iron(III) triflimide activation of NCS have been developed. In particular, a procedure that utilizes catalytic amounts of both iron(III) chloride and [BMIM]NTf₂ was optimised for the regioselective mono-chlorination of activated arene substrates, while the use of higher loadings and the ionic liquid as a solvent was effective for more deactivated aromatic compounds. The reactions were also extended for dihalogenation, including the development of a selective one-pot tandem iron(III)-catalyzed process where different halogens could be introduced in a highly regioselective manner. The synthetic utility of both the single-step chlorination and the one-pot dihalogenations has been demonstrated with the rapid and efficient synthesis of a range of chlorobenzene-containing natural products and biologically active targets. In particular, the three-pot regioselective synthesis of helitenuone (**3**) demonstrates how highly functional aromatic compounds can be quickly accessed using these methods. Further studies to extend these strategies and concepts for the synthesis of other halogenated arenes are currently underway.

EXPERIMENTAL SECTION

All reagents and starting materials were obtained from commercial sources and used as received. The iron(III) chloride used in this study is reagent grade (97%). All dry solvents were purified using a solvent purification system. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Brine refers to a saturated solution of sodium chloride. Flash column chromatography was performed using silica gel 60 (35–70 μm). Aluminium-backed plates pre-coated with silica gel 60F₂₅₄ were used for thin layer chromatography and were visualized with a UV lamp or by staining with potassium permanganate. ¹H NMR spectra were recorded on a NMR spectrometer at either 400 or 500 MHz and data are reported as follows: chemical shift in ppm relative to tetramethylsilane as the internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of nonequivalent resonances, integration). ¹³C NMR spectra were recorded on a NMR spectrometer at either 101 or 126 MHz and data are reported as follows: chemical shift in ppm

1 relative to tetramethylsilane or the solvent (CDCl₃, δ 77.0 ppm or DMSO-*d*₆, δ 39.5 ppm) as internal
2 standard, multiplicity with respect to hydrogen (deduced from DEPT experiments, C, CH, CH₂ or CH₃).
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4 Conversions (Table 1) were measured by ¹H NMR spectroscopy, using dimethyl sulfone as an internal
5 standard. Infrared spectra were recorded on a FTIR spectrometer; wavenumbers are indicated in cm⁻¹.
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7 Mass spectra were recorded using electron impact, chemical ionization or electrospray techniques.
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9 HRMS spectra were recorded using a dual-focusing magnetic analyzer mass spectrometer. Melting
10 points are uncorrected.
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16 **General Chlorination Procedure A.** Iron(III) chloride (0.0250 mmol) was dissolved in 1-butyl-3-
17 methylimidazolium bis(trifluoromethanesulfonyl)imide (0.0750 mmol), stirred for 0.5 h at room
18 temperature and then added to a solution of *N*-chlorosuccinimide (1.05 mmol) in tetrahydrofuran (0.6
19 mL) under an atmosphere of air. The substrate (1.00 mmol) was then added and the reaction mixture
20 was heated to 60 °C, resulting in a homogeneous solution. Upon completion, the reaction mixture was
21 cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with a 1 M sodium
22 thiosulfate solution (10 mL) and brine (10 mL). The organic phase was dried (MgSO₄), filtered and
23 concentrated *in vacuo*. The crude product was purified by flash column chromatography.
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36 **General Chlorination Procedure B.** *N*-Chlorosuccinimide (1.05 mmol) was added to a solution of
37 iron(III) chloride (0.0500 mmol) in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide
38 (0.3 mL) under an atmosphere of air. The mixture was stirred at room temperature for 0.5 h before the
39 substrate (1.00 mmol) in acetonitrile (0.1 mL) was added. The reaction mixture was heated to 70 °C
40 resulting in a homogeneous mixture. Upon completion, the reaction mixture was then extracted with 5%
41 ethyl acetate in hexane (3 × 50 mL) using sonication in a water bath for 0.1 h. The suspension was
42 washed with an aqueous solution of 1 M sodium thiosulfate (10 mL), brine (10 mL), dried (MgSO₄) and
43 then filtered through a pad of Celite[®]. The solvent was removed under reduced pressure and the crude
44 product was purified by flash column chromatography.
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Work Up for Carboxylic acids and phenol derivatives. The reaction mixture was diluted with dichloromethane (10 mL) and extracted with an aqueous solution of 1 M sodium hydroxide (20 mL). The aqueous phase was separated, acidified with 1 M hydrochloric acid and extracted with dichloromethane (2×50 mL). The organic phase was dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.

4-Chloroanisole (7a).²⁴ The reaction was performed as described in general procedure A using anisole (**6a**) (108 μL , 1.00 mmol). The reaction mixture was heated to 60 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 4-chloroanisole (**7a**) (131 mg, 92%) as a colorless oil. Spectroscopic data were consistent with the literature.²⁴ ^1H NMR (500 MHz, CDCl_3) δ 3.77 (s, 3H), 6.80–6.85 (m, 2H), 7.21–7.26 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 55.5 (CH_3), 115.2 ($2 \times \text{CH}$), 125.5 (C), 129.3 ($2 \times \text{CH}$), 158.2 (C); MS (EI) m/z 142 (M^+ , 100), 127 (46), 99 (39), 84 (16).

