Regioselective Functionalization of Arenes using Iron Triflimide Catalysis

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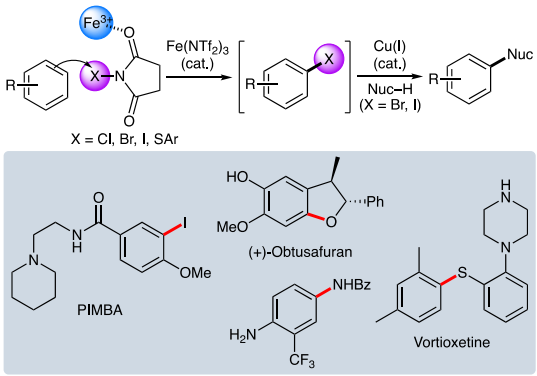
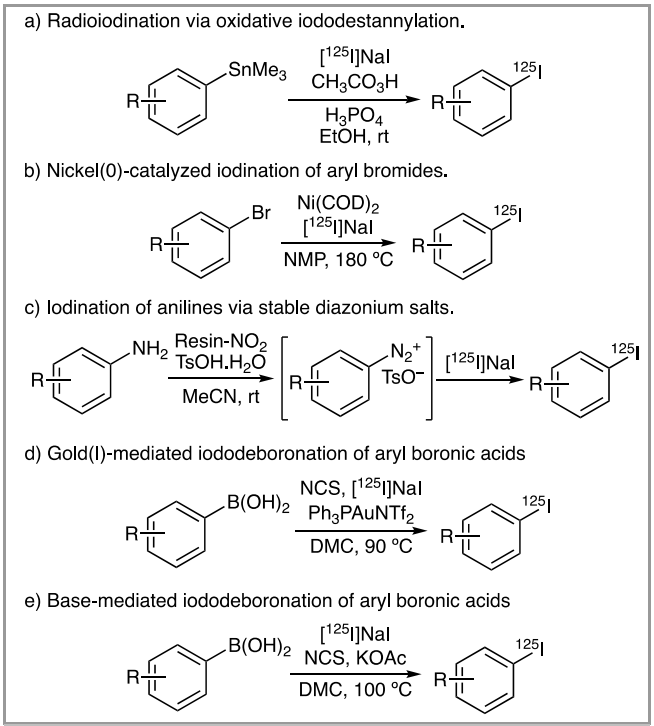


Abstract Here we present our development of the super Lewis acid, iron(III) triflimide as an activating agent of *N*-halo- and *N*-thioaryl succinimides for the regioselective functionalization of arenes. We also describe how the iron(III)-catalyzed halogenation reactions were further exploited by combination with copper(I)-catalyzed Ullmann-type coupling reactions for the development of one-pot, multi-step processes, including intermolecular aryl C–H amination. This account also illustrates intramolecular versions of these one-pot processes for the preparation of benzannulated heterocycles, as well as the application of these methods for the synthesis of biologically active compounds and natural products.

1 Introduction

Traditionally, the most common method for the radioiodination of aromatic compounds to generate single photon emission computed tomography (SPECT) tracers for medical imaging involved oxidative iodination of aryl stannanes (Scheme 1a).[1] However, organotin compounds are highly toxic, often unstable and, iododestannylation methods typically use strong oxidizing agents such as chloramine-T, peracetic acid and iodogen. For these reasons, milder methods using less toxic and more stable precursors have recently been developed.[2] The issues associated with the preparation of aryl stannanes in our SPECT tracer development programme led us to investigate new methods for iodination of aromatic compounds and over the last decade, we reported various transformations that were highly effective for the synthesis of [$^{123/125}$I]-labelled compounds. These included a nickel(0)-catalyzed halogen exchange reaction of aryl bromides (Scheme 1b)[3] and a one-pot Sandmeyer-type reaction of anilines via stable diazonium salts, formed under mild conditions and using a resin-bound nitrite agent (Scheme 1c).[4] Iododeboronation methods of aryl boronic acids mediated by gold(I) and base were also developed, allowing the effective preparation of a wide range of radioiodinated arenes with high radiochemical yields (Scheme 1d and 1e).[5,6]



Scheme 1 Methods for the radioiodination of arenes.

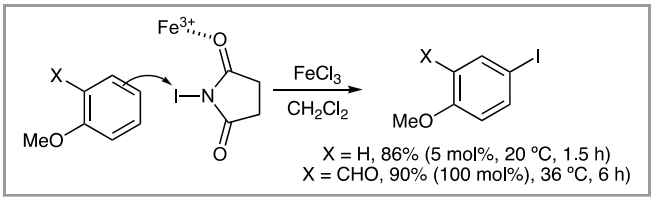
Although these methods have been used for the preparation of SPECT imaging agents[3–6] and provide a non-toxic alternative to the use of organotin precursors, a limitation of this general approach is the requirement of prefunctionalized arenes. For this reason, we

were interested in developing a research programme focused on the radioiodination of arenes by activation and substitution of C–H bonds. This led to the discovery of super Lewis acids such as the triflimide salts of iron(III) and silver(I), for the activation of *N*-halo succinimides and the rapid halogenation of arenes. While the initial focus of this programme was the development of halogenation reactions and in particular, a new procedure for radioiodination of aromatic compounds, we quickly realized that both the synthetic utility of aryl halides and the mild nature of these transformations meant they could be combined with other reactions for the one-pot, multi-step synthesis of functionalized arenes and benzannulated heterocycles. This account describes the discovery of iron(III) triflimide catalysis for the halogenation of arenes and combination of this with copper(I)-catalyzed coupling reactions for the one-pot conversion of aryl C–H bonds to C–N, C–O and C–S bonds.

