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Silver(I)-Catalyzed Iodination of Arenes: Tuning the Lewis Acidity of *N*-Iodosuccinimide Activation

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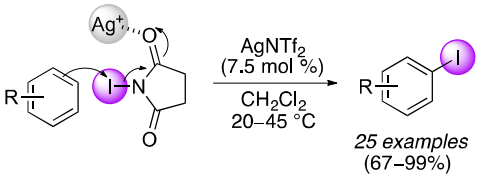


Abstract: A mild and rapid method for the iodination of arenes that utilizes silver(I) triflimide as a catalyst for activation of *N*-iodosuccinimide has been developed. The transformation was found to be general for a wide range of anisole, aniline, acetanilide and phenol derivatives and allowed the late-stage iodination of biologically active compounds such as PIMBA, a SPECT imaging agent of breast cancer and (–)-IBZM, a dopamine D_2 receptor antagonist. The method was also modified for the radioiodination of arenes using a one-pot procedure involving the in situ generation of [^{125}I]-*N*-iodosuccinimide followed by the silver(I)-catalyzed iodination.

Keywords: Iodination, silver catalysis, *N*-iodosuccinimide, SPECT imaging agents.

INTRODUCTION

Aryl iodides are highly important building blocks widely used in total synthesis, medicinal chemistry and material science. This general versatility is due to the higher reactivity of the C-I bond compared to the corresponding aryl bromide or chloride, allowing their use in highly effective metal-catalyzed cross-coupling reactions, nucleophilic aromatic substitution reactions and for the generation of free-radical intermediates.[1–3] Aryl iodides are also found as components in a number of medicinally important compounds such as 8-iodoharmaline (**1**), a potent monoamine oxidase inhibitor,[4] and 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) (**2**), a 5-HT_{2A} receptor agonist and inhibitor of tumor necrosis factor-α-induced inflammation (Figure 1).[5] When used in combination with single photon emission computed tomography (SPECT) imaging, radioiodinated aryl compounds also have significant impact on healthcare, finding application in clinical diagnosis, drug development and biomedical research.[6] For example, [^{123}I]-PIMBA (**3**)[7] and (–)-[^{123}I]-IBZM (**4**)[8] are SPECT imaging agents of human breast cancer and the human D_2 receptor, respectively, while the iodinated benzoxazole, [^{125}I]-IBOX (**5**) has been used to image amyloid plaques in the brain (Figure 1).[9]

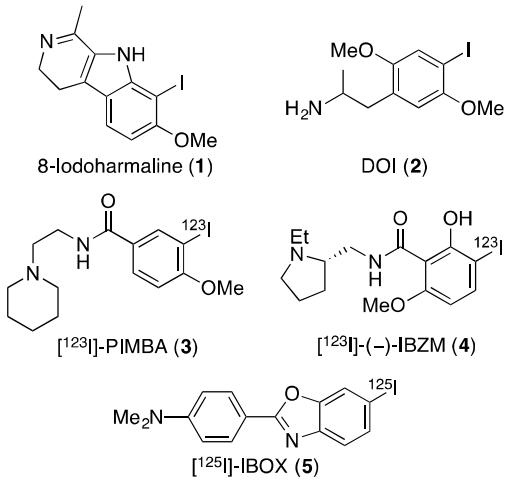
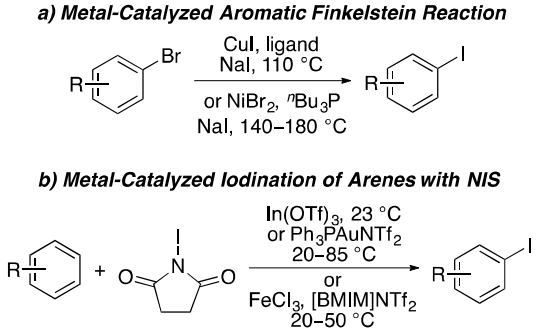


Figure 1. Structures of aryl iodide-containing inhibitors and SPECT imaging agents.

Due to the importance of aryl iodides, there has been much focus on the development of general methods for their synthesis that overcome the harsh reagents and conditions associated with more traditional approaches such as electrophilic aromatic substitution with iodine and the Sandmeyer reaction.[10,11] A recent advance has been the discovery of copper or nickel catalyzed Finkelstein reaction of aryl bromides (Scheme 1a).[12–14] Other iodide exchange reactions using leaving groups such as triflates and boronic acids have also been reported.[15,16] More direct methods that negate the need for installation of a leaving group and which can be performed at lower temperatures have also been developed.[17,18] A common approach is the activation of electrophilic iodine-containing reagents such as *N*-iodosuccinimide (NIS).[19] For example, Olah and co-workers used a combination of boron trifluoride and water for the Brønsted acid activation of NIS and the iodination of electron-deficient arenes,[20] while the groups of Romo and Frontier used indium(III)- and gold(I)-complexes, respectively, for the Lewis acid activation of NIS and the iodination of electron-rich arenes (Scheme 1b).[21]

We have a longstanding interest in rapid and efficient methods for the iodination and radioiodination of arenes that can facilitate the development of novel SPECT imaging agents.[22] To this end, we recently reported an iron(III)-catalyzed method for NIS activation and the subsequent iodination of activated arenes (Scheme 1b).[23] While this method could be accelerated using a triflimide based ionic liquid, leading to faster reactions at lower temperatures compared to other metal-catalyzed methods, some limitations were observed. In particular, we found that reaction of particularly active substrates such as phenols with the highly charged, hard iron(III) Lewis acid led to the formation of bis-iodinated products, thereby restricting the yield of the major mono-iodinated compounds. As SPECT imaging agents often contain electron rich aryl moieties including phenols (see Figure 1), we decided to investigate softer metals that would tune the activation of NIS leading to cleaner reactions of highly activated aryl compounds. Herein, we report the development of a silver(I) triflimide catalyzed iodination method that can be used for a wide range of substrates. As well as demonstrating the application of this procedure for the iodination of medicinally important compounds, it is also shown that this reaction can be modified for the radioiodination of activated arenes.

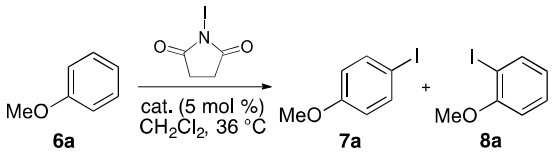
Scheme 1. Metal-Catalyzed Methods for Iodination of Arenes



RESULTS AND DISCUSSION

Having previously shown that iron(III) was highly effective for activation of NIS (Table 1, entry 2),[23] initial studies focused on screening softer, less charged Lewis acids that could result in cleaner iodination reactions. Both copper(I) chloride and iron(II) chloride showed little activity for the iodination of anisole (**6a**) (entries 3 and 4), and while a palladium(II) complex eventually gave good conversion, the rate of the reaction was relatively slow (entry 5). A similarly slow reaction but good overall conversion was observed when using silver(I) hexafluoroantimonate (entry 6). Interestingly, the use of this silver(I) salt showed very clean conversion and so other more active silver(I) salts were investigated. In our previous studies, we found that the Lewis acidic nature of a metal could be enhanced by forming the triflimide salt.[23] The combination of the highly delocalized nature of the triflimide anion and its steric hindrance results in significant positive charge density on the metal cation leading to powerful Lewis acidic character.[24] Using this reasoning, silver(I) triflimide was next attempted and this showed complete conversion after 1.5 h (entry 7). Further investigation revealed an optimal catalyst loading of 7.5 mol % that gave after 1.5 h, an 86% isolated yield of iodoanisole as a 93:7 mixture of *p*- and *o*-isomers, respectively.

Table 1. Activity Screen of Metal Catalysts for Iodination of Anisole (6a)[a,b]



entry	catalyst	conversion at 1.5 h (%)	conversion at 21 h (%)
1	---	<2	11
2	$FeCl_3$	100	---
3	CuCl	<2	24
4	$FeCl_2$	<2	24
5	$Pd(MeCN)_2Cl_2$	7	96
6	$AgSbF_6$	12	74
7	$AgNTf_2$	100	---

[a]Conversions were measured using ^{1}H NMR spectroscopy. [b]For all reactions, a ratio of >9:1 was observed in favor of the *para*-isomer.