4-Chloro-2-methylanisole (7b).²⁵ The reaction was performed as described in general procedure A using 2-methylanisole (**6b**) (124 μL , 1.00 mmol). The reaction mixture was heated to 60 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 4-chloro-2-methylanisole (**7b**) (133 mg, 85%) as a yellow oil. Spectroscopic data were consistent with the literature.²⁵ ^1H NMR (400 MHz, CDCl_3) δ 2.21 (s, 3H), 3.81 (s, 3H), 6.73 (d, $J = 9.2$ Hz, 1H), 7.09–7.15 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 16.2 (CH_3), 55.6 (CH_3), 111.1 (CH), 125.1 (C), 126.4 (CH), 128.6 (C), 130.5 (CH), 156.5 (C); MS (EI) m/z 156 (M^+ , 100), 141 (63), 83 (35), 77 (45), 57 (38).

5-Chloro-2,4-dimethoxybenzaldehyde (7c).²⁶ The reaction was performed as described in general procedure A using 2,4-dimethoxybenzaldehyde (**6c**) (166 mg, 1.00 mmol). The reaction mixture was heated to 60 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 10:1) gave 5-chloro-2,4-dimethoxybenzaldehyde (**7c**) (154 mg, 77%) as a white solid. Spectroscopic data were consistent with the literature.²⁶ Mp 130–132 °C; ^1H NMR (500 MHz, CDCl_3) δ 3.93 (s, 3H), 3.97 (s, 3H), 6.46 (s, 1H), 7.81 (s, 1H), 10.23 (s, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 56.0 (CH_3), 56.4

(CH₃), 95.7 (CH), 115.3 (C), 118.7 (C), 129.7 (CH), 160.8 (C), 162.4 (C), 187.2 (CH); MS (ESI) *m/z* 223 (MNa⁺, 100).

5-Chloro-2,4-dimethoxybenzoic acid (7d). The reaction was performed as described in general procedure A using 2,4-dimethoxybenzoic acid (**6d**) (182 mg, 1.00 mmol). The reaction mixture was heated to 60 °C for 24 h. Purification by flash column chromatography (dichloromethane/methanol, 19:1) gave 5-chloro-2,4-dimethoxybenzoic acid (**7d**) (181 mg, 84%) as a white solid. Mp 166–168 °C. IR (neat) 2970, 2569, 1694, 1599, 1243, 1213, 1021, 904, 820, 727 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.98 (s, 3H), 4.08 (s, 3H), 6.53 (s, 1H), 8.13 (s, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 56.6 (CH₃), 57.1 (CH₃), 96.0 (CH), 110.6 (C), 116.1 (C), 134.5 (CH), 158.4 (C), 160.0 (C), 164.6 (C); MS (EI) *m/z* 218 (M⁺, 36), 216 (100), 199 (47), 169 (42), 142 (22), 78 (27), 63 (32); HRMS (EI) calcd for C₉H₉³⁷ClO₄ (M⁺) 218.0163, found 218.0167.

5-Chloro-2,4-dimethoxy-6-hydroxybenzaldehyde (7e). The reaction was performed as described in general procedure A using 2,4-dimethoxy-6-hydroxybenzaldehyde (**6e**) (182 mg, 1.00 mmol). The reaction mixture was heated to 60 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 5-chloro-2,4-dimethoxy-6-hydroxybenzaldehyde (**7e**) (182 mg, 84%) as a light yellow solid. Mp 184–186 °C; IR (neat) 2953, 1631, 1595, 1470, 1453, 1417, 1410, 1292, 1227, 1186, 1119, 1100, 790, 731 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.91 (s, 3H), 3.97 (s, 3H), 5.99 (s, 1H), 10.09 (s, 1H), 12.80 (s, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 56.0 (CH₃), 56.5 (CH₃), 86.7 (CH), 101.4 (C), 106.1 (C), 160.3 (C), 162.5 (C), 162.8 (C), 192.0 (CH); MS (ESI) *m/z* 239 (MNa⁺, 100); HRMS (ESI) calcd for C₉H₉³⁵ClNaO₄ (MNa⁺) 239.0082, found 239.0083.

4-Chlorophenol (7f).²⁷ The reaction was performed as described in general procedure A using phenol (**6f**) (94 mg, 1.0 mmol). The reaction mixture was heated to 60 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 4-chlorophenol (**7f**) (96 mg, 75%) as a colorless oil. Spectroscopic data were consistent with the literature.²⁷ ¹H NMR (500 MHz, CDCl₃) δ

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4.77 (br s, 1H), 6.74–6.79 (m, 2H), 7.17–7.22 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 116.7 (2 \times CH), 125.8 (C), 129.5 (2 \times CH), 154.0 (C); MS (EI) m/z 128 (M^+ , 100), 102 (34), 84 (90), 66 (98), 57 (27).