2 Iron(III)-Catalyzed Halogenation of Arenes

When we began this programme of research, we were aware of other transition metal-catalyzed methods for arene iodination that used *N*-iodosuccinimide (NIS). These included a gold-catalyzed dual-activation process, where gold(III) chloride was used to form both an arylgold(III) species and act as a Lewis acid for coordination with NIS.[7] The groups of Roma and Frontier reported the use of $In(OTf)_3$ and $Ph_3PAuNTF_2$, respectively, as Lewis acid catalysts for the activation of NIS and subsequent arene iodination.[8,9] While these methods were highly effective, we were interested in developing a method that avoided precious transition metals and permitted rapid reaction times that were compatible for radioiodination with [^{123}I]iodide ($t_{1/2}$ = 13.2 h).

Our study began by screening the reaction of anisole with NIS, in the presence of a range of first row transition metal complexes.[10] While some complexes such as copper(II) chloride and zinc(II) chloride showed some activity, the most impressive results were found using iron(III) chloride (5 mol%), which gave the *p*-iodinated isomer in 86% yield after a reaction time of 1.5 hours (Scheme 2). However, when arenes bearing a deactivating group, such as 2-methoxybenzaldehyde were subjected to the same conditions, only 20% conversion was observed after a similar reaction time. To achieve complete conversion, stoichiometric amounts of iron(III) chloride and higher temperatures were required, which gave the corresponding iodinated product in 90% yield after 6 hours.



Scheme 2 Iron(III) chloride catalyzed iodination of anisole and 2-methoxybenzaldehyde.

To avoid using stoichiometric quantities of the Lewis acid, particularly for less activated substrates, we sought more active forms of iron(III) species. We became aware of the use of metal triflimides as super Lewis acids for a range of transformations, due to the highly delocalized nature of the triflimide counterion.[11] This included iron(III) triflimide that had been previously prepared from $FeCl_3$ and $AgNTf_2$ and used for addition reactions of alkenes and alkynes.[12] A literature survey also showed that iron(III) triflimide could be generated from iron(III) chloride and the inexpensive ionic liquid, 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([BMIM]NTf_2) (Figure 1a).[13] As well as forming the iron(III) triflimide complex in situ, we proposed that an additional benefit of using [BMIM]NTf_2 as the solvent was that the high cohesive pressure of the ionic liquid would further accelerate the reaction. Iodination of 2-methoxybenzaldehyde using $Fe(NTf_2)_3$ generated in situ was achieved catalytically (5 mol%) and gave the product in 88% yield (Figure 1b). Although, a slightly higher temperature (36 °C) was used compared to the $FeCl_3$-catalyzed iodination of anisole, the

reaction was complete after only 2.5 hours. The rate accelerated $Fe(NTf_2)_3$-catalyzed iodination of 2-methoxybenaldehyde was demonstrated by conversion graphs, which showed the benefits of this process compared to other Lewis acid triflimides and even sub-stoichiometric quantities (0.5 equiv.) of $FeCl_3$ (Figure 1c).

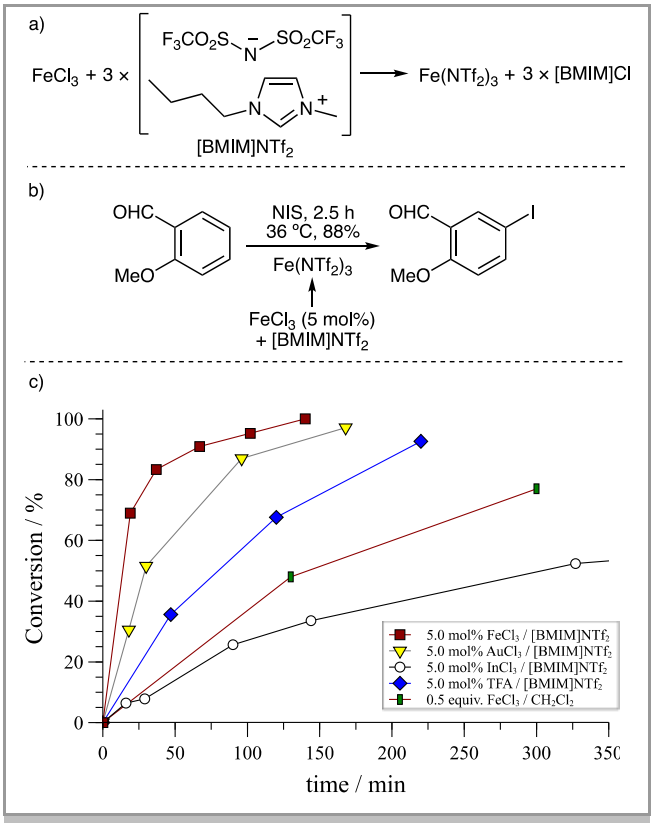
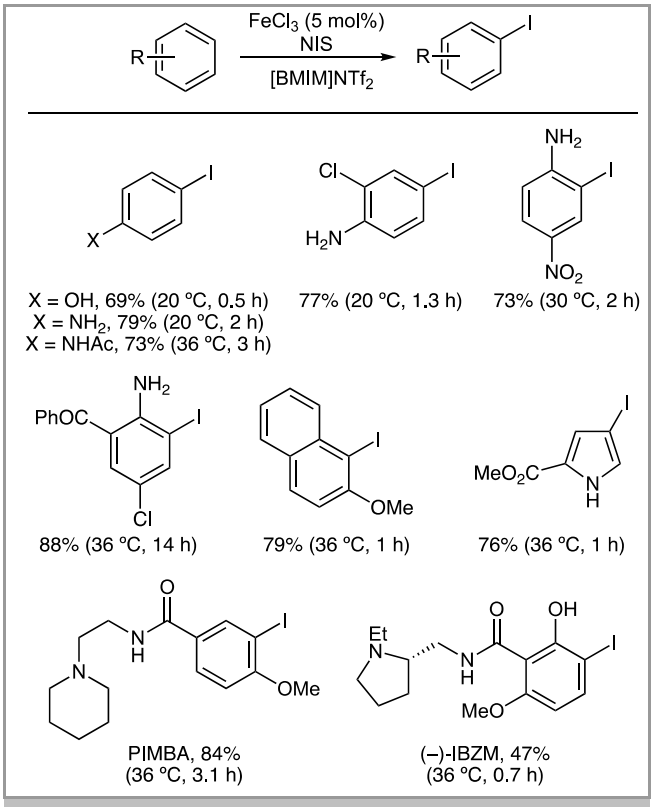


Figure 1 (a) Formation of iron(III) triflimide. (b) Iodination of 2-methoxybenzaldehyde using $Fe(NTf_2)_3$ (5 mol%). (c) Iodination of 2-methoxybenzaldehyde using various Lewis acid triflimides and $FeCl_3$.