To further evaluate the suitability of silver(I) triflimide as a catalyst for NIS-mediated arene iodination reactions, the relative rate of reaction of anisole (**6a**) was compared with other metal-based Lewis acids known to perform this transformation (Figure 2).[21,23] At 36 °C and using a catalyst loading of 7.5 mol %, silver(I) triflimide was found to be significantly faster than both indium(III) triflate and the gold(I) triflimide complex. For comparison, data using iron(III) chloride under the optimized conditions of 5 mol % catalyst loading and a reaction temperature of 20 °C is also presented in figure 2. Although the optimized conditions for the silver(I) triflimide procedure requires a slightly higher catalyst loading and reaction temperature, the relative rate of reaction with the softer Lewis acid compares favorably to the iron(III) chloride method.

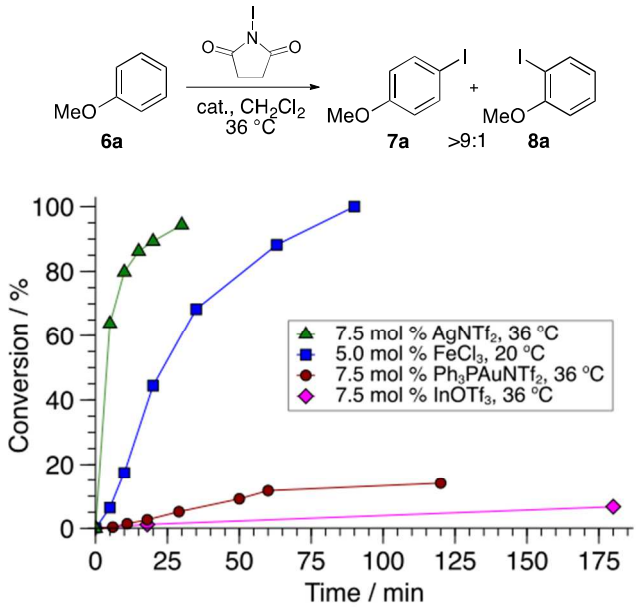
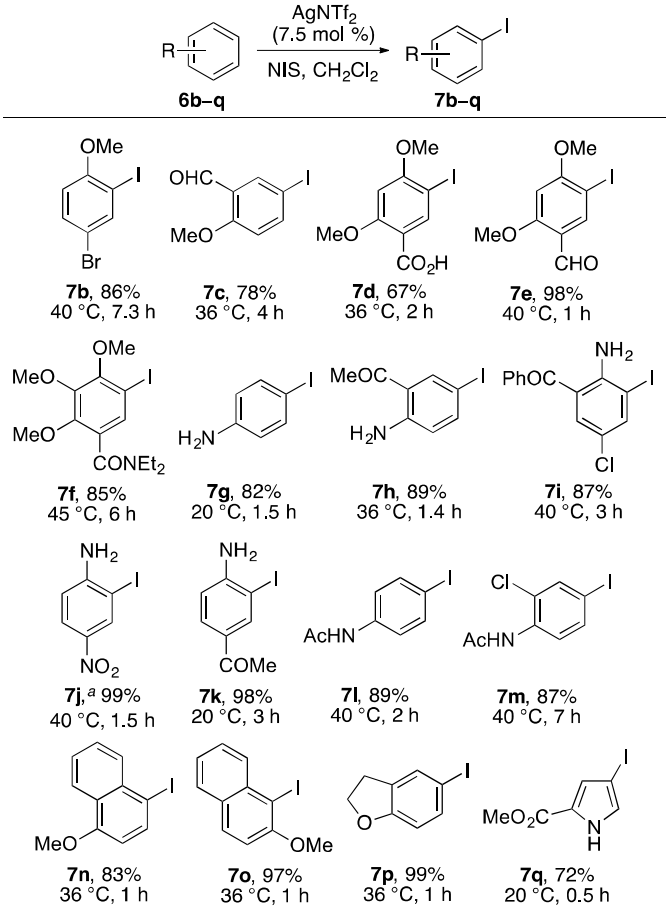


Figure 2. Iodination of anisole (**6a**) with various Lewis acids.

The scope of iodination using silver(I) triflimide was then explored using a range of anisole, aniline, and acetanilide derivatives (Scheme 2). For all substrates investigated, the silver(I)-catalyzed iodination was found to be compatible with a wide range of functional groups, generating the products cleanly and efficiently.[25] Analysis of crude reaction mixtures by ^{1}H NMR spectroscopy showed the presence in all cases of only a single monoiodinated regioisomer. Substrates such as **7h–7k** with strongly deactivating groups also showed high reactivity giving the products in nearly quantitative yields after only a few hours reaction time. The ability to use this procedure for multi-gram synthesis of iodinated arenes was investigated using 4-nitroaniline **6j**. It was found that on scale-up, the catalyst loading of the silver(I) triflimide could be lowered to 2 mol %. This lower catalyst loading in combination with the standard reaction conditions (40 °C, 1.5 h) gave **7j** on a gram scale, in 90% yield. Further exploration of the scope of this procedure with other activated substrates such as methoxynaphthalenes **6n** and **6o**, 2,3-dihydrobenzofuran (**6p**) and pyrrole **6q** similarly gave iodinated products **7n–7q** in high yields.

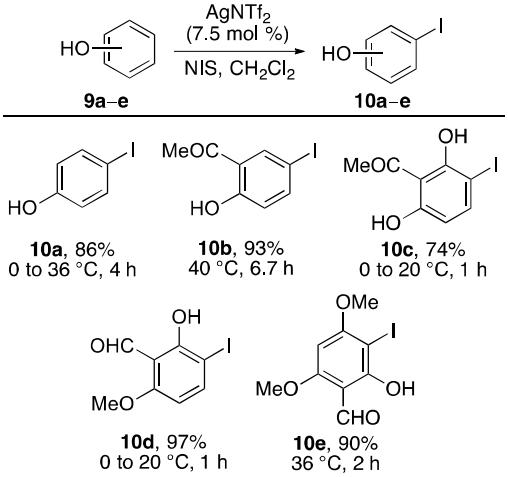
Scheme 2. Scope of Silver(I) Triflimide Catalyzed Iodination



[a]Gram scale synthesis using a catalyst loading of 2 mol % gave **7j** in 90% yield.

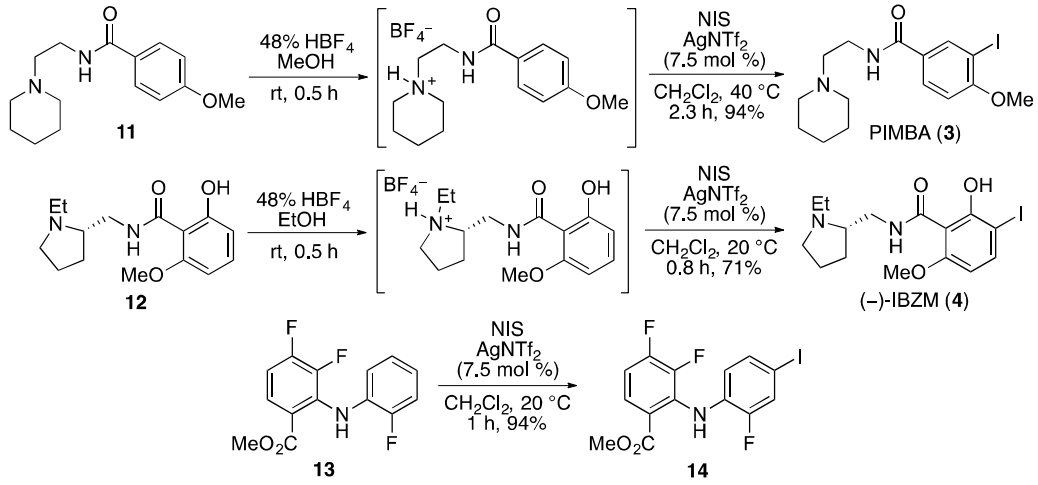
The ability of the silver(I) triflimide procedure for iodination of highly activated phenol substrates was next investigated (Scheme 3). For the majority of compounds it was found that initial cooling of the reaction mixture in combination with the soft silver(I) Lewis acid led to the suppression of over-iodination and the rapid and efficient formation of the monoiodinated compounds.[26] Again, inspection of the reaction mixtures by ^{1}H NMR spectroscopy revealed the presence of only a single iodinated regioisomer. It should be noted that even highly active diol **9c** gave only a single product, 3-iodoacetophenone **10c**, in 74% yield.