4-Chloro-2-methylphenol (7g).²⁸ The reaction was performed as described in general procedure A using 2-methylphenol (**6g**) (108 mg, 1.00 mmol). The reaction mixture was heated to 60 °C for 12 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 4-chloro-2-methylphenol (**7g**) (115 mg, 81%) as a yellow solid. Mp 46–48 °C (lit.²⁸ 46–47 °C); ^1H NMR (500 MHz, CDCl_3) δ 2.22 (s, 3H), 5.02 (br s, 1H), 6.69 (d, J = 8.5 Hz, 1H), 7.03 (dd, J = 8.5, 2.7 Hz, 1H), 7.10 (d, J = 2.7 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 15.7 (CH_3), 116.1 (CH), 125.3 (C), 125.8 (C), 126.8 (CH), 130.7 (CH), 152.3 (C); MS (CI) m/z 143 (MH^+ , 48), 113 (45), 97 (40), 85 (68), 71 (100), 69 (54).

4-Chloro-3,5-dimethylphenol (4).²⁹ The reaction was performed as described in general procedure A using 3,5-dimethylphenol (122 mg, 1.00 mmol). The reaction mixture was heated to 60 °C for 12 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 4-chloro-3,5-dimethylphenol (**4**) (119 mg, 76%) as a white solid. Mp 112–114 °C (lit.²⁹ 116 °C); ^1H NMR (500 MHz, CDCl_3) δ 2.32 (s, 6H), 4.72 (s, 1H), 6.58 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 20.8 (2 \times CH_3), 115.3 (2 \times CH), 126.3 (C), 137.4 (2 \times C), 153.2 (C); MS (CI) m/z 157 (MH^+ , 26), 113 (66), 97 (43), 85 (69), 71 (100), 69 (53).

4-Chloroaniline (7h).³⁰ The reaction was performed as described in general procedure A using aniline (**6h**) (91 μL , 1.0 mmol). The reaction mixture was heated to 40 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 4-chloroaniline (**7h**) (67 mg, 53%) as a yellow solid. Mp 58–60 °C (lit.³⁰ 63–65 °C); ^1H NMR (400 MHz, CDCl_3) δ 3.64 (br s, 2H), 6.56–6.65 (m, 2H), 7.07–7.14 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 116.3 (2 \times CH), 123.3 (C), 129.2 (2 \times CH), 145.1 (C); MS (EI) m/z 127 (M^+ , 100), 92 (16), 84 (19), 64 (19).

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4-Chloro-2-fluoroaniline (7i).³¹ The reaction was performed as described in general procedure A using 2-fluoroaniline (**6i**) (111 mg, 1.00 mmol). The reaction mixture was heated to 60 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 4-chloro-2-fluoroaniline (**7i**) (109 mg, 75%) as a brown oil. Spectroscopic data were consistent with the literature.³¹ ¹H NMR (500 MHz, CDCl₃) δ 3.70 (br s, 2H), 6.69 (dd, *J* = 9.4, 8.5 Hz, 1H), 6.92 (ddd, *J* = 8.5, 2.3, 1.2 Hz, 1H), 7.00 (dd, *J* = 10.8, 2.3 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 115.9 (CH, d, ²*J*_{CF} = 22.0 Hz), 117.3 (CH, d, ³*J*_{CF} = 4.4 Hz), 122.5 (C, d, ³*J*_{CF} = 9.2 Hz), 124.5 (CH, d, ⁴*J*_{CF} = 3.6 Hz), 133.3 (C, d, ²*J*_{CF} = 13.0 Hz), 151.2 (C, d, ¹*J*_{CF} = 242.3 Hz); MS (EI) *m/z* 145 (M⁺, 32), 84 (100).

4-Chloro-2-trifluoromethylaniline (7j).³² The reaction was performed as described in general procedure A using 2-trifluoromethylaniline (**6j**) (126 μL, 1.00 mmol), iron(III) chloride (8.00 mg, 0.0500 mmol) and [BMIM]NTf₂ (44.0 μL, 0.150 mmol) in tetrahydrofuran (600 μL). The reaction mixture was heated to 70 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 4-chloro-2-trifluoromethylaniline (**7j**) (139 mg, 71%) as a pale yellow oil. Spectroscopic data were consistent with the literature.³² ¹H NMR (500 MHz, CDCl₃) δ 4.17 (br s, 2H), 6.67 (d, *J* = 8.7 Hz, 1H), 7.24 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 114.8 (C, q, ²*J*_{CF} = 30.8 Hz), 118.4 (CH), 122.4 (C), 124.1 (C, q, ¹*J*_{CF} = 272.4 Hz), 126.3 (CH, q, ³*J*_{CF} = 5.5 Hz), 132.8 (CH), 143.1 (C); MS (EI) *m/z* 195 (M⁺, 59), 175 (45), 148 (36), 107 (19), 84 (100), 77 (46).

2-Chloro-4-nitroaniline (7k).³³ The reaction was performed as described in general procedure A using 4-nitroaniline (**6k**) (138 mg, 1.00 mmol). The reaction mixture was heated to 60 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 2-chloro-4-nitroaniline (**7k**) (153 mg, 89%) as a yellow solid. Mp 98–100 °C (lit.³³ 99–101 °C); ¹H NMR (500 MHz, CDCl₃) δ 4.85 (br s, 2H), 6.75 (d, *J* = 8.9 Hz, 1H), 7.98 (dd, *J* = 8.9, 2.5 Hz, 1H), 8.19 (d, *J* = 2.5 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 113.7 (CH), 117.7 (C), 124.4 (CH), 126.0 (CH), 138.8 (C), 148.9 (C); MS (EI) *m/z* 172 (M⁺, 100), 142 (60), 126 (28), 99 (21), 90 (70), 63 (29).

4-Amino-3-chlorobenzonitrile (7l).³⁴ The reaction was performed as described in general procedure A using 4-aminobenzonitrile (**6l**) (118 mg, 1.00 mmol), iron(III) chloride (8.00 mg, 0.0500 mmol) and [BMIM]NTf₂ (44.0 μL, 0.150 mmol) in tetrahydrofuran (600 μL). The reaction mixture was heated to 70 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 4-amino-3-chlorobenzonitrile (**7l**) (142 mg, 93%) as a white solid. Mp 102–104 °C (lit.³⁴ 105.7–107.9 °C); ¹H NMR (400 MHz, CDCl₃) δ 4.65 (br s, 2H), 6.75 (d, *J* = 8.4 Hz, 1H), 7.31 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.50 (d, *J* = 1.8 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 100.7 (C), 115.1 (CH), 118.5 (C), 119.0 (C), 132.0 (CH), 133.3 (CH), 147.2 (C); MS (EI) *m/z* 152 (M⁺, 100), 125 (45), 117 (46), 90 (47), 76 (40), 63 (45).

4-Chloroacetanilide (7m).³⁵ The reaction was performed as described in general procedure A using acetanilide (**6m**) (135 mg, 1.00 mmol). The reaction mixture was heated to 60 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 4-chloroacetanilide (**7m**) (132 g, 78%) as a white solid. Mp 174–176 °C (lit.³⁵ 175–178 °C); ¹H NMR (500 MHz, CDCl₃) δ 2.17 (s, 3H), 7.21–7.30 (m, 3H), 7.42–7.48 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 24.6 (CH₃), 121.0 (2 × CH), 129.0 (2 × CH), 129.3 (C), 136.4 (C), 168.2 (C); MS (ESI) *m/z* 192 (MNa⁺, 100).

1-Chloro-4-methoxynaphthalene (7n).³⁶ The reaction was performed as described in general procedure A using 1-methoxynaphthalene (**6n**) (144 μL, 1.00 mmol). The reaction mixture was heated to 60 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1-chloro-4-methoxynaphthalene (**7n**) (175 mg, 91%) as a colorless oil. Spectroscopic data were consistent with the literature.³⁶ ¹H NMR (400 MHz, CDCl₃) δ 4.00 (s, 3H), 6.73 (d, *J* = 8.3 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.54 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.62 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 8.20 (br d, *J* = 8.4 Hz, 1H), 8.29 (br d, *J* = 8.3 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 55.7 (CH₃), 103.8 (CH), 122.4 (CH), 123.2 (C), 124.2 (CH), 125.7 (CH), 125.9 (CH), 126.6 (C), 127.5 (CH), 131.3 (C), 154.6 (C); MS (EI) *m/z* 192 (M⁺, 100), 177 (52), 149 (66), 114 (14), 84 (46).

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1-Chloro-2-methoxynaphthalene (7o).^{11a} The reaction was performed as described in general procedure A using 2-methoxynaphthalene (**6o**) (158 mg, 1.00 mmol), iron(III) chloride (8.00 mg, 0.0500 mmol) and [BMIM]NTf₂ (44.0 μL, 0.150 mmol) in tetrahydrofuran (600 μL). The reaction mixture was heated to 70 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 1-chloro-2-methoxynaphthalene (**7n**) (173 mg, 90%) as a white solid. Mp 64–66 °C (lit.^{11a} 68–69 °C); ¹H NMR (400 MHz, CDCl₃) δ 4.03 (s, 3H), 7.29 (d, *J* = 9.0 Hz, 1H), 7.41 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.58 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.80 (br d, *J* = 8.2 Hz, 1H), 8.21–8.26 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 57.1 (CH₃), 113.8 (CH), 117.0 (C), 123.6 (CH), 124.4 (CH), 127.6 (CH), 128.1 (2 × CH), 129.6 (C), 132.0 (C), 152.7 (C); MS (EI) *m/z* 192 (M⁺, 27), 149 (25), 97 (18), 84 (91), 66 (100), 57 (43).

1-Chloro-2-naphthol (7p).³⁷ The reaction was performed as described in general procedure A using 2-naphthol (**6p**) (144 mg, 1.00 mmol). The reaction mixture was heated to 60 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 1-chloro-2-naphthol (**7p**) (174 mg, 97%) as an off-white solid. Mp 64–66 °C (lit.³⁷ 66 °C); ¹H NMR (500 MHz, CDCl₃) δ 5.87 (s, 1H), 7.26 (d, *J* = 8.9 Hz, 1H), 7.40 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1H), 7.57 (ddd, *J* = 8.5, 6.8, 1.2 Hz, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.79 (br d, *J* = 8.1 Hz, 1H), 8.06 (br d, *J* = 8.5 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 113.4 (C), 117.3 (CH), 122.8 (CH), 124.2 (CH), 127.6 (CH), 128.2 (CH), 128.5 (CH), 129.5 (C), 131.1 (C), 149.4 (C); MS (ESI) *m/z* 177 ([M-H]⁻, 100).

5-Chloro-2,3-dihydrobenzofuran (7q).³⁸ The reaction was performed as described in general procedure A using 2,3-dihydrobenzofuran (**6q**) (113 μL, 1.00 mmol). The reaction mixture was heated to 60 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 5-chloro-2,3-dihydrobenzofuran (**7q**) (133 mg, 86%) as a colorless oil. Spectroscopic data were consistent with the literature.³⁸ ¹H NMR (500 MHz, CDCl₃) δ 3.20 (t, *J* = 8.7 Hz, 2H), 4.58 (t, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 1H), 7.05 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.13–7.16 (m, 1H, m); ¹³C NMR (126

1 MHz, CDCl₃) δ 29.7 (CH₂), 71.6 (CH₂), 110.2 (CH), 125.0 (C and CH), 127.8 (CH), 128.9 (C), 158.7
2 (C); MS (EI) m/z 154 (M⁺, 80), 91 (41), 84 (100).

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6 **2,4-Dichlorophenol (2).**³⁹ The reaction was performed as described in general procedure A using
7 phenol (**6f**) (94.0 mg, 1.00 mmol), NCS (280 mg, 2.10 mmol) in tetrahydrofuran (1.2 mL). The reaction
8 mixture was heated to 60 °C for 48 h. Purification by flash column chromatography (petroleum
9 ether/diethyl ether 19:1) gave 2,4-dichlorophenol (**2**) (131 mg, 81%) as a light orange solid. Mp 40–42
10 °C (lit.³⁹ 43–44 °C); ¹H NMR (400 MHz, CDCl₃) δ 5.49 (s, 1H), 6.95 (d, J = 8.7 Hz, 1H), 7.15 (dd, J =
11 8.7, 2.5 Hz, 1H), 7.33 (d, J = 2.5 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 117.3 (CH), 120.6 (C), 125.8
12 (C), 128.7 (2 × CH), 150.4 (C); MS (EI) m/z 162 (M⁺, 100), 153 (21), 136 (18), 107 (46), 89 (38).
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23 **5-Chloro-2-methoxybenzaldehyde (7r).**⁴⁰ The reaction was performed as described in general
24 procedure B using 2-methoxybenzaldehyde (**6r**) (60 mg, 0.44 mmol). The reaction mixture was heated
25 to 70 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 9:1)
26 gave 5-chloro-2-methoxybenzaldehyde (**7r**) (51 mg, 68%) as a white solid. Mp 78–79 °C (lit.⁴⁰ 80–81
27 °C); ¹H NMR (400 MHz, CDCl₃) δ 3.93 (s, 3H), 6.95 (d, J = 8.9 Hz, 1H), 7.50 (dd, J = 8.9, 2.8 Hz, 1H),
28 7.79 (d, J = 2.8 Hz, 1H), 10.41 (s, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 56.0 (CH₃), 113.3 (CH), 125.7
29 (C), 126.4 (C), 128.0 (CH), 135.4 (CH), 160.3 (C), 188.5 (CH); MS (EI) m/z 170 (M⁺, 17), 153 (6), 84
30 (100), 49 (79), 44 (32).
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43 **3-Chloro-4-methoxybenzaldehyde (7s).**⁴¹ The reaction was performed as described in general
44 procedure B using 4-methoxybenzaldehyde (**6s**) (122 μ L, 1.00 mmol) and NCS (160 mg, 1.20 mmol).
45 The reaction mixture was heated to 70 °C for 18 h. Purification by flash column chromatography
46 (petroleum ether/ethyl acetate 19:1) gave 3-chloro-4-methoxybenzaldehyde (**7s**) (141 mg, 83%) as a
47 pale yellow solid. Mp 52–54 °C (lit.⁴¹ 53–55 °C); ¹H NMR (400 MHz, CDCl₃) δ 3.99 (s, 3H), 7.04 (d, J
48 = 8.5 Hz, 1H), 7.77 (dd, J = 8.5, 2.0 Hz, 1H), 7.91 (d, J = 2.0 Hz, 1H), 9.85 (s, 1H); ¹³C NMR (101
49 MHz, CDCl₃) δ 56.5 (CH₃), 111.7 (CH), 123.7 (C), 130.3 (C), 130.5 (CH), 131.2 (CH), 159.8 (C), 189.6
50 (CH); MS (EI) m/z 169 (M⁺, 100), 143 (13), 126 (15), 115 (19), 99 (14), 83 (16), 75 (12), 63 (26).
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3-Chloro-4-methoxybenzoic acid (7t).⁴² The reaction was performed as described in general procedure B using 4-methoxybenzoic acid (**6t**) (76 mg, 0.50 mmol). The reaction mixture was heated to 70 °C for 24 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 17:3) gave 3-chloro-4-methoxybenzoic acid (**7t**) (86 mg, 92%) as a white solid. Mp 208–210 °C (lit.⁴² 211–214 °C); ¹H NMR (400 MHz, CDCl₃) δ 3.99 (s, 3H), 6.99 (d, *J* = 8.7 Hz, 1H), 8.02 (dd, *J* = 8.7, 2.1 Hz, 1H), 8.13 (d, *J* = 2.1 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 56.6 (CH₃), 111.5 (CH), 122.4 (C), 122.9 (C), 130.8 (CH), 132.5 (CH), 159.5 (C), 170.0 (C); MS (EI) *m/z* 186 (M⁺, 83), 169 (41), 115 (13), 83 (100), 63 (11).

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2-Chloro-4-nitrophenol (1).⁴³ The reaction was performed as described in general procedure B using 4-nitrophenol (70 mg, 0.50 mmol). The reaction mixture was heated to 70 °C for 48 h. Purification by flash column chromatography (petroleum ether/ethyl acetate 3:1) gave 2-chloro-4-nitrophenol (**1**) (64 mg, 74%) as a yellow solid. Mp 108–110 °C (lit.⁴³ 110–112 °C); ¹H NMR (400 MHz, CDCl₃) δ 6.34 (s, 1H), 7.13 (d, *J* = 9.0 Hz, 1H), 8.12 (dd, *J* = 9.0, 2.7 Hz, 1H), 8.29 (d, *J* = 2.7 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 116.4 (CH), 120.5 (C), 124.7 (CH), 125.5 (CH), 141.7 (C), 157.0 (C); MS (EI) *m/z* 173 (M⁺, 100), 143 (39), 107 (21), 99 (37), 84 (65), 63 (36).

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***N*-(2-Acetyl-4-chlorophenyl)acetamide (7u).** The reaction was performed as described in general procedure B using *N*-(2-acetylphenyl)acetamide (**6u**) (99 mg, 0.50 mmol). The reaction mixture was heated to 70 °C for 48 h. Purification by flash column chromatography (petroleum ether/diethyl ether, 9:1) gave *N*-(2-acetyl-4-chlorophenyl)acetamide (**7u**) (101 mg, 95%) as a white solid. Mp 126–128 °C; IR (neat) 3218, 2359, 1685, 1657, 1588, 1501, 1400, 1360, 1311, 1286, 1246, 1224, 828, 773, 637 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.22 (s, 3H), 2.65 (s, 3H), 7.49 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.82 (d, *J* = 2.5 Hz, 1H), 8.72 (d, *J* = 9.1 Hz, 1H), 11.56 (br s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 25.6 (CH₃), 28.7 (CH₃), 122.4 (CH), 122.9 (C), 127.3 (C), 131.2 (CH), 135.0 (CH), 139.7 (C), 169.6 (C), 201.9 (C); MS (EI) *m/z* 211 (M⁺, 44), 169 (97), 154 (100); HRMS (EI) calcd for C₁₀H₁₀³⁵ClNO₂ (M⁺) 211.0400, found 211.0402.

3,5-Dichloro-4-hydroxybenzonitrile (5). The reaction was performed as described in general procedure B using 4-hydroxybenzonitrile (60.0 mg, 0.500 mmol), NCS (147 mg, 1.10 mmol). The reaction mixture was heated to 70 °C and stirred for 36 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave 3,5-dichloro-4-hydroxybenzonitrile (**5**) (68 mg, 73%) as a white solid. Mp 128–130 °C; IR (neat) 3255, 2924, 2243, 1483, 1302, 1150, 909 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.48 (br s, 1H), 7.59 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 105.4 (C), 116.7 (C), 122.3 (2 × C), 132.2 (2 × CH), 152.3 (C); MS (EI) *m/z* 187 (M⁺, 100); HRMS (EI) calcd for C₇H₃³⁵Cl₂NO (M⁺) 186.9592, found 186.9583.

4-Bromo-2-chloroanisole (8).⁴⁴ *N*-Bromosuccinimide (178 mg, 1.00 mmol) was added to a solution of iron(III) chloride (8.00 mg, 0.0500 mmol) in [BMIM]NTf₂ (0.40 mL) under an atmosphere of air. The mixture was stirred at room temperature for 0.5 h before anisole (**6a**) (108 μL, 1.00 mmol) in acetonitrile (0.10 mL) was added. The reaction mixture was heated to 40 °C for 1.5 h. The reaction mixture was cooled to room temperature and *N*-chlorosuccinimide (160 mg, 1.20 mmol) was then added. The reaction mixture was heated to 70 °C for 24 h. The reaction was worked up according to general chlorination procedure B. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 4-bromo-2-chloroanisole (**8**) (197 mg, 89%) as a pale yellow solid. Mp 66–68 °C (lit.⁴⁴ 66.5–68.2 °C); ¹H NMR (400 MHz, CDCl₃) δ 3.88 (s, 3H), 6.79 (d, *J* = 8.8 Hz, 1H), 7.33 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.50 (d, *J* = 2.4 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 56.3 (CH₃), 112.5 (C), 113.3 (CH), 123.7 (C), 130.5 (CH), 132.7 (CH), 154.4 (C); MS (EI) *m/z* 222 (M⁺, 86), 179 (100), 126 (36).

2-Bromo-4-chloroanisole (9).⁴⁵ The reaction was performed as described in general procedure B using anisole (**6a**) (108 μL, 1.00 mmol). The reaction mixture was heated to 60 °C for 6 h. On completion of the chlorination step, the reaction mixture was cooled to room temperature and *N*-bromosuccinimide (178 mg, 1.00 mmol) was then added. The reaction mixture was heated to 40 °C for 18 h. Purification by flash column chromatography (petroleum ether/ethyl acetate, 17:3) gave 2-bromo-4-chloroanisole (**9**) (178 mg, 81%) as a colorless oil. Spectroscopic data were consistent with the

1 literature.⁴⁵ ¹H NMR (500 MHz, CDCl₃) δ 3.88 (s, 3H), 6.82 (d, *J* = 8.8 Hz, 1H), 7.24 (dd, *J* = 8.8, 2.5
2 Hz, 1H), 7.54 (d, *J* = 2.5 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 56.6 (CH₃), 112.3 (C), 112.7 (CH),
3 126.1 (C), 128.4 (CH), 132.9 (CH), 154.9 (C); MS (EI) *m/z* 222 (M⁺, 100), 207 (50), 179 (36), 126 (10),
4 75 (12), 63 (21).
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10 ***N*-(5'-Chloro-2'-methoxyphenyl)-4-chlorobenzenesulfonamide (10).**²² To a solution of 2-bromo-4-
11 chloroanisole (**9**) (110 mg, 0.500 mmol) in toluene (0.50 mL) was added 4-chlorobenzenesulfonamide
12 (115 mg, 0.600 mmol), copper(I) iodide (10.0 mg, 0.0500 mmol), *N,N'*-dimethylethylenediamine (11.0
13 μL, 0.100 mmol), cesium carbonate (326 mg, 1.00 mmol) and water (0.30 mL). The reaction mixture
14 was degassed under argon for 0.1 h and then heated to 150 °C for 24 h. The reaction mixture was then
15 cooled to room temperature, diluted with ethyl acetate (10 mL), washed with 1 M sodium thiosulfate
16 solution (10 mL) and brine (10 mL). The organic phase was dried (MgSO₄), filtered and concentrated *in*
17 *vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave *N*-(5'-
18 chloro-2'-methoxyphenyl)-4-chlorobenzenesulfonamide (**10**) (107 mg, 65%) as a white solid. Mp 142–
19 144 °C (lit.²² 144–146 °C); ¹H NMR (400 MHz, CDCl₃) δ 3.66 (s, 3H), 6.67 (d, *J* = 8.7 Hz, 1H), 7.01
20 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.03 (br s, 1H), 7.38–7.42 (m, 2H), 7.53 (d, *J* 2.5 Hz, 1H), 7.69–7.74 (m, 2H);
21 ¹³C NMR (101 MHz, CDCl₃) δ 56.0 (CH₃), 111.5 (CH), 121.0 (CH), 125.3 (CH), 126.2 (C), 126.5 (C),
22 128.6 (2 × CH), 129.2 (2 × CH), 137.4 (C), 139.7 (C), 148.0 (C); MS (EI) *m/z* 331 (M⁺, 100), 296 (52),
23 262 (18), 158 (32), 156 (100), 126 (19), 111 (27), 93 (48), 75 (16).
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44 ***N*-(5'-Chloro-2'-methoxyphenyl)benzenesulfonamide (11).**²³ The reaction was performed as
45 described for 4-chloro-*N*-(5'-chloro-2'-methoxyphenyl)benzenesulfonamide (**10**) using 2-bromo-4-
46 chloroanisole (**9**) (221 mg, 1.00 mmol) and benzenesulfonamide (189 mg, 1.20 mmol). Purification by
47 flash column chromatography (petroleum ether/ethyl acetate, 7:3) gave *N*-(5'-chloro-2'-
48 methoxyphenyl)benzenesulfonamide (**11**) (199 mg, 67%) as a white solid. Mp 140–142 °C (lit.²³ 140–
49 142 °C); ¹H NMR (400 MHz, CDCl₃) δ 3.63 (s, 3H), 6.64 (d, *J* = 8.7 Hz, 1H), 6.98 (dd, *J* = 8.7, 2.6 Hz,
50 1H), 7.02 (br s, 1H), 7.40–7.47 (m, 2H), 7.50–7.53 (m, 1H), 7.55 (d, *J* = 2.6 Hz, 1H), 7.76–7.82 (m,
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2H); ^{13}C NMR (101 MHz, CDCl_3) δ 56.0 (CH_3), 111.5 (CH), 120.8 (CH), 124.9 (CH), 126.1 (C), 126.9 (C), 127.2 (2 \times CH), 128.9 (2 \times CH), 133.1 (CH), 139.0 (C), 148.0 (C); MS (EI) m/z 297 (M^+ , 79), 156 (100), 93 (70), 77 (40), 51 (27).

***N*-(5'-Chloro-2'-methoxyphenyl)-*N*-methylbenzenesulfonamide (12).**²³ To a solution of *N*-(5'-chloro-2'-methoxyphenyl)benzenesulfonamide (**11**) (38 mg, 0.13 mmol) in DMF (0.7 mL) was added potassium carbonate (53 mg, 0.38 mmol) and iodomethane (24 μL , 0.38 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched with water (2 mL) and extracted with diethyl ether (3 \times 3 mL). The organic layers were combined, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave *N*-(5'-chloro-2'-methoxyphenyl)-*N*-methylbenzenesulfonamide (**12**) (37 mg, 93%) as a colorless oil. Spectroscopic data were consistent with the literature.²³ ^1H NMR (500 MHz, CDCl_3) δ 3.18 (s, 3H), 3.36 (s, 3H), 6.71 (d, $J = 8.8$ Hz, 1H), 7.23 (dd, $J = 8.8, 2.7$ Hz, 1H), 7.29 (d, $J = 2.7$ Hz, 1H), 7.44–7.50 (m, 2H), 7.53–7.59 (m, 1H), 7.66–7.71 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 37.8 (CH_3), 55.3 (CH_3), 112.6 (CH), 125.1 (C), 127.5 (2 \times CH), 128.6 (2 \times CH), 129.4 (CH), 129.9 (C), 131.8 (CH), 132.4 (CH), 139.2 (C), 155.2 (C); MS (EI) m/z 311 (M^+ , 41), 170 (100), 155 (39), 84 (15), 77 (19).

2-(5-Acetylthien-2-yl)-4-chloroanisole (14). To a solution of 2-bromo-4-chloroanisole (**9**) (160 mg, 0.730 mmol) in 1,4-dioxane (8 mL) was added 5-acetylthiophene-2-boronic acid (148 mg, 0.870 mmol), potassium carbonate (303 mg, 2.19 mmol) and water (6.0 mL). The reaction mixture was degassed with argon for 0.1 h. Bis(triphenylphosphine)palladium(II) dichloride (51.0 mg, 0.0730 mmol) was added and the reaction mixture was heated to 80 $^\circ\text{C}$ for 4 h. The reaction mixture was cooled to room temperature and the organic solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (15 mL), extracted with water (10 mL) and washed with brine (10 mL). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 19:1) gave 2-(5-acetylthien-2-yl)-4-chloroanisole (**14**) (154 mg, 79%) as yellow solid. Mp 128–130 $^\circ\text{C}$; IR 2941, 1653, 1436, 1277, 1259, 1021, 807, 677

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cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 2.57 (s, 3H), 3.95 (s, 3H), 6.93 (d, $J = 8.8$ Hz, 1H), 7.27 (dd, $J = 8.8, 2.6$ Hz, 1H), 7.47 (d, $J = 4.1$ Hz, 1H), 7.64–7.67 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 26.8 (CH₃), 55.9 (CH₃), 112.9 (CH), 123.6 (C), 126.0 (C), 126.2 (CH), 128.0 (CH), 129.3 (CH), 132.1 (CH), 143.8 (C), 146.1 (C), 154.6 (C), 191.1 (C); MS (ESI) m/z 289 (MNa^+ , 100); HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{11}^{35}\text{ClNaO}_2\text{S}$ (MNa^+) 289.0060, found 289.0052.

2-(5-Acetylthien-2-yl)-4-chlorophenol (3).^{5b} 2-(5-Acetylthien-2-yl)-4-chloroanisole (**14**) (50.0 mg, 0.190 mmol) was dissolved in dichloromethane (3.0 mL) and cooled to -78 °C. Boron tribromide (1 M in dichloromethane) (374 μL , 0.370 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 1 h, before warming to room temperature over 5 h. The reaction mixture was quenched by the addition of a saturated solution of sodium bicarbonate (2 mL) and then extracted with dichloromethane (4×3 mL). The organic layers were combined, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 4:1) gave 2-(5-acetylthien-2-yl)-4-chlorophenol (**3**) (41.0 mg, 87%) as yellow solid. Mp 212–214 °C (lit.^{5b} 218 °C); ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 2.53 (s, 3H), 7.00 (d, $J = 8.7$ Hz, 1H), 7.25 (dd, $J = 8.7, 2.6$ Hz, 1H), 7.79 (d, $J = 4.1$ Hz, 1H), 7.84 (d, $J = 2.6$ Hz, 1H), 7.89 (d, $J = 4.1$ Hz, 1H), 11.00 (br s, 1H); ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ 27.0 (CH₃), 118.5 (CH), 121.7 (C), 123.7 (C), 126.7 (CH), 127.3 (CH), 129.8 (CH), 133.8 (CH), 143.5 (C), 146.0 (C), 153.4 (C), 191.5 (C); MS (ESI) m/z 251 ($[\text{M}-\text{H}]^-$, 100).

SUPPORTING INFORMATION AVAILABLE. ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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