Highly Regioselective Iodination of Arenes via Iron(III)-Catalyzed Activation of *N*-Iodosuccinimide
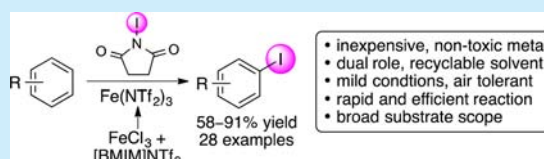
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S *Supporting Information*

ABSTRACT: An iron(III)-catalyzed method for the rapid and highly regioselective iodination of arenes has been developed. Use of the powerful Lewis acid, iron(III) triflimide, generated in situ from iron(III) chloride and a readily available triflimide-based ionic liquid allowed activation of *N*-iodosuccinimide (NIS) and efficient iodination under mild conditions of a wide range of substrates including biologically active compounds and molecular imaging agents.

- inexpensive, non-toxic metal
- dual role, recyclable solvent
- mild conditions, air tolerant
- rapid and efficient reaction
- broad substrate scope

58–91% yield
28 examples

Aryl halides are highly important intermediates in synthetic chemistry, used for a wide range of applications including cross-coupling reactions, the formation of organometallic reagents, and the generation of free-radical intermediates.[1] The reactivity and versatility of aryl iodides in particular have made these important building blocks for total synthesis, medicinal chemistry, and material science. Radioiodinated aryl compounds are also becoming increasingly important in medical imaging, in understanding diseases associated with neurology and oncology.[2]

For these reasons, significant efforts have been made to develop general methods for the synthesis of aryl iodides.[3] These include metal-catalyzed halogen exchange reactions from less reactive aryl bromides[4] and substitution reactions using leaving groups such as boronic acids[5] and diazonium salts.[6] While these methods are widely used, they require the installation of a functional handle and occasionally harsh conditions. More direct iodination methods using NIS have been reported. Olah et al. used BF₃ in water for the efficient iodination of deactivated arenes.[3a] Pd(II)- and Ru(0)-catalyzed C−H activation processes have been developed for the synthesis of *ortho*-iodinated aryl compounds using pyridines and amides as directing groups,[7] while In(III)- and Au(I)-catalyzed iodination of electron-rich arenes have also been described (Scheme 1a).[8]
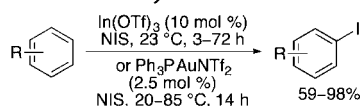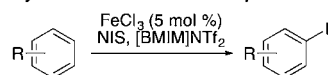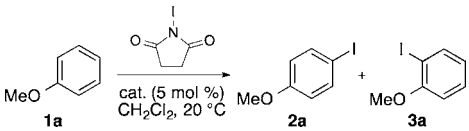
Although these processes are efficient, many of them require the use of expensive and toxic late transition metals. The issues associated with late transition metal catalysts have resulted in the development of reactions which use first-row transition metals, such as Fe, Co, and Ni that are much more abundant, inexpensive, and significantly less toxic.[9,10] We were interested in developing an iodination method of arenes that utilized a nontoxic first row transition metal and that could be extended for the production of iodinated imaging agents.[11] Herein, we report the use of iron(III) chloride for the rapid iodination of arenes (Scheme 1b). As well as demonstrating the use of a triflimide-based ionic liquid to enhance the Lewis acidity of the iron catalyst and accelerate the reaction, we show this method can be used for the late stage iodination of medicinally important compounds.

Initial studies focused on the iodination of anisole (**1a**) with NIS using a range of first row transition metal catalysts (Table 1, entries 2−7). While modest conversions were observed after 21 h for the chloride salts of Mn, Co, Cu, and Zn, the reaction with FeCl₃ was complete after 1.5 h and gave an 86% isolated yield of iodoanisole as a 93:7 mixture of *p*- and *o*-isomers, respectively.[12,13] To assess the relative activity of FeCl₃, the reaction was repeated using a range of more traditional electrophilic aromatic substitution catalysts as well as various late transition metal catalysts (entries 8−12). Only AuCl₃ which has been reported to perform this transformation via a dual activation process (formation of an arylgold(III) species and coordination to NIS)[8a] showed similar levels of activity.

Having identified FeCl₃ as a suitable catalyst, we began to examine the scope of the process. Although activated substrates gave iodinated products in high yield, it became apparent that, for less active compounds such as 2-methoxybenzaldehyde (**1b**), significantly higher catalyst loadings (100 mol %) were required for an efficient process (Table 2, entry 1). Due to the limited

Scheme 1. Iodination of Arenes Using NIS

a) Late transition metal catalyzed iodination of activated arenes

In(OTf)₃ (10 mol %)
NIS, 23 °C, 3–72 h
or Ph₃PAuNTf₂ (2.5 mol %)
NIS, 20–85 °C, 14 h
59–98%

b) This work: Fe(III)-catalyzed iodination of activated arenes, accelerated by a triflimide based ionic liquid

FeCl₃ (5 mol %)
NIS, [BMIM]NTf₂
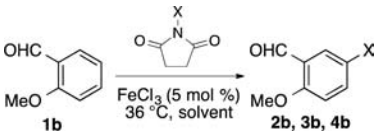
Table 1. Activity Screen of Metal Catalysts for Iodination of Anisole (1a)[a,b,c]

entry	catalyst	conversion at 1.5 h (%)	conversion at 21 h (%)
1	–	<2	11
2	$MnCl_2$	54	55
3	$FeCl_3$	100	–
4	$CoCl_2 \cdot 6H_2O$	<2	59
5	$NiCl_2$	0	12
6	$CuCl_2$	0	63
7	$ZnCl_2$	30	67
8	$AlCl_3$	85	100
9	$RuCl_3$	4	83
10	$InCl_3$	60	99
11	$PtCl_4$	34	100
12	$AuCl_3$	100	–

[a]Reactions were performed using 1.1 equiv of NIS. [b]Conversions were measured using ^{1}H NMR spectroscopy. [c]For all reactions, a ratio of >9:1 was observed in favor of the *para*-isomer.

Table 2. Halogenation of 1b

entry	solvent	time (h)	X	yield (%)
1[a]	CH_2Cl_2	6	I (2b)	90
2	[BMIM]NTf$_2$	2.5	I (2b)	88
3	[BMIM]NTf$_2$	1.5	Br (3b)	88
4[b]	[BMIM]NTf$_2$	18	Cl (4b)	68

[a]$FeCl_3$ (100 mol %) was used. [b]Reaction was done at 70 °C and using MeCN as a cosolvent.

substrate scope, a more active form of Fe(III) was required. Recently, metal triflimides have received significant attention as powerful Lewis acids due to the highly delocalized nature of the triflimide counterion.[14] For example, it has been reported that iron(III) triflimide salt (formed in situ from $FeCl_3$ and $AgNTf_2$) is an effective Lewis acid catalyst for addition reactions.[15] An alternative method of generating $Fe(NTf_2)_3$ which avoids the use of late transition metals involves the dissolution of $FeCl_3$ in the readily available and inexpensive ionic liquid, 1-butyl-3-methyl-imidazolium bis(trifluoromethylsulfonyl)imide ([BMIM]-NTf$_2$).[16] Thus, the combination of an iron catalyst with an air-stable ionic liquid that has low vapor pressure, has high cohesive pressure for acceleration of reactions, and can be easily separated from the product seemed an ideal system for the general iodination of arenes.[17,18] The iodination of anisole (1a) was repeated using [BMIM]NTf$_2$ as the solvent. Although similar results were obtained (93:7 ratio of *p*- and *o*-isomers in 89% yield), a significant difference in the rate of reaction was observed compared to using dichloromethane as the solvent (Figure 1). In [BMIM]NTf$_2$, complete conversion was achieved in around 0.5 h, while over 1.5 h were required for the same conversion in dichloromethane.

The difference in reactivity was more pronounced with less reactive substrates. Iodination of 2-methoxybenzaldehyde (1b)
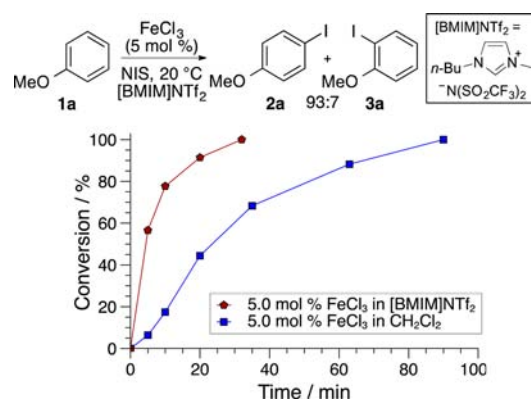
Figure 1. Iodination of **1a**; [BMIM]NTf$_2$ versus dichloromethane (measured using ^{1}H NMR spectroscopy).

in [BMIM]NTf$_2$ required only a 5 mol % loading of $FeCl_3$ and gave the 5-iodinated compound **2b** as the sole product after 2.5 h in 88% yield (Table 2, entry 2). To achieve a similar result, using dichloromethane required a stoichiometric amount of catalyst and a reaction time of 6 h (entry 1). Thus, the combination of a more active catalyst, $Fe(NTf_2)_3$, and the greater cohesive pressure of the ionic liquid resulted in a faster reaction at a significantly lower catalyst loading.[19] A study was performed to compare some of the most active catalysts from Table 1 for the iodination of **1b** using [BMIM]NTf$_2$. The harder Lewis acid, $Fe(NTf_2)_3$, was the most active and gave full conversion of iodinated product **2b** more quickly than the other catalysts (see Supporting Information for rate plot). While the focus of this study was the development of an efficient iodination process of arenes, it was shown by using **1b** that other halogenations can be performed using the $FeCl_3$/[BMIM]NTf$_2$ system (Table 2). Bromination using NBS under similarly mild conditions gave **3b** in 88% yield. Chlorination of **1b** required a longer reaction time at a higher temperature, but still gave **4b** in 68% yield.

Following optimization, the scope of the $Fe(NTf_2)_3$-catalyzed iodination was explored (Scheme 2). The transformation was found to be compatible and efficient for a wide range of aryl compounds with standard activating groups.[20] In nearly all cases, the iodination gave a single regioisomer.[21] Strongly deactivating groups were also tolerated and gave efficient iodinations. For example, iodination of 4-nitroaniline (**1k**) was complete after 2 h and gave **2k** as the sole product in 73% yield. The only limitation with the procedure was the formation of bis-iodinated products for particularly active substrates, such as phenols **1c** and **1q** and pyrrole **1y**. However, under the optimized conditions for these substrates, the bis-iodinated compounds were only ever formed in trace amounts and easily removed by column chromatography. The ionic liquid utilized in this procedure, [BMIM]NTf$_2$, has a number of electrochemical applications and, for this reason, is relatively inexpensive compared to other ionic liquids.[22] Nevertheless, we wanted to demonstrate that [BMIM]NTf$_2$ could be easily recovered and reused in subsequent reactions. Following iodination of anisole (**1a**), the residual ionic liquid was washed with water to remove succinimide and dried under high vacuum. In two successive iodination reactions of **1a** using the recovered ionic liquid, consistent yields of around 90% were achieved.

The mechanism of halogenation of arenes using *N*-halosuccinimides has been postulated to involve coordination of the metal to the oxygen carbonyl atom of the succinimide, which activates halogenation of the aryl ring via an electrophilic

Scheme 2. Scope of Fe(NTf₂)₃-Catalyzed Iodination
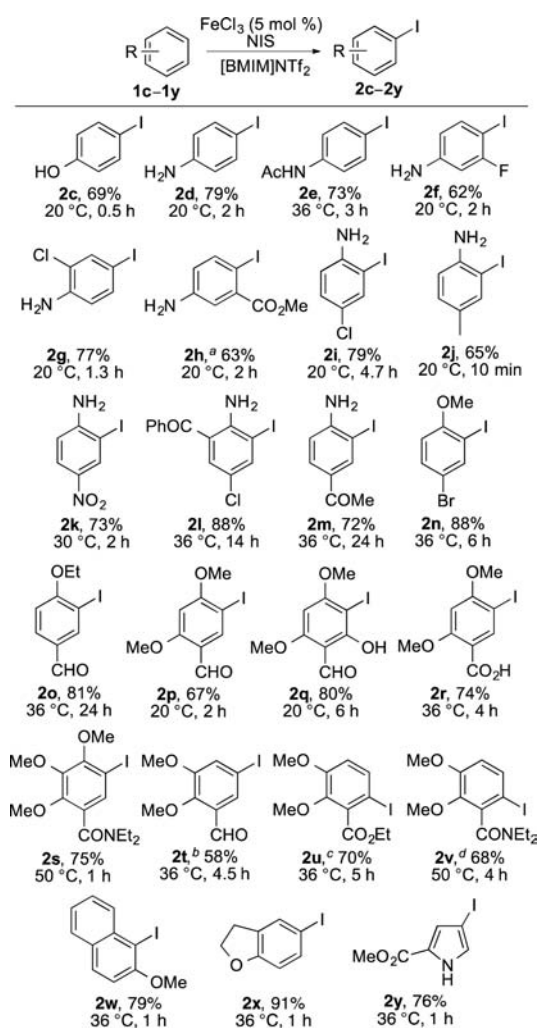
^{a}4-I isomer was isolated in 21% yield. ^{b}6-I isomer was isolated in 24% yield. ^{c}5-I isomer was isolated in 7% yield. ^{d}5-I isomer was isolated in 4% yield.

aromatic substitution process.[8] Halogenation via such a mechanism is directed by the activating groups. However, during our studies, it was found that the position of iodination could be redirected by the use of Fe(III)-complexing substituents. For example, 2,3-dimethoxybenzaldehyde (**1t**), which has a weakly

coordinating carbonyl group, gave the 5-iodo product **2t** in 58% yield (Scheme 2), along with the 6-iodo regioisomer in 24% yield. Using the same substituent pattern but carbonyl groups (ester **1u** and amide **1v**) that bind more strongly to the Fe-NIS complex switched the outcome of this process to significantly favor the 6-iodo products **2u** and **2v**.

Application of this method for the preparation of medicinally important compounds was next investigated. We were aware that NIS is incompatible with compounds bearing nucleophilic groups and so chose particular targets where this would be an issue.[8b] The first target selected was PIMBA (**6**), a compound used in its [^{123}I]-form for the imaging of human breast cancer tumors.[23] Initial attempts at direct iodination of precursor **5** with NIS and the FeCl₃/[BMIM]NTf₂ system gave no iodinated product. In these reactions, the solutions were observed to turn black shortly after addition of NIS. Protection of the nucleophilic piperidine ring as a salt was then investigated. While the hydrochloride salt gave the same negative outcome, formation of the softer tetrafluoroborate salt by treatment of **5** with tetrafluoroboric acid followed by iodination under the optimized conditions gave PIMBA (**6**) in 84% yield over the two steps (Scheme 3).[24] This approach was then extended to the synthesis of (−)-IBZM (**8**), an imaging agent and antagonist of the human D₂ receptor,[25] and 8-iodoharmaline (**10**), a potent monoamine oxidase inhibitor.[26] Again, formation of the tetrafluoroborate salts, followed by reaction with NIS and the in situ generated Fe(NTf₂)₃, gave the iodinated products in 47% and 73% overall yield, respectively.[27]

In summary, a highly regioselective, efficient iron(III)-catalyzed iodination of activated arenes that can be accelerated using a triflimide based ionic liquid has been developed. The process requires only a 5 mol % loading of an inexpensive, nontoxic first row transition metal catalyst, and the ionic liquid which acts as both the reaction solvent and Fe(III) activator can be easily recycled after washing with water. This combination results in faster reactions at lower temperatures compared to previous metal-catalyzed methods with NIS,[8] allowing iodination of relatively deactivated compounds such as **2k** and **2l**. Furthermore, the process can be used for the late-stage iodination of medicinally important compounds. In this regard, the limitations of using NIS for iodination of nucleophilic substrates were overcome by the identification of tetrafluoroborate salts as suitable precursors. Investigation of further applications of this procedure is currently underway.

Scheme 3. Synthesis of PIMBA (6), (−)-IBZM (8), and 8-Iodoharmaline (10)
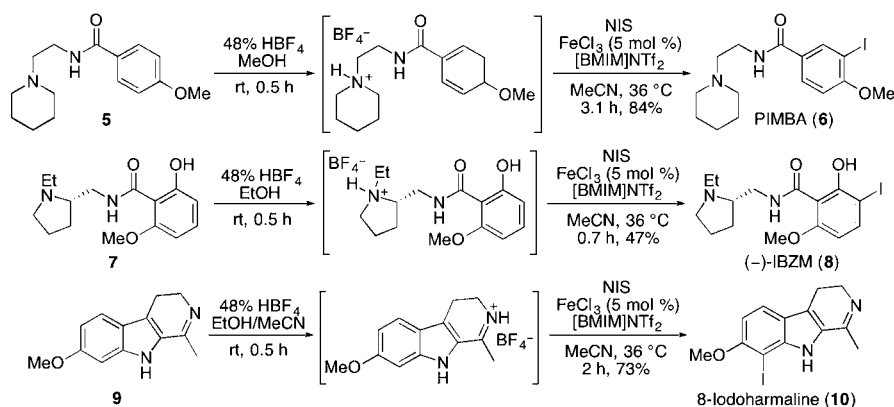
ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02345.

Experimental details, compound characterization, and NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

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(19) A control experiment investigating the iodination of **1b** in the absence of FeCl$_3$, with NIS in [BMIM]NTf$_2$ (36 °C), showed no conversion after 2 h.

(20) In accordance with other transition metal catalyzed iodinations of arenes by *N*-halosuccinimides (see ref 8), strongly deactivated compounds such as methyl benzoate or 2-nitro-3-methoxybenzaldehyde showed no conversion with the Fe(NTf$_2$)$_3$ catalyzed process.

(21) For the majority of compounds in Scheme 2, only a single monoiodinated isomer was detected by ^{1}H NMR spectroscopy. Only for the reaction of compounds **1h** and **1t–v** could a second minor isomer be detected and isolated.

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(27) The modest isolated yield for compound **8** was due to the formation of small quantities of byproducts. For example, like other highly activated phenols, some of the bis-iodinated product (<10%) was also observed by NMR spectroscopy in the crude reaction mixture.