Scheme 3. Silver(I) Triflimide Catalyzed Iodination of Phenols



The silver(I)-catalyzed method was then extended for the synthesis of medicinally important iodine-containing compounds (Scheme 4). PIMBA (**3**),[7] the SPECT imaging agent of human breast cancer was prepared in two steps from amide **11**. As NIS is known to react with nucleophilic groups,[21a,23] the amine functionality of **11** was initially protected as the tetrafluoroborate salt. Iodination with silver(I) triflimide then gave **3** in 94% yield over the two steps. In a similar fashion, (–)-IBZM (**4**),[8] the SPECT imaging agent of the dopamine D_2 receptor was prepared in 71% yield from **12**. When iron(III) was used to activate NIS for the synthesis of (–)-IBZM (**4**) in our previous study, the procedure was complicated by the formation of the bis-iodinated product, resulting in a 47% yield of **4**.[23] Here, the use of the softer silver(I) catalyst circumvented this issue with a cleaner iodination reaction and a higher yield of the target compound. The selective iodination of a bis-arylated compound, **13** was also examined. Reaction of **13** with NIS and silver(I) triflimide was complete after 1 h at 20 ºC and gave iodinated compound **14** as a single product in 94% yield. In this case, only the *para*-position of the more activated aryl ring was iodinated. The carboxylic acid of compound **14** is a nanomolar inhibitor of the kinase, MEK1 and a metabolite of PD0325901, a compound active against malignant tumours.[27]

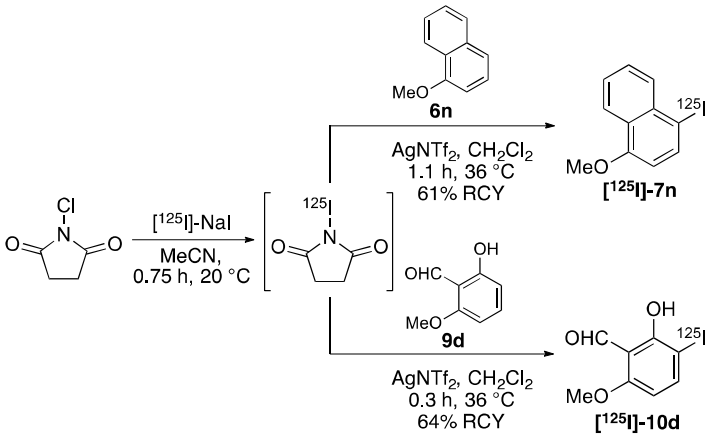
Scheme 4. Iodination of Medicinally Relevant Compounds



Having achieved the main objective of this research programme, the identification of a soft metal based Lewis acid for the rapid, general and selective iodination of a range of arenes, the final goal was the modification of this procedure for radioiodination. Radiolabeled iodide is produced in the form of the sodium salt and it was proposed that this could be used as part of a one-pot radioiodination process by reaction with *N*-chlorosuccinimide (NCS) to produce radiolabeled NIS,[28,29] followed by the silver(I) triflimide catalyzed reaction with arenes. In a preliminary study, it has been shown that a one-pot procedure can be used from NCS to give radioiodinated compounds in good radiochemical yields (RCY) (Scheme 5).[30] Due to the high sensitivity of SPECT, [^{123}I]- and [^{125}I]-imaging agents are generally prepared in low micromole quantities and so during this part of the project, the scale of the iodination procedure was adjusted to mimic these conditions (3 micromole of substrate). [^{125}I]-NIS was initially prepared from NCS and 5.3 MBq of [^{125}I]-NaI and this was used for the radioiodination of 1-methoxynaphthalene (**6n**). With [^{125}I]-NIS as the limiting reagent in these reactions, optimization studies found that 0.6 equivalents of silver(I) triflimide gave the best conversion of **6n**. Analysis using radio-HPLC showed a 61% radiochemical yield of [^{125}I]-**7n** after a reaction time of 1.1 hours. 2-Hydroxy-6-methoxybenzaldehyde (**9d**), a mimic of the aryl component of (–)-IBZM (**4**) was next investigated. Using [^{125}I]-NIS prepared from 2.7 MBq of [^{125}I]-NaI and then 0.3 equivalents of silver(I) triflimide gave [^{125}I]-**10d** after 0.3 hours in 64% radiochemical yield. Some side-products were observed

by radio-HPLC during the radioiodination of both compounds, but these were generally in small amounts and easily separable from the major product. While these results are preliminary, they show that this one-pot approach can be used to access radioiodinated compounds.

Scheme 5. One-Pot Radioiodination of 6n and 9d



CONCLUSIONS

In summary, a method for the iodination of arenes via the activation of NIS using silver(I) triflimide has been developed. The combination of using a soft, low-charged silver(I) Lewis acid which is still relatively active due to the non-complexing triflimide counterion led to the fast and efficient iodination of a wide range of arenes. This tuning of NIS activation using silver(I) supresses over-iodination resulting in mono-iodination of highly activated substrates such as phenols. The utility of this method has been demonstrated with the high yielding regioselective synthesis of a range of medicinally important imaging agents including phenol containing dopamine D_2 SPECT tracer (–)-IBZM (**4**). The generality of this procedure was further exemplified by the one-pot, two-step synthesis of [^{125}I]-labelled compounds from NCS and [^{125}I]-NaI. Further studies to extend the scope and application of this method are underway.

EXPERIMENTAL SECTION

All reagents and starting materials were obtained from commercial sources and used as received. All dry solvents were purified using a solvent purification system. All reactions were performed open to air 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 $60F_{254}$ were used for thin layer chromatography and were visualized with a UV lamp or by staining with potassium permanganate. ^{1}H 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). ^{13}C NMR spectra were recorded on a NMR spectrometer at either 101 or 126 MHz and data are reported as follows: chemical shift in ppm relative to tetramethylsilane or the solvent as internal standard ($CDCl_3$, δ 77.0 ppm; CD_3OD, δ 44.0 ppm; or DMSO-d_6, δ 39.5 ppm), multiplicity with respect to hydrogen (deduced from DEPT experiments, C, CH, CH_2 or CH_3). Infrared spectra were recorded on a FTIR spectrometer; wavenumbers are indicated in cm^{-1}. Mass spectra were recorded using electron impact, chemical ionization or electrospray techniques. HRMS spectra were recorded using a dual-focusing magnetic analyzer mass spectrometer. Melting points are uncorrected. A solution of 74 MBq of [^{125}I]-sodium iodide in 3–4 μL of 0.01 M sodium hydroxide solution was azeotropically dried under argon at 110 °C and reconstituted in anhydrous acetonitrile. Analytical HPLC was performed using a 80 Å column (150 × 4.6 mm) with 10 mm guard cartridge, UV 220 nm, radiodetection and flow of 1 mL/min. Analysis of the reaction mixture (to assess radioiodide incorporation) used a gradient profile of 0.1% trifluoroacetic acid in water and 0.1% trifluoroacetic acid in acetonitrile.

General Iodination Procedure. To a dry flask (10 mL), fitted with a magnetic stirrer were added substrate (1.0 equiv.), *N*-iodosuccinimide (1.0–1.1 equiv.), silver triflimide (7.5 mol %) and dichloromethane (5–6 mL) under an atmosphere of air. The reaction mixture was stirred in the dark at the required temperature. The reaction progress was monitored by ^{1}H NMR spectroscopy. The reactions

were stopped once all substrate was consumed. The reaction mixture was diluted with dichloromethane (15 mL) and washed with dilute aqueous solutions of sodium hydrogen carbonate (20 mL), sodium thiosulfate (20 mL), and sodium chloride (20 mL). The organic layer was dried over magnesium sulfate and filtered. The solvent was removed under reduced pressure and the product was purified by either column chromatography or by recrystallization.

Iodination of highly reactive / phenol substrates. To a dry flask fitted with a magnetic stirrer were added substrate (1.0 equiv.), silver triflimide (7.5 mol %) and dichloromethane (4 mL) under an atmosphere of air. The mixture was cooled to 0 °C and a solution of *N*-iodosuccinimide (1.03 equiv.) in dichloromethane (30 mL) was added dropwise over 10 min. The reaction was then allowed to warm up to room temperature, and if necessary heated to 36 °C in the dark. The reaction progress was monitored by ^{1}H NMR spectroscopy. The reactions were stopped once all substrate was consumed and worked up as described above.

Measurement of the rate of iodination of anisole (6a). Iodination of anisole (**6a**) was performed as described in the general procedure above, using anisole (36 μL, 0.33 mmol), NIS (74 mg, 0.33 mmol) and either $InOTf_3$ (13.9 mg, 7.5 mol %), $Ph_3PAuNTf_2$ (38 mg, 7.5 mol %), $FeCl_3$ (2.7 mg, 5.0 mol %) or $AgNTf_2$ (9.6 mg, 7.5 mol %) at the temperatures shown in Figure 2. At the various time points indicated in Figure 2, an aliquot (0.5 mL) was removed from the reaction mixture. The sample was diluted with dichloromethane (3 mL) and washed with dilute aqueous solutions of sodium hydrogen carbonate (5 mL), sodium thiosulfate (5 mL), and sodium chloride (5 mL). The dichloromethane layer was dried over magnesium sulfate and filtered. The solvent was removed under reduced pressure. The resulting residue was dissolved in $CDCl_3$ and the conversion of the reaction was measured using ^{1}H NMR spectroscopy. The calculation was based on the integral values of iodoanisole (**7a**) signals at 7.52–7.58 ppm compared to the starting material, anisole (**6a**) signals at 7.27–7.30 ppm.

4-Iodoanisole (7a).[31] The reaction was performed as described in the general procedure using anisole (**6a**) (53 μL, 0.49 mmol) and NIS (110 mg, 0.49 mmol). The reaction mixture was heated to 36 °C for

1.5 h. Purification by column chromatography eluting with 10% ethyl acetate in petroleum ether gave the product as a white solid (98 mg, 86%; inseparable mixture of 4-iodoanisole (**7a**) and 2-iodoanisole (**8a**), 93:7). Mp 40–43 °C. (lit.[31] 43–45 °C). The spectroscopic data are reported only for the major isomer, **7a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 6.65–6.72 (m, 2H), 7.52–7.58 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 55.3 (CH_3), 82.7 (C), 116.4 (2 × CH), 138.2 (2 × CH), 159.5 (C); MS (EI) *m/z* 234 (M^+, 96), 219 (55), 191 (12), 84 (100), 49 (66).

2-Iodo-4-bromoanisole (7b).[32] The reaction was performed as described in the general procedure using 4-bromoanisole (**6b**) (56 μL, 0.44 mmol) and NIS (115 mg, 0.51 mmol). The reaction mixture was heated to 40 °C for 7.3 h. Purification by column chromatography eluting with 15% ethyl acetate in petroleum ether gave 2-iodo-4-bromoanisole (**7b**) (120 mg, 86%) as a light brown oil. The data were consistent with the literature.[32] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.69 (d, *J* 8.7 Hz, 1H), 7.41 (dd, *J* 8.7, 2.4 Hz, 1H), 7.88 (d, *J* 2.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 56.6 (CH_3), 86.7 (C), 112.0 (CH), 113.4 (C), 132.2 (CH), 141.2 (CH), 157.5 (C); MS (EI) *m/z* 312 (M^+, 100), 297 (44), 269 (13), 170 (26), 127 (6), 63 (19).

2-Methoxy-5-iodobenzaldehyde (7c).[33] The reaction was performed as described in the general procedure using 2-methoxybenzaldehyde (**6c**) (60.5 mg, 0.44 mmol) and NIS (110 mg, 0.49 mmol). The reaction mixture was heated to 36 °C for 4 h. Recrystallization from ethyl acetate and petroleum ether gave 2-methoxy-5-iodobenzaldehyde (**7c**) (90 mg, 78%) as an off-white solid. Mp 141–142 °C (lit.[33] 140–141 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (s, 3H), 6.78 (d, *J* 8.8 Hz, 1H), 7.81 (dd, *J* 8.8, 2.4 Hz, 1H), 8.09 (d, *J* 2.4 Hz, 1H), 10.34 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.9 (CH_3), 83.0 (C), 114.1 (CH), 126.6 (C), 137.1 (CH), 144.1 (CH), 161.4 (C), 188.2 (CH); MS (ESI) *m/z* 284 (MNa^+, 35), 236 (100), 218 (10).

2,4-Dimethoxy-5-iodobenzoic acid (7d).[34] The reaction was performed as described in the general procedure using 2,4-dimethoxybenzoic acid (**6d**) (80 mg, 0.44 mmol) and NIS (114 mg, 0.51 mmol).

The reaction mixture was heated to 36 °C for 2 h. Recrystallization from ethyl acetate and petroleum ether gave 2,4-dimethoxy-5-iodobenzoic acid (**7d**) (91 mg, 67%) as a white solid. Mp 204–205 °C (lit.[34] 209.5–210.5 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.87 (s, 3H), 3.93 (s, 3H), 6.70 (s, 1H), 8.04 (s, 1H), 12.45 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 56.6 (CH_3), 57.3 (CH_3), 74.1 (C), 97.7 (CH), 114.9 (C), 141.6 (CH), 161.7 (C), 162.2 (C), 165.7 (C); MS (EI) *m/z* 308 (M^+, 100), 291 (16), 261 (14), 233 (10), 152 (11), 95 (7).

2,4-Dimethoxy-5-iodobenzaldehyde (7e).[35] The reaction was performed as described in the general procedure using 2,4-dimethoxybenzaldehyde (**6e**) (74 mg, 0.44 mmol) and NIS (115 mg, 0.51 mmol). The reaction mixture was heated to 40 °C for 1 h. Recrystallization from ethyl acetate and petroleum ether gave 2,4-dimethoxy-5-iodobenzaldehyde (**7e**) (127 mg, 98%) as a white solid. Mp 171–172 °C (lit.[35] 170–172 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H), 3.97 (s, 3H), 6.40 (s, 1H), 8.22 (s, 1H), 10.20 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.9 (CH_3), 56.6 (CH_3), 75.6 (C), 94.8 (CH), 120.5 (C), 139.3 (CH), 163.8 (C), 164.1 (C), 186.9 (CH); MS (EI) *m/z* 292 (M^+, 100), 246 (15), 148 (13), 84 (29), 49 (27).

***N*,*N*-Diethyl-2,3,4-trimethoxy-5-iodobenzamide (7f).** The reaction was performed as described in the general procedure using *N*,*N*-diethyl-2,3,4-trimethoxybenzamide (**6f**) (68 mg, 0.25 mmol) and NIS (63 mg, 0.28 mmol). The reaction mixture was heated to 45 °C for 6 h. Purification by column chromatography eluting with 20% ethyl acetate in petroleum ether gave *N*,*N*-diethyl-2,3,4-trimethoxy-5-iodobenzamide (**7f**) (85 mg, 85%) as a colorless oil. IR (neat) 2973, 1626, 1580, 1455, 1394, 1292, 1220, 1070, 999 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, *J* 7.2 Hz, 3H), 1.24 (t, *J* 7.2 Hz, 3H), 3.17 (q, *J* 7.2 Hz, 2H), 3.43 (br s, 1H), 3.66 (br s, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 7.33 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.8 (CH_3), 14.0 (CH_3), 39.0 (CH_2), 43.1 (CH_2), 60.9 (CH_3), 61.1 (CH_3), 61.7 (CH_3), 85.6 (C), 129.8 (C), 130.3 (CH), 146.6 (C), 150.6 (C), 154.1 (C), 166.6 (C); MS (EI) *m/z* 393 (M^+, 56), 321 (100), 266 (10), 195 (5), 105 (8), 73 (7); HRMS (EI) calcd for $C_{14}H_{20}INO_4$ (M^+), 393.0437, found 393.0435.

4-Iodoaniline (7g).[36] The reaction was performed as described in the general procedure using aniline (**6g**) (45 μL, 0.49 mmol) and NIS (110 mg, 0.49 mmol). The reaction mixture was stirred at room temperature for 1.5 h. Purification by column chromatography eluting with 10% ethyl acetate in petroleum ether gave 4-iodoaniline (**7g**) (88 mg, 82%) as a light brown solid. Mp 53–55 ºC (lit.[36] 55–56.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 2H), 6.44–6.49 (m, 2H), 7.38–7.43 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 79.4 (C), 117.3 (2 × CH), 137.9 (2 × CH), 146.0 (C); MS (EI) *m/z* 219 (M^+, 100), 191 (3), 127 (12), 92 (43), 65 (31).

2-Amino-5-iodoacetophenone (7h).[37] The reaction was performed as described in the general procedure using 2-aminoacetophenone (**6h**) (59 μL, 0.48 mmol) and NIS (110 mg, 0.49 mmol). The reaction mixture was heated to 36 °C for 1.4 h. Recrystallization from dichloromethane gave 2-amino-5-iodoacetophenone (**7h**) (112 mg, 89%) as a light brown solid. Mp 95–97 °C (lit.[37] 98.5–99 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 3H), 6.31 (br s, 2H), 6.45 (d, *J* 8.7 Hz, 1H), 7.46 (dd, *J* 8.7, 2.1 Hz, 1H), 7.96 (d, *J* 2.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 27.8 (CH_3), 75.2 (C), 119.4 (CH), 120.4 (C), 140.3 (CH), 142.4 (CH), 149.6 (C), 199.6 (C); MS (EI) *m/z* 261 (M^+, 100), 246 (52), 218 (20), 91 (18), 84 (18).

2-Amino-3-iodo-5-chlorobenzophenone (7i). The reaction was performed as described in the general procedure using 2-amino-5-chlorobenzophenone (**6i**) (109 mg, 0.47 mmol) and NIS (115 mg, 0.51 mmol). The reaction mixture was heated to 40 °C for 3 h. Purification by column chromatography eluting with 10% ethyl acetate in petroleum ether gave 2-amino-3-iodo-5-chlorobenzophenone (**7i**) (146 mg, 87%) as a bright yellow solid. Mp 88–90 °C; IR (neat) 3396, 3289, 1634, 1596, 1564, 1518, 1226, 952, 880 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (br s, 2H), 7.44 (d, *J* 2.4 Hz, 1H), 7.46–7.51 (m, 2H), 7.55–7.64 (m, 3H), 7.81 (d, *J* 2.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 86.7 (C), 118.4 (C), 120.2 (C), 128.4 (2 × CH), 129.2 (2 × CH), 131.9 (CH), 133.8 (CH), 138.7 (C), 143.0 (CH), 148.7 (C), 197.3 (C); MS (EI) *m/z* 357 (M^+, 100), 280 (12), 229 (13), 125 (14), 105 (21), 77 (23); HRMS (EI) calcd for $C_{13}H_9{}^{35}ClINO$ (M^+), 356.9417, found 356.9419.

2-Iodo-4-nitroaniline (7j).[38] The reaction was performed as described in the general procedure using 4-nitroaniline (**6j**) (71 mg, 0.51 mmol) and NIS (110 mg, 0.49 mmol). The reaction mixture was heated to 40 °C for 1.5 h. Recrystallization from ethyl acetate and petroleum ether gave 2-iodo-4-nitroaniline (**7j**) (124 mg, 99%) as a bright yellow solid. Mp 99–100 °C (lit.[38] 103–104 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (br s, 2H), 6.70 (d, *J* 9.0 Hz, 1H), 8.06 (dd, *J* 9.0, 2.5 Hz, 1H), 8.57 (d, *J* 2.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 80.5 (C), 112.3 (CH), 125.7 (CH), 135.5 (CH), 139.3 (C), 152.3 (C); MS (EI) *m/z* 264 (M^+, 100), 234 (38), 218 (11), 127 (5), 91 (31).

3-Iodo-4-aminoacetophenone (7k).[39] The reaction was performed as described in the general procedure using 4-aminoacetophenone (**6k**) (66 mg, 0.48 mmol) and NIS (110 mg, 0.49 mmol). The reaction mixture was stirred at room temperature for 3 h. Purification by column chromatography eluting with 20% ethyl acetate in petroleum ether gave 3-iodo-4-aminoacetophenone (**7k**) (124 mg, 98%) as a yellow oil. The data were consistent with the literature.[39] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (s, 3H), 4.62 (br s, 2H), 6.71 (d, *J* 8.4 Hz, 1H), 7.76 (dd, *J* 8.4, 2.0 Hz, 1H), 8.27 (d, *J* 2.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.0 (CH_3), 82.6 (C), 113.1 (CH), 129.3 (C), 130.3 (CH), 140.3 (CH), 150.9 (C), 195.1 (C); MS (CI) *m/z* 262 (MH^+, 100), 136 (48), 85 (10), 69 (18).

***N*-(4-Iodophenyl)acetamide (7l).**[13c] The reaction was performed as described in the general procedure using *N*-phenylacetamide (**6l**) (59 mg, 0.44 mmol) and NIS (110 mg, 0.49 mmol). The reaction mixture was heated to 40 °C for 2 h. Recrystallization from ethyl acetate and petroleum ether gave *N*-(4-iodophenyl)acetamide (**7l**) (104 mg, 89%) as a white solid. Mp 174–176 °C (lit.[13c] 178–180 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 7.12 (br s, 1H), 7.29 (d, *J* 8.7 Hz, 2H), 7.62 (d, *J* 8.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.7 (CH_3), 87.4 (C), 121.6 (2 × CH), 137.6 (C), 137.9 (2 × CH), 168.2 (C); MS (EI) *m/z* 261 (M^+, 100), 219 (93), 92 (26).

***N*-(2-Chloro-4-iodophenyl)acetamide (7m).**[40] The reaction was performed as described in the general procedure using *N*-(2-chlorophenyl)acetamide (**6m**) (73 mg, 0.43 mmol) and NIS (110 mg, 0.49 mmol). The reaction mixture was heated to 40 °C for 7 h. Recrystallization from ethyl acetate and petroleum

ether gave *N*-(2-chloro-4-iodophenyl)acetamide (**7m**) (110 mg, 87%) as a white powder. Mp 138–139 °C (lit.[40] 144 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 3H), 7.52–7.59 (m, 2H), 7.69 (d, *J* 2.0 Hz, 1H), 8.17 (d, *J* 8.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.9 (CH_3), 86.2 (C), 122.8 (CH), 123.1 (C), 134.5 (C), 136.8 (CH), 137.0 (CH), 168.2 (C); MS (EI) *m/z* 295 (M^+, 48), 253 (100), 224 (6), 126 (15), 90 (15).

4-Iodo-1-methoxynaphthalene (7n).[41] The reaction was performed as described in the general procedure using 1-methoxynaphthalene (**6n**) (69 μL, 0.48 mmol) and NIS (110 mg, 0.49 mmol). The reaction mixture was heated to 36 °C for 1 h. Purification by column chromatography eluting with 2.5% ethyl acetate in petroleum ether gave 4-iodo-1-methoxynaphthalene (**7n**) (114 mg, 83%) as a colorless oil. The data were consistent with the literature.[41] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.99 (s, 3H), 6.60 (d, *J* 8.1 Hz, 1H), 7.51 (ddd, *J* 8.3, 6.8, 1.1 Hz, 1H), 7.58 (ddd, *J* 8.4, 6.8, 1.3 Hz, 1H), 7.95 (d, *J* 8.1 Hz, 1H), 8.02 (ddd, *J* 8.4, 1.1, 0.6, 1H), 8.23 (ddd, *J* 8.3, 1.3, 0.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 55.7 (CH_3), 88.2 (C), 105.6 (CH), 122.5 (CH), 126.0 (CH), 126.7 (C), 128.2 (CH), 131.8 (CH), 134.7 (C), 136.9 (CH), 156.3 (C); MS (EI) *m/z* 284 (M^+, 100), 269 (35), 241 (31), 114 (30).

1-Iodo-2-methoxynaphthalene (7o).[19] The reaction was performed as described in the general procedure using 2-methoxynaphthalene (**6o**) (76 mg, 0.48 mmol) and NIS (110 mg, 0.49 mmol). The reaction mixture was heated to 36 °C for 1 h. Purification by column chromatography eluting with 5% ethyl acetate in petroleum ether gave 1-iodo-2-methoxynaphthalene (**7o**) (132 mg, 97%) as an off-white solid. Mp 84–86 °C (lit.[19] 86–87 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (s, 3H), 7.22 (d, *J* 8.9 Hz, 1H), 7.38 (ddd, *J* 8.1, 6.9, 1.2 Hz, 1H), 7.54 (ddd, *J* 8.6, 6.9, 1.2 Hz, 1H), 7.74 (ddd, *J* 8.1, 1.2, 0.6 Hz, 1H), 7.83 (d, *J* 8.9 Hz, 1H), 8.14 (ddd, *J* 8.6, 1.2, 0.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 57.3 (CH_3), 87.7 (C), 112.9 (CH), 124.4 (CH), 128.1 (CH), 128.2 (CH), 129.9 (C), 130.4 (CH), 131.2 (CH), 135.6 (C), 156.6 (C); MS (EI) *m/z* 284 (M^+, 52), 241 (21), 142 (20), 114 (23), 84 (24), 44 (100).

5-Iodo-2,3-dihydrobenzofuran (7p).[42] The reaction was performed as described in the general procedure using 2,3-dihydrobenzofuran (**6p**) (54 μL, 0.48 mmol) and NIS (110 mg, 0.49 mmol). The

reaction mixture was heated to 36 °C for 1 h. Purification by column chromatography eluting with 2.5% ethyl acetate in petroleum ether gave 5-iodo-2,3-dihydrobenzofuran (**7p**) (117 mg, 99%) as a white solid. Mp 61–63 °C (lit.[42] 64–65 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (br t, *J* 8.7 Hz, 2H), 4.56 (t, *J* 8.7 Hz, 2H), 6.57 (d, *J* 8.4 Hz, 1H), 7.38 (ddt, *J* 8.4, 1.9, 0.7 Hz, 1H), 7.47 (dt, *J* 1.9, 1.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.5 (CH_2), 71.4 (CH_2), 81.6 (C), 111.7 (CH), 130.1 (C), 133.7 (CH), 136.7 (CH), 160.0 (C); MS (EI) *m/z* 246 (M^+, 89), 232 (10), 117 (20), 91 (41), 84 (39), 44 (100).

Methyl 4-iodo-1H-pyrrole-2-carboxylate (7q).[43] The reaction was performed as described in the general procedure using methyl 1H-pyrrole-2-carboxylate (**6q**) (61 mg, 0.48 mmol) and NIS (110 mg, 0.49 mmol). The reaction mixture was stirred at room temperature for 0.5 h. Purification by column chromatography eluting with 15% ethyl acetate in petroleum ether gave methyl 4-iodo-1H-pyrrole-2-carboxylate (**7q**) (87 mg, 72%) as a white solid. Mp 87–90 °C (lit.[43] 87–89 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.98 (dd, *J* 2.7, 1.5 Hz, 1H), 7.00 (dd, *J* 2.7, 1.5 Hz, 1H), 9.10 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.8 (CH_3), 61.7 (C), 121.7 (CH), 124.4 (C), 127.6 (CH), 160.5 (C); MS (EI) *m/z* 251 (M^+, 100), 219 (70), 192 (11), 124 (5), 93 (6), 65 (8), 44 (10).

4-Iodophenol (10a).[44] The reaction was performed as described in the highly reactive substrate procedure using phenol (**9a**) (46 mg, 0.49 mmol) and NIS (113 mg, 0.50 mmol) at 0 °C. After 15 min, the reaction mixture was slowly heated to 36 °C for 4 h. Purification by column chromatography, eluting with 10% ethyl acetate in petroleum ether gave 4-iodophenol (**10a**) (93 mg, 86%) as waxy solid. The data were consistent with the literature.[44] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (s, 1H), 6.63 (d, *J* 8.8 Hz, 2H), 7.52 (d, *J* 8.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 82.7 (C), 117.8 (2 × CH), 138.5 (2 × CH), 155.3 (C); MS (EI) *m/z* 220 (M^+, 100), 191 (3), 127 (6), 93 (37), 65 (20).

2-Hydroxy-5-iodoacetophenone (10b).[45] The reaction was performed as described in the general procedure using 2-hydroxyacetophenone (**9b**) (56 μL, 0.46 mmol) and NIS (109 mg, 0.49 mmol). The reaction mixture was heated to 40 °C for 6.7 h. Recrystallization from ethyl acetate and petroleum ether gave 2-hydroxy-5-iodoacetophenone (**10b**) (112 mg, 93%) as a light yellow solid. Mp 84–86 °C (lit.[45]

90 °C); δ_H (400 MHz, $CDCl_3$) δ 2.62 (s, 3H), 6.78 (d, *J* 8.8 Hz, 1H), 7.71 (dd, *J* 8.8, 2.2 Hz, 1H), 8.01 (d, *J* 2.2 Hz, 1H), 12.19 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.8 (CH_3), 79.7 (C), 120.9 (CH), 121.8 (C), 139.1 (CH), 144.8 (CH), 162.0 (C), 203.5 (C); MS (EI) *m/z* 262 (M^+, 100), 247 (72), 219 (19), 120 (10), 92 (14), 63 (9).

2,6-Dihydroxy-3-iodoacetophenone (10c). The reaction was performed as described in the highly reactive substrate procedure using 2,6-dihydroxyacetophenone (**9c**) (75 mg, 0.49 mmol) and NIS (115 mg, 0.51 mmol) at 0 °C for 10 min. The reaction mixture was warmed to room temperature and stirred for 1 h. Recrystallization from ethyl acetate and petroleum ether gave 2,6-dihydroxy-3-iodoacetophenone (**10c**) (100 mg, 74%) as a yellow solid. Mp 143–146 °C (decomp.); IR (neat) 3254, 2922, 1607, 1575, 1419, 1409, 1362, 1339, 1263, 1206, 1132, 1046, 803 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (s, 3H), 6.38 (d, *J* 8.8 Hz, 1H), 7.48 (br s, 1H), 7.64 (d, *J* 8.8 Hz, 1H), 11.82 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 33.4 (CH_3), 74.1 (C), 110.3 (C), 112.1 (CH), 143.7 (CH), 157.2 (C), 163.8 (C), 204.8 (C); MS (EI) *m/z* 278 (M^+, 54), 263 (56), 247 (11), 137 (22), 108 (10), 44 (100); HRMS (EI) calcd for $C_8H_7IO_3$ (M^+), 277.9440, found 277.9439.

2-Hydroxy-3-iodo-6-methoxybenzaldehyde (10d). The reaction was prepared as described in the highly reactive substrate procedure using 2-hydroxy-6-methoxybenzaldehyde (**9d**) (72 mg, 0.47 mmol) and NIS (109 mg, 0.49 mmol) at 0 °C. After 10 min, the reaction mixture was warmed to room temperature and stirred for 1 h. Recrystallization from ethyl acetate and petroleum ether gave 2-hydroxy-3-iodo-6-methoxybenzaldehyde (**10d**) (127 mg, 97%) as a yellow solid. Mp 123–125 °C; IR (neat) 2942, 2900, 1634, 1597, 1384, 1283, 1246, 1089, 780 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (s, 3H), 6.29 (d, *J* 8.8 Hz, 1H), 7.85 (d, *J* 8.8 Hz, 1H), 10.21 (s, 1H), 12.83 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 56.1 (CH_3), 74.2 (C), 103.7 (CH), 111.0 (C), 146.9 (CH), 162.1 (C), 162.9 (C), 193.7 (C); MS (EI) *m/z* 278 (M^+, 71), 260 (10), 218 (7), 133 (9), 105 (8), 84 (96), 49 (100); HRMS (EI) calcd for $C_8H_7IO_3$ (M^+), 277.9440, found 277.9438.

2,4-Dimethoxy-5-iodo-6-hydroxybenzaldehyde (10e). The reaction was performed as described in the general procedure using 2,4-dimethoxy-6-hydroxybenzaldehyde (**9e**) (84 mg, 0.46 mmol) and NIS (110 mg, 0.49 mmol). The reaction mixture was heated to 36 °C for 2 h. Recrystallization from ethyl acetate and petroleum ether gave 2,4-dimethoxy-5-iodo-6-hydroxybenzaldehyde (**10e**) (128 mg, 90%) as an off-white solid. Mp 205–208 °C (decomp.); IR (neat) 3022, 2943, 1635, 1603, 1462, 1449, 1293, 1233, 1210, 1177, 1127, 1080, 977, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 3.98 (s, 3H), 6.00 (s, 1H), 10.00 (s, 1H), 13.22 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 56.0 (CH_3), 56.7 (CH_3), 65.7 (C), 86.7 (CH), 106.4 (C), 164.0 (C), 164.8 (C), 166.0 (C), 191.5 (C); MS (EI) 308 (M^+, 100), 277 (13), 246 (11), 163 (20), 91 (8), 69 (7); HRMS (EI) calcd for $C_9H_9IO_4$ (M^+), 307.9546, found 307.9547.

***N*-[2'-(1"-Piperidinyl)ethyl]-4-methoxybenzamide (11).**[7a] 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.44 g, 7.5 mmol), hydroxybenzotriazole (1.08 g, 8.0 mmol) and 4-methoxybenzoic acid (761 mg, 5.0 mmol) were dissolved in dichloromethane (20 mL). *N,N*-Diisopropylethylamine (2.8 mL, 16 mmol) was added and the mixture was stirred at room temperature for 1 h. 2-(1'-Piperidyl)ethylamine (1.00 mL, 5.0 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. The mixture was diluted with dichloromethane (100 mL) and extracted with 1 M hydrochloric acid (100 mL). The aqueous layer was neutralized with 1 M sodium hydroxide (~120 mL) and extracted with dichloromethane (3 × 100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil. Purification by column chromatography eluting with 5% to 10% methanol in dichloromethane gave *N*-[2'-(1"-piperidinyl)ethyl]-4-methoxybenzamide (**11**) (916 mg, 70%) as a colorless solid. The data were consistent with the literature.[7a] Mp 71–73 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 1.42–1.51 (m, 2H), 1.57–1.66 (m, 4H), 2.39–2.49 (br m, 4H), 2.55 (t, *J* 6.1 Hz, 2H), 3.51 (td, *J* 6.1, 4.7 Hz, 2H), 3.85 (s, 3H), 6.86 (br s, 1H), 6.91–6.97 (m, 2H), 7.73–7.78 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.4 (CH_2), 26.1 (2 × CH_2), 36.4 (CH_2), 54.2 (2 × CH_2), 55.4 (CH_3), 57.0 (CH_2), 113.7 (2 × CH), 127.1 (C), 128.7 (2 × CH), 162.0 (C), 166.8 (C); MS (ESI) *m/z* 263 (MH^+, 75), 178 (100).

***N*-[2'-(1"-Piperidinyl)ethyl]-3-iodo-4-methoxybenzamide (3).**[7a] *N*-[2'-(1"-Piperidinyl)ethyl]-4-methoxybenzamide (**11**) (50 mg, 0.19 mmol) was suspended in acetonitrile (3 mL) and then tetrafluoroboric acid (25 μL, 0.19 mmol, 48% wt in water) was added at room temperature. The resulting solution was concentrated to a yellowish gum under reduced pressure. The reaction was then performed as described in the general procedure using the HBF_4 salt and NIS (56 mg, 0.25 mmol). The reaction mixture was heated to 40 °C for 2.3 h. Purification by column chromatography eluting with 5% to 10% methanol in dichloromethane gave *N*-[2'-(1"-piperidinyl)ethyl]-3-iodo-4-methoxybenzamide (**3**) (70 mg, 94%) as a viscous colorless oil. The data were consistent with the literature.[7a] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42–1.51 (m, 2H), 1.56–1.64 (m, 4H), 2.35–2.48 (br m, 4H), 2.54 (t, *J* 6.1 Hz, 2H), 3.49 (td, *J* 6.1, 4.7 Hz, 2H), 3.93 (s, 3H), 6.80 (br s, 1H), 6.84 (d, *J* 8.6 Hz, 1H), 7.77 (dd, *J* 8.6, 2.2 Hz, 1H), 8.21 (d, *J* 2.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.4 (CH_2), 26.1 (2 × CH_2), 36.5 (CH_2), 54.3 (2 × CH_2), 56.5 (CH_3), 57.0 (CH_2), 85.7 (C), 110.1 (CH), 128.7 (CH), 128.9 (C), 138.5 (CH), 160.3 (C), 165.5 (C); MS (ESI) *m/z* 389 (MH^+, 100), 304 (43).

(2'*S*)-2-Hydroxy-6-methoxy-*N*-[(1'-ethyl-2'-pyrrolidinyl)methyl]benzamide (12).[8a] 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (494 mg, 2.57 mmol), hydroxybenzotriazole (371 mg, 2.75 mmol) and 2-hydroxy-6-methoxybenzoic acid (289 mg, 1.72 mmol) were dissolved in dichloromethane (5 mL). *N,N*-Diisopropylethylamine (747 μL, 4.29 mmol) was added and the mixture was stirred at room temperature for 0.1 h. (*S*)-(–)-1-Ethyl-2-aminomethylpyrrolidine (239 μL, 1.72 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. The mixture was diluted with dichloromethane (50 mL) and washed with 1 M sodium hydroxide (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography eluting with 0% to 3.5% methanol in dichloromethane gave (2'*S*)-2-hydroxy-6-methoxy-*N*-[(1'-ethyl-2'-pyrrolidinyl)methyl]benzamide (**12**) (363 mg, 76%) as a colorless oil. The data were consistent with the literature.[8a] $[\alpha]_D^{23}$ –78.0 (*c* 2.0, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (t, *J* 7.2 Hz, 3H), 1.63 (dt, *J* 12.6, 5.9 Hz, 1H), 1.67–1.76 (m, 2H), 1.91 (dq, *J* 12.6, 8.5 Hz, 1H), 2.17–2.29 (m, 2H), 2.65 (m,

1H), 2.85 (dq, *J* 13.5, 7.2 Hz, 1H), 3.17–3.33 (m, 2H), 3.70 (ddd, *J* 13.8, 7.2, 2.5 Hz, 1H), 3.92 (s, 3H), 6.39 (dd, *J* 8.3, 1.0 Hz, 1H), 6.62 (dd, *J* 8.4, 1.0 Hz, 1H), 7.26 (dd, *J* 8.4, 8.3 Hz, 1H), 8.92 (br s, 1H), 14.14 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.2 (CH_3), 23.0 (CH_2), 28.5 (CH_2), 40.7 (CH_2), 47.9 (CH_2), 53.6 (CH_2), 55.9 (CH_3), 61.9 (CH), 100.8 (CH), 104.2 (C), 111.6 (CH), 133.0 (CH), 158.8 (C), 164.5 (C), 170.3 (C); MS (EI) *m/z* 278 (M^+, 4), 151 (41), 136 (10), 98 (100), 70 (22).

(2'*S*)-2-Hydroxy-3-iodo-6-methoxy-*N*-[(1'-ethyl-2'-pyrrolidinyl)methyl]benzamide (4).[8a] (2'*S*)-2-Hydroxy-6-methoxy-*N*-[(1'-ethyl-2'-pyrrolidinyl)methyl]benzamide (**12**) (69 mg, 0.25 mmol) was suspended in ethanol (3 mL) and then tetrafluoroboric acid (32.4 μL, 0.25 mmol, 48% wt in water) was added at room temperature. After 0.5 h, the resulting solution was concentrated to a yellowish gum under reduced pressure. The reaction was then performed as described in the general procedure using the prepared salt and NIS (57 mg, 0.25 mmol). The reaction mixture was stirred at room temperature for 0.8 h. Purification by column chromatography eluting with 2% to 5% methanol in dichloromethane gave (2'*S*)-2-hydroxy-3-iodo-6-methoxy-*N*-[(1'-ethyl-2'-pyrrolidinyl)methyl]benzamide (**4**) (71 mg, 71%) as a colorless viscous oil. The data were consistent with the literature.[8a] $[\alpha]_D^{24}$ –47.3 (*c* 1.0 in acetone); ^{1}H NMR (500 MHz, CD_3OD) δ 1.19 (t, *J* 7.3 Hz, 3H), 1.62–1.72 (m, 1H), 1.74–1.88 (m, 2H), 2.01 (dq, *J* 12.7, 8.3 Hz, 1H), 2.35–2.50 (m, 2H), 2.83–2.91 (m, 1H), 3.01 (dq, *J* 12.2, 7.3 Hz, 1H), 3.26–3.33 (m, 1H), 3.41 (dd, *J* 13.8, 5.6 Hz, 1H), 3.63 (dd, *J* 13.8, 4.0 Hz, 1H), 3.95 (s, 3H), 6.43 (d, *J* 8.8 Hz, 1H), 7.74 (d, *J* 8.8 Hz, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 12.3 (CH_3), 22.2 (CH_2), 28.0 (CH_2), 40.9 (CH_2), 48.5 (CH_2), 53.4 (CH_2), 55.8 (CH_3), 63.2 (CH), 75.7 (C), 103.5 (CH), 103.9 (C), 142.2 (CH), 159.4 (C), 162.1 (C), 169.8 (C); MS (EI) *m/z* 404 (M^+, 3), 277 (22), 261 (9), 234 (5), 149 (8), 98 (100), 70 (14).

3,4-Difluoro-2-(2'-fluorophenylamino)benzoic acid.[46] 2,3,4-Trifluorobenzoic acid (250 mg, 1.42 mmol) was dissolved in THF (10 mL) under an atmosphere of argon. 2-Fluoroaniline (0.28 mL, 2.84 mmol) was added and the mixture was cooled to –78 °C. Lithium bis(trimethylsilyl)amide (1 M in THF, 4.4 mL, 4.26 mmol) was slowly added over 0.1 h. The reaction mixture was warmed to room temperature and stirred for 72 h. The reaction was quenched with water (10 mL) and acidified to pH 2

with dilute hydrochloric acid. The mixture was extracted with ethyl acetate (3 × 80 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting brown residue was recrystallized from ethyl acetate and hexane to give 3,4-difluoro-2-(2'-fluorophenylamino)benzoic acid (232 mg, 61%) as white solid. Mp 174–175 °C (lit.[46] 170–172 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (td, *J* 9.2, 6.8 Hz, 1H), 6.98–7.16 (m, 4H), 7.89 (ddd, *J* 9.2, 5.8, 2.1 Hz, 1H), 8.91 (s, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 108.6 (d, *J* 18.4 Hz, CH), 115.9 (C), 116.1 (d, *J* 19.4 Hz, CH), 121.9 (d, *J* 5.8 Hz, CH), 124.5 (d, *J* 7.5 Hz, CH), 125.1 (d, *J* 3.7 Hz, CH), 129.1 (dd, *J* 9.6, 4.0 Hz, CH), 131.2 (d, *J* 10.0 Hz, C), 138.0 (d, *J* 7.6 Hz, C), 142.1 (dd, *J* 247.9, 14.9 Hz, C), 155.4 (dd, *J* 252.3, 11.2 Hz, C), 156.1 (d, *J* 243.3 Hz, C), 170.3 (C); ^{19}F NMR (377 MHz, $CDCl_3$) δ –144.2 (d, *J* 18.6 Hz, 1F), –127.4 (s, 1F), –126.3 (d, *J* 18.6 Hz, 1F); MS (EI) *m/z* 267 (M^+, 51), 249 (100), 221 (23), 201 (16), 84 (64), 49 (44).

Methyl 3,4-difluoro-2-(2'-fluorophenylamino)benzoate (13). 3,4-Difluoro-2-(2'-fluorophenylamino)benzoic acid (160 mg, 0.60 mmol) was dissolved in toluene (6 mL) under an atmosphere of argon. Thionyl chloride (2.6 mL) was added and the reaction mixture was heated to 80 °C for 5 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in toluene (4 mL) and a mixture of methanol (6 mL) and triethylamine (1.5 mL) was added. The mixture was stirred overnight at room temperature. The volatiles were removed under reduced pressure. The resulting residue was dissolved in dichloromethane (40 mL) and washed with a saturated solution of sodium hydrogencarbonate (40 mL). The aqueous layer was extracted with dichloromethane (2 × 50 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by filtration through a plug of silica eluting with 4% ethyl acetate in hexane to give methyl 3,4-difluoro-2-(2'-fluorophenylamino)benzoate (**13**) (150 mg, 89%) as white solid. Mp 65–67 °C; IR (neat) 3281, 2955, 1692, 1611, 1501, 1437, 1258, 1192, 1134, 1103, 1053, 1003, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 6.73 (td, *J* 9.1, 6.9 Hz, 1H), 6.93–7.14 (m, 4H), 7.79 (ddd, *J* 9.1, 5.9, 2.2 Hz, 1H), 9.08 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.4 (CH_3), 107.6 (d, *J* 18.3 Hz, CH), 113.7 (t, *J* 2.7 Hz, C), 115.4

(d, *J* 19.3 Hz, CH), 120.9 (dd, *J* 6.0, 1.8 Hz, CH), 123.5 (d, *J* 7.4 Hz, CH), 123.8 (d, *J* 3.8 Hz, CH), 127.3 (dd, *J* 9.5, 4.2 Hz, CH), 129.7 (dd, *J* 11.2, 2.5 Hz, C), 136.8 (dd, *J* 7.7, 3.4 Hz, C), 141.9 (dd, *J* 249.7, 14.7 Hz, C), 154.3 (dd, *J* 254.6, 11.4 Hz, C), 154.8 (d, *J* 244.8 Hz, C), 167.5 (d, *J* 2.7 Hz, C); ^{19}F NMR (377 MHz, $CDCl_3$) δ –143.7 (d, *J* 18.7 Hz, 1F), –128.3 (d, *J* 18.7 Hz, 1F), –128.1 (s, 1F); HRMS (ESI) calcd for $C_{14}H_{10}F_3NNaO_2$ (MNa^+), 304.0556, found 304.0552.

Methyl 3,4-difluoro-2-(2'-fluoro-4'-iodophenylamino)benzoate (14).[46] The reaction was performed as described in the general procedure using methyl 3,4-difluoro-2-(2'-fluorophenylamino)benzoate (**13**) (47 mg, 0.17 mmol) and NIS (38 mg, 0.17 mmol). The reaction mixture was stirred at room temperature for 1 h. The residue was purified by filtration through a plug of silica eluting with 4% ethyl acetate in hexane to give methyl 3,4-difluoro-2-(2'-fluoro-4'-iodophenylamino)benzoate (**14**) (64 mg, 94%) as an off-white solid. The data were consistent with the literature.[46] Mp 109–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 6.68 (td, *J* 8.5, 5.8 Hz, 1H), 6.77 (td, *J* 9.1, 7.0 Hz, 1H), 7.35 (dt, *J* 8.5, 1.5 Hz, 1H), 7.42 (dd, *J* 10.2, 2.0 Hz, 1H), 7.80 (ddd, *J* 9.1, 5.8, 2.0 Hz, 1H), 9.05 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.5 (s, CH_3), 83.6 (d, *J* 7.6 Hz, C), 108.3 (d, *J* 18.3 Hz, CH), 114.1 (t, *J* 2.6 Hz, C), 121.8 (dd, *J* 6.5, 2.1 Hz, CH), 124.4 (d, *J* 21.7 Hz, CH), 127.4 (dd, *J* 9.4, 4.1 Hz, CH), 130.0 (dd, *J* 10.1, 2.5 Hz, C), 132.9 (d, *J* 3.9 Hz, CH), 135.9 (dd, *J* 7.9, 3.7 Hz, C), 142.0 (dd, *J* 250.2, 14.8 Hz, C), 154.1 (d, *J* 250.4 Hz, C), 154.2 (dd, *J* 255.3, 11.4 Hz, C), 167.4 (d, *J* 2.7 Hz, C); ^{19}F NMR (377 MHz, $CDCl_3$) δ –142.9 (d, *J* 18.7 Hz, 1F), –127.8 (d, *J* 18.7 Hz, 1F), –125.8 (s, 1F); MS (ESI) *m/z* 430 (MNa^+, 100), 381 (54), 353 (19), 317 (99), 257 (22), 117 (53).

[^{125}I]-4-Iodo-1-methoxynaphthalene ([^{125}I]-7n). To a vial was added *N*-chlorosuccinimide (0.44 mg, 3.3 μmol) in acetonitrile (0.1 mL) and [^{125}I]-sodium iodide in acetonitrile (5 μL, 5.3 MBq). The mixture was stirred at ambient temperature for 0.75 h. Silver triflimide (0.72 mg, 1.86 μmol) in dichloromethane (0.3 mL) and 1-methoxynaphthalene (**6n**) (0.45 μL, 3.1 μmol) in dichloromethane (0.3 mL) were then added via syringe and the reaction mixture was stirred at 36 °C for 1.1 h. A 50% aqueous acetonitrile solution (0.8 mL) was added and the reaction volume was concentrated by blowing argon over the

solution. The mixture was diluted with aqueous acetonitrile solution and passed through a 0.22 μm filter. The filtrate was analyzed by analytical radio-HPLC which showed incorporation of radioiodide to obtain [^{125}I]-4-iodo-1-methoxynaphthalene **([^{125}I]-7n)** in 61% radiochemical yield.

[^{125}I]-2-Hydroxy-3-iodo-6-methoxybenzaldehyde ([^{125}I]-10d). To a vial was added *N*-chlorosuccinimide (0.43 mg, 3.2 μmol) in acetonitrile (0.1 mL) and [^{125}I]-sodium iodide in acetonitrile (4 μL, 2.7 MBq). The mixture was stirred at ambient temperature for 0.75 h. Silver triflimide (0.36 mg, 0.93 μmol) in dichloromethane (0.3 mL) and 2-hydroxy-6-methoxybenzaldehyde (**9d**) (0.45 mg, 3.0 μmol) in dichloromethane (0.3 mL) were then added via syringe and the reaction mixture was stirred at 36 °C for 0.3 h. The reaction volume was concentrated by blowing argon over the solution. A 50% aqueous acetonitrile solution (0.7 mL) was added and the mixture was passed through a 0.22 μm filter. The filtrate was analyzed by analytical radio-HPLC which showed incorporation of radioiodide to obtain [^{125}I]-2-hydroxy-3-iodo-6-methoxybenzaldehyde (**[^{125}I]-10d**) in 64% radiochemical yield.

SUPPORTING INFORMATION AVAILABLE. Radio-HPLC chromatograms of [^{125}I]-**7n** and [^{125}I]-**10d** and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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