Following development of the $Fe(NTf_2)_3$-catalyzed iodination, the scope of the transformation was explored (Scheme 3). With activated arenes, the transformation was found to be fast at moderate temperatures (20–36 °C) and gave the *para*-iodinated isomer, usually as the sole product in high yield. For compounds with the *para*-position blocked, *ortho*-iodination proceed smoothly. In terms of electronic requirements, the scope showed that deactivated arenes such as nitrobenzene were not tolerated. However, aromatic compounds with at least one activating group but also bearing electron-deficient substituents (e.g. *p*-nitroaniline) exhibited good activity. The synthetic utility of the method was also demonstrated for SPECT compounds, including PIMBA,[14] used for imaging of human breast cancer and (–)-IBZM, an imaging agent of the D_2 receptor.[15] For these targets, we choose highly functional compounds that also possessed nucleophilic amines incompatible with NIS. Direct $Fe(NTf_2)_3$-catalyzed iodination turned the reaction mixture black and gave no product, however, temporary protection of the amines as tetrafluoroborate salts, allowed clean synthesis of both PIMBA and (–)-IBZM.

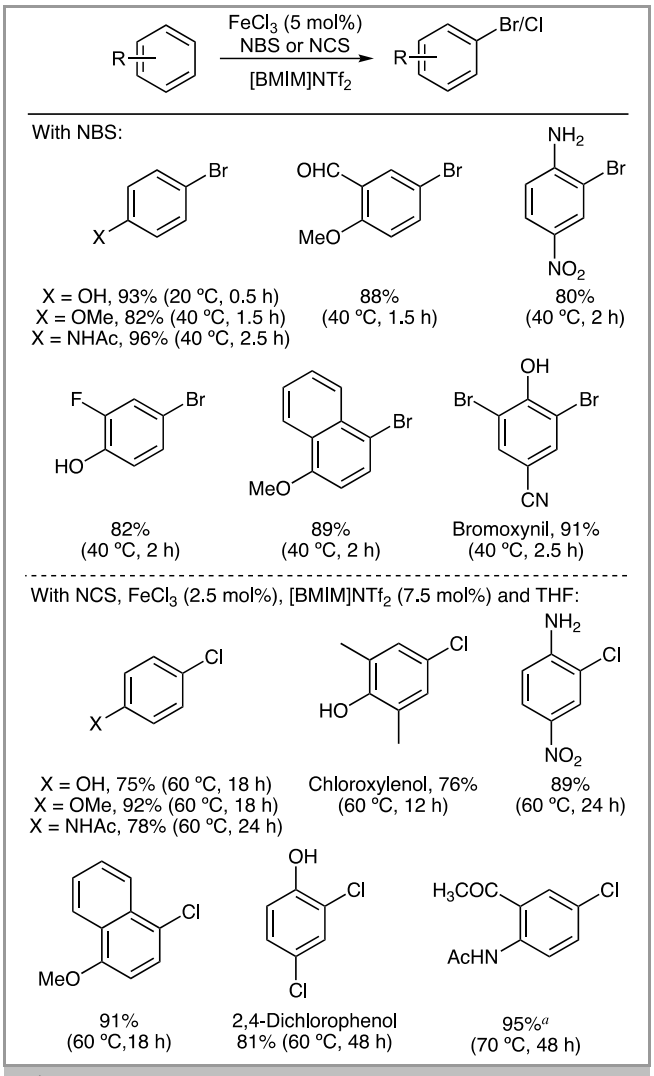


Scheme 3 Scope of iron(III) triflimide-catalyzed iodination.

The use of iron(III) triflimide as a Lewis acid catalyst for other halogenations was also investigated. Although, fluorination using $Fe(NTf_2)_3$ and electrophilic sources of fluorine such as Selectfluor gave no product, facile bromination and chlorination with the corresponding *N*-halo succinimides was observed. Bromination using $Fe(NTf_2)_3$ (5 mol%), *N*-bromosuccinimide (NBS) and the ionic liquid as the reaction solvent showed a similar reactivity profile as the iodination process (Scheme 4).[16] For example, fast bromination was observed with activated arenes, while compounds also bearing

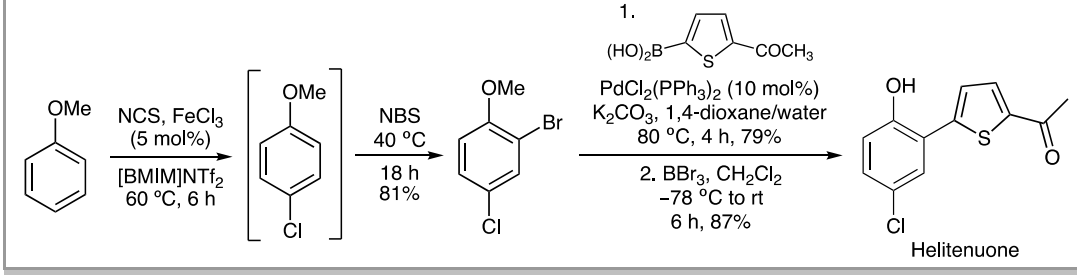
electron-deficient substituents required slightly higher temperatures. The method could also be used for dibromination and the direct synthesis of the herbicide, bromoxynil,[17] in 91% yield from *para*-cyanophenol. In contrast, the corresponding chlorination reaction using the less reactive *N*-chlorosuccinimide (NCS), required more forcing conditions.[18] Even with highly activated arenes, reaction temperatures of 60 °C were typical and reaction times of >12 hours. In addition, the use of the smaller halogenating reagent resulted in formation of the *ortho*-isomers as side-products (20–30%). Nevertheless, $Fe(NTf_2)_3$-catalyzed chlorination gave the products in high yields and access to medicinally important compounds, such as the antiseptic agent, chloroxylenol[19] and the growth hormone 2,4-dichlorophenol,[20] formed by dichlorination from phenol.

The other significant development from the $Fe(NTf_2)_3$-catalyzed chlorination was the discovery that $[BMIM]NTf_2$ was not required as the solvent (Scheme 4).[18] Using catalytic amounts of both iron(III) chloride (2.5 mol%) and $[BMIM]NTf_2$ (7.5 mol%) with THF as the solvent led to complete reaction conversion. Although these conditions resulted in slower reactions (18 h versus 5 h for 5 mol% of $FeCl_3$ in ionic liquid), this was an important insight for the subsequent development of one-pot multi-step processes, in which an organic solvent was necessary for the post-halogenation reaction.



Scheme 4 Scope of iron(III) triflimide-catalyzed bromination and chlorination. [a]Performed using $[BMIM]NTf_2$ as solvent.

The observation of very different rates of reactivity in these reactions between NCS and NBS allowed the development of regioselective, one-pot iron(III)-catalyzed poly-halogenation of arenes.[18] This was used for the total synthesis of helitenuone, a thiophene-derived phenol from *Helichrysum* species (Scheme 5).[21]



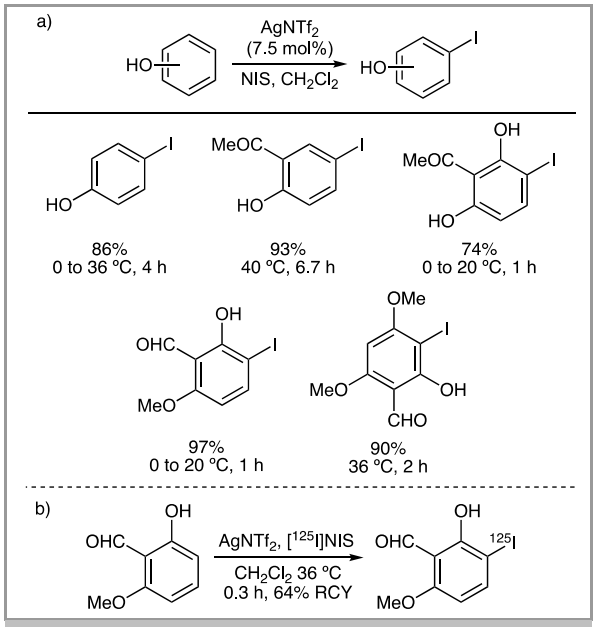
Scheme 5 Total Synthesis of helitenuone using a one-pot tandem iron(III) triflimide-catalyzed halogenation of anisole.

Initially, chlorination of anisole with $Fe(NTf_2)_3$ (5 mol%) and NCS gave the *para*-chloro isomer (Scheme 5). With the *para*-position blocked, cooling the reaction temperature to 40 °C and addition of NBS, allowed a second iron(III)-catalyzed halogenation reaction with mono-bromination at the *ortho*-position. This gave the dihalogenated product, 2-bromo-4-chloroanisole in 81% yield over the two steps. Suzuki-Miyaura reaction with 5-acetylthiophene-2-boronic acid, followed by boron tribromide-mediated demethylation completed the three-pot synthesis of helitenuone in 56% overall yield from anisole.

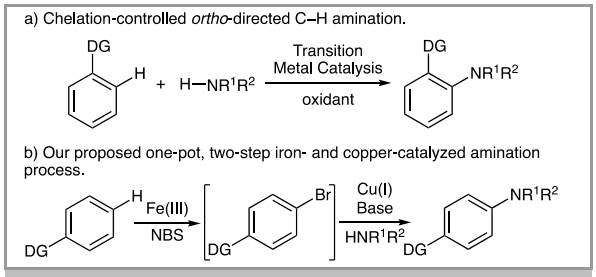
One of the limitations of the iron(III)-catalyzed halogenation reaction was that highly activated arenes such as phenols often gave bis-halogenated by-products. This was attributed to the highly charged, hard iron(III) Lewis acid species. We also found that the reactive nature of iron(III) for radioiodination, where the iron triflimide was used in excess (to allow complete conversion of the limiting [^{125}I]NaI), led to over-iodination. To overcome these limitations, we investigated a softer Lewis acid, the commercially available silver(I) triflimide.[22] As a Lewis acid catalyst for general iodination of arenes, silver(I) triflimide allowed fast and high yielding reactions under similar conditions and in comparable yields to the corresponding iron(III)-catalyzed reaction. More significantly, this process permitted the clean mono-iodination of a range of phenols (Scheme 6a). The softer Lewis acidity of the silver(I) species was also compatible with conditions for radioiodination. The in situ generation of [^{125}I]NIS from the reaction of [^{125}I]NaI with NCS, followed by radioiodination of arenes in the presence of silver(I) triflimide gave [^{125}I]-labelled products in good radiochemical yield (RCY). For example, radioiodination of 2-hydroxy-6-methoxybenzaldehyde, an aryl mimic of the SPECT imaging agent (–)-IBZM gave the [^{125}I]-labelled product in 64% RCY after a reaction time of 0.3 h (Scheme 6b).

3 One-Pot Intermolecular Aryl C–H Amination

Following the successful development of the iron(III) triflimide-catalyzed halogenation reaction, we were interested in employing this process for other applications. In particular, we believed that the mild nature of this reaction could be combined with other transformations for the one-pot synthesis of functionalized arenes. During the last two decades, a range of transition-metal catalyzed methods have been developed for the direct amination of arenes.[23] These include intermolecular *ortho*-amination via transition metal-catalyzed chelation-directed aryl C–H activation under oxidative conditions (Scheme 7a).[23] We proposed that combining a copper(I)-catalyzed Ullmann-Goldberg reaction with our iron(III)-catalyzed halogenation process, would allow one-pot *para*-amination of arenes (Scheme 7b),[16] thereby providing an orthogonal transformation to the chelation-controlled *ortho*-directed processes. In addition, this one-pot, two-step process would avoid precious transition metals and oxidative conditions.

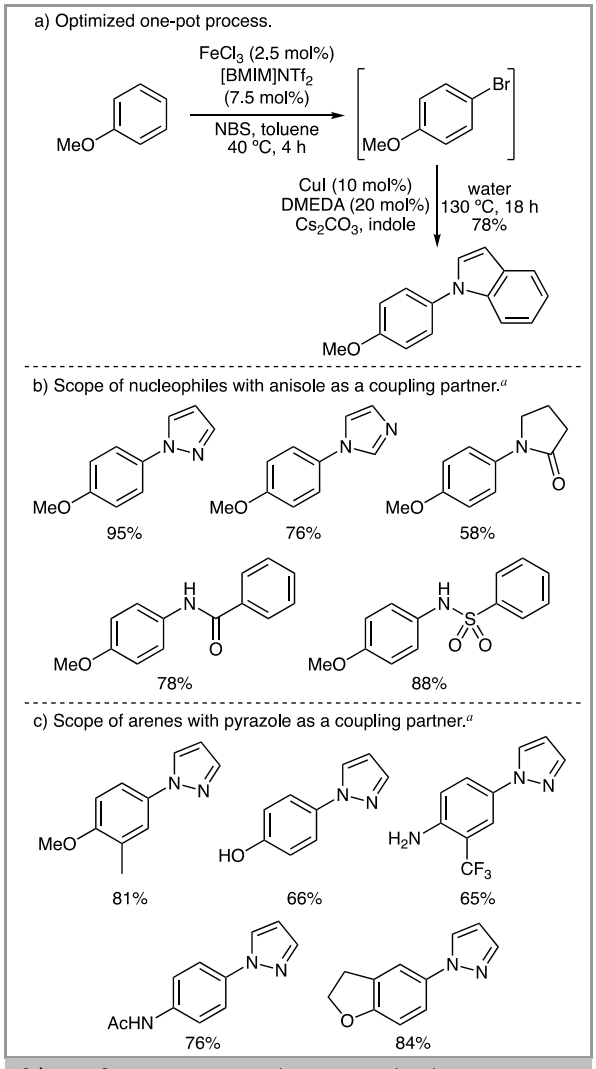


Scheme 6 (Radio)iodination of phenols using silver(I) triflimide.



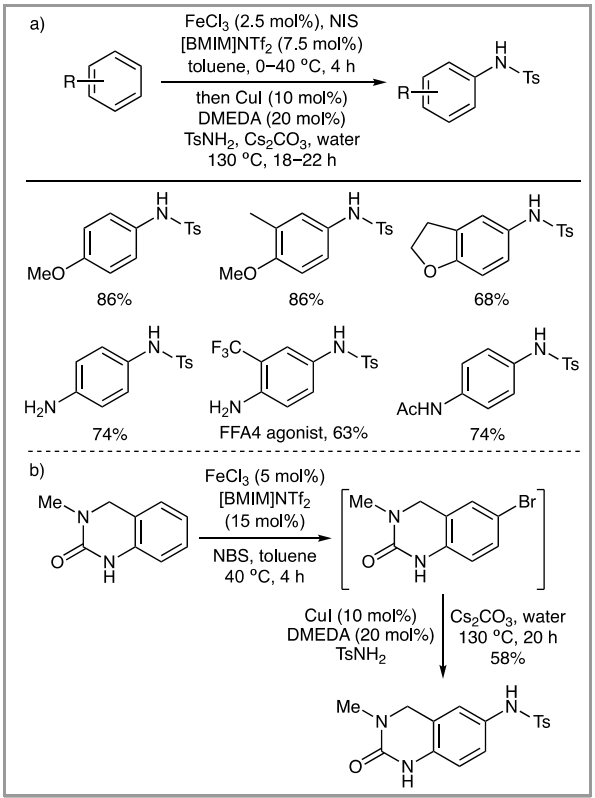
Scheme 7 Transition metal-catalyzed aryl amination (DG = directing group).

Initially, an iron(III) triflimide-catalyzed bromination was developed using a high boiling point solvent that would be compatible with a copper(I)-catalyzed amination reaction.[16] Toluene was found to be the optimal solvent, resulting in complete bromination of anisole at 40 °C, after a 4 h reaction time using catalytic quantities of both $FeCl_3$ and the ionic liquid (Scheme 8a). This was then combined with a copper(I)-catalyzed coupling reaction with indole as the nucleophile, using DMEDA as a ligand and caesium carbonate as a base. For several weeks, development of the one-pot process was hampered by low conversion to the indole-coupled product. This was rectified by the realization that poor solubility of caesium carbonate in toluene was responsible for the low conversion. To overcome this, water was used as a co-solvent to solubilize the base during the second step of the one-pot process. This adjustment resulted in reactions with complete conversion to the C–N coupled products. On optimization of the one-pot process, the scope of the nucleophile was explored using anisole as the arene (Scheme 8b). The scope of the arene component was also investigated using common nucleophiles such as pyrazole (Scheme 8c). In all cases, *para*-substituted products were generated cleanly in modest to high yields. Interestingly, arenes bearing nucleophilic substituents, such as anilines and phenols gave the desired coupled products, without the need for protecting groups.



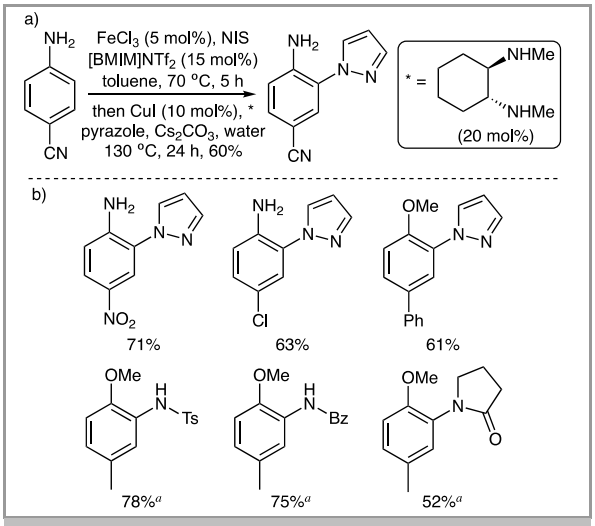
Scheme 8 One-pot iron and copper-catalyzed *para*-amination process. [a]The copper-catalyzed step was performed at temperatures from 130–150 °C and for 18–20 h.

As diaryl sulfonamides are found as a key component in therapeutic agents, we were interested in extending the one-pot process for the general synthesis of this compound class (Scheme 9a).[24] This allowed the efficient synthesis of a diverse range of diaryl sulfonamides using electro-rich arenes and (hetero)aryl sulfonamides under standard conditions. This included the one-pot synthesis of medicinally active compounds, such as a potent agonist of the free fatty acid receptor 4 (FFA4)[25] and, quinazolinone-derived sulfonamides (Scheme 9b), which are used as inhibitors of the BET family of bromodomains.[26]



Scheme 9 One-pot synthesis of diaryl sulfonamides.

Although the one-pot intermolecular amination process was highly effective for *para*-directed reactions, a limitation was found during attempted *ortho*-coupling of *para*-substituted arenes with *N*-nucleophiles.[16] Using substrates such as 4-nitroaniline, the relatively slow Ullmann-Goldberg coupling with pyrazole returned the starting aniline as a significant by-product, following proto-decupration of the iodide intermediate.[16] For this reason, we conducted a study to specifically optimize the one-pot process for *ortho*-coupling reactions.[27] This involved the investigation of other ligands for the copper-catalyzed step, in an effort to suppress the competing reduction of the aryl iodide intermediate. By screening various ligands, we found that using racemic *trans*-*N*,*N*'-dimethylcyclohexane-1,2-diamine (20 mol%) as a copper ligand, the competing reductive pathway could be suppressed. Optimization of this new one-pot process with 4-cyanoaniline and using pyrazole as the nucleophile gave only the coupled product in 60% yield (Scheme 10a). This result correlated nicely with work previously reported by the Buchwald group, that showed this rigid bidentate ligand can promote more difficult copper-catalyzed coupling reactions.[28] The scope of the optimized one-pot *ortho*-amination process was then demonstrated using anisole, anilines and phenols and, using various nucleophiles such as *N*-heterocycles, amides and suflonamides (Scheme 10b). In all cases, this gave only the *ortho*-coupled products, in moderate to high yields. The one-pot coupling process was also applied to the amination of 3,4-dihydroquinolin-2-ones for the preparation of a TRIM24 bromodomain inhibitor.[29]

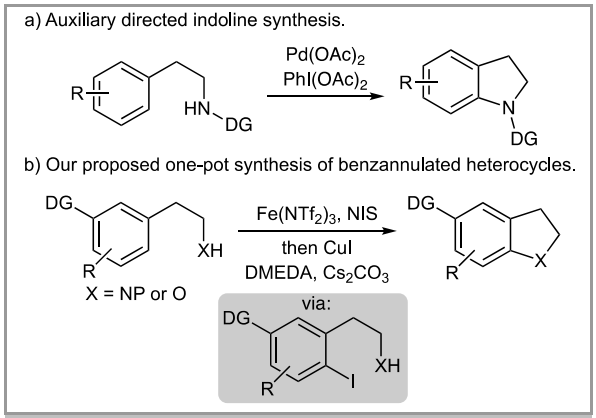


Scheme 10 One-pot *ortho*-amination of arenes. [a]Copper-catalyzed step was done at 150 °C.

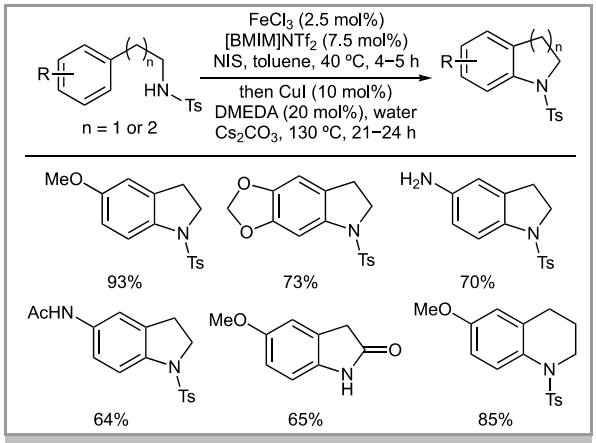
4 One-Pot Intramolecular C–N, C–O and C–S Bond Forming Processes

Having developed a one-pot arene amination process, we believed that an intramolecular version of this transformation using a nucleophile appended to an arene ring could be used for the preparation of benzannulated heterocycles. This idea was inspired by the examples of indoline synthesis, in which an *N*-chelating group facilitates oxidative palladium C–H activation and cyclization (Scheme 11a).[23,30] In a similar manner, we proposed that these ring systems could be prepared by a one-pot intramolecular iron(III)-catalyzed iodination and copper-catalyzed cyclization (Scheme 11b). An advantage of our approach would be that the non-oxidative conditions would be compatible with hydroxyl-based nucleophiles, which led to side-reactions under the oxidative palladium-catalyzed method.[31]

A concern we had about the likely success of this approach was that the steric hinderance of the ethyl amine or ethyl alcohol side-chain might block the desired *para*-iodination (see Scheme 11b, insert) and instead lead to halogenation at the least hindered *ortho*-position to the directing group. However, using a range of *N*-protected 2-phenylethylamines, iron-catalyzed iodination gave only the desired *para*-iodide.[32] Subsequent copper(I)-catalyzed cyclization completed the one-pot synthesis of indolines. Using the *N*-tosyl protecting group, the scope of the one-pot process was explored with variation of the aryl activating group. The one-pot transformation was tolerant for a range of substrates (anisoles, anilines and acetanilides), allowing the preparation of indolines in good to high yields (Scheme 12). In addition, other ring systems such as 2-oxindoles and tetrahydroquinolines could also be prepared using the one-pot method. To further investigate why the iron(III) triflimide-catalyzed iodination was *para*-selective, DFT calculations were performed using one of the substrates. In this study, the use of atomic Fukui indices clearly showed that the p_z atomic orbital at the *para*-position made the largest contribution to the HOMO, hence, confirming the observed regioselectivity.

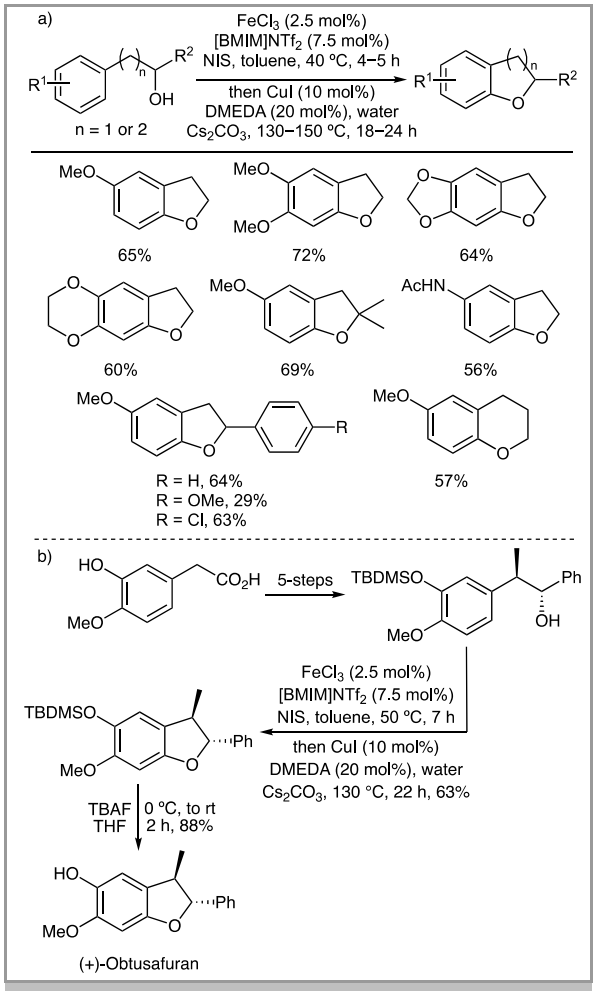


Scheme 11 Directed metal-catalyzed synthesis of benzannulated heterocycles.



Scheme 12 One-pot intramolecular amination.

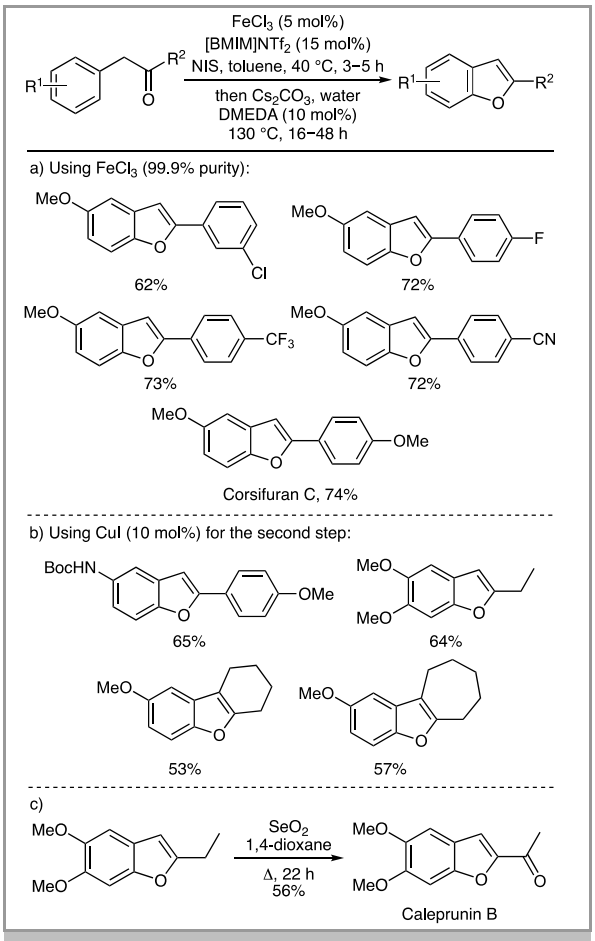
We then examined the use of this approach for the synthesis of dihydrobenzofurans (Scheme 13a).[32] Phenethyl alcohols bearing various arene activating groups were found to be substrates for the one-pot process, forming the corresponding dihydrobenzofuran in good yields. The only limitation was found with compounds containing electron-rich arenes within the ethyl alcohol side-chain, where competitive iodination between the two activated aryl rings led to the dihydrobenzofurans in low yields. The one-pot method was also used for the synthesis of six-membered analogues, dihydrobenzopyrans and as the key step for a total synthesis of (+)-obtusafuran (Scheme 13b), a neolignan natural product, which has been shown to possess antiplasmodial activity.[33] In our 8-step total synthesis, a chiral phenethyl alcohol was initially prepared by an enantioselective hydrogenation.[32] Application of the one-pot iodination and cyclization process gave the dihydrobenzofuran ring system of (+)-obtusafuran in 63% yield. Despite a highly activated ring system and a secondary alcohol, no by-products from over-iodination or oxidation were observed.



Scheme 13 One-pot synthesis of *O*-Heterocycles and (+)-obtusafuran.

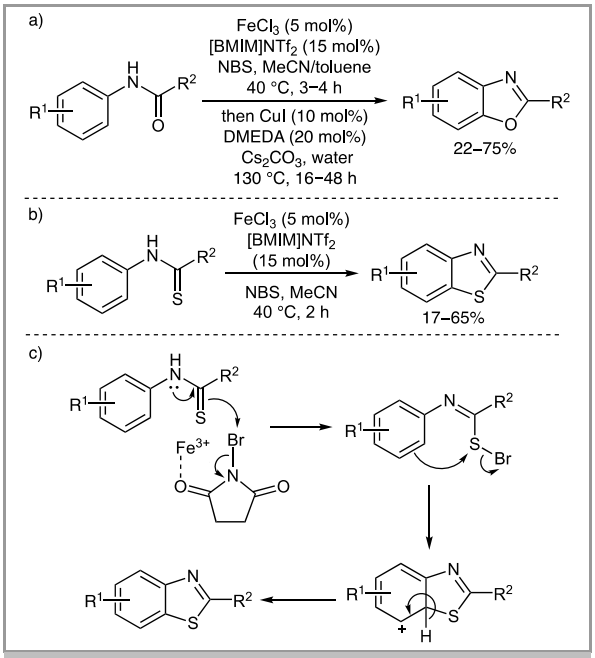
The one-pot intramolecular process was extended to the synthesis of benzo[*b*]furans by the activation and cyclization of 1-aryl- or 1-alkyl-benzylketones (Scheme 14).[34] The reactive nature of these compounds for the cyclization step allowed the development of a one-pot, tandem catalytic process where iron(III) could be used for both steps. For example, the use of ultrapure iron(III) nitrate (copper-free) as the only source of transition metal catalyst gave benzofurans in moderate yields. The scope of the transformation was found to be more general when copper was present for the cyclization step. For compounds with highly activated aryl rings and with an 1-arylketone side-chain, a one-pot process was developed using iron(III) chloride (99.9% purity), where the copper impurities from the $FeCl_3$ were sufficient to

catalyze the cyclization step (Scheme 14a). For substrates with less activated aryl rings or less reactive alkyl ketones, the standard amount of CuI (10 mol%) was necessary for an effective cyclization (Scheme 14b). For both one-pot processes, this allowed the efficient synthesis of a wide-range of benzofurans, including biologically important targets and natural products. This included a short synthesis of caleprunin B, a naturally occurring 2-acetylbenzo[*b*]furan from *Eupatorium sternbergianum* and *Calea berteriana* (Scheme 14c).[35] Following the synthesis of a 2-ethyl-substituted benzofuran, the natural product was prepared by allylic oxidation using selenium dioxide.



Scheme 14 (a) One-pot synthesis of benzofurans using $FeCl_3$ (99.9% purity). (b) One-pot synthesis of benzofurans from less activated substrates using copper iodide during the second step. (c) Synthesis of caleprunin B.

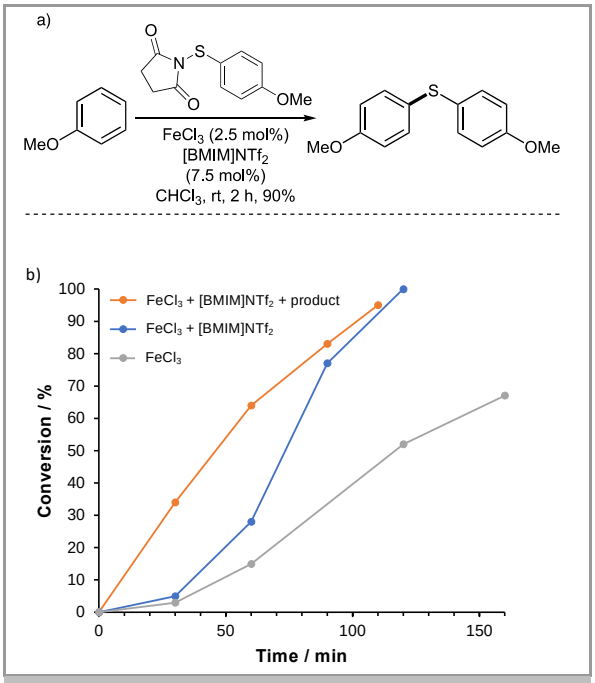
Following the successful one-pot synthesis of benzofurans, the benzannulation of arenes with other carbonyl side-chains was investigated. Using *N*-arylbenzamides, the standard iron(III)-catalyzed bromination and copper(I)-catalyzed cyclization led to the synthesis of 2-arylbenzoxazoles (Scheme 15a).[36] The substrate scope was more limited than previous one-pot transformations, requiring highly activated aromatic rings and benzamides as the nucleophile. Acetamides leading to 2-alkylbenzoxazoles did not undergo cyclization. An interesting deviation of the standard iron and copper-catalyzed process was discovered during the investigation of *N*-arylthiobenzamides for the synthesis of benzothiazoles (Scheme 15b). With these substrates, the corresponding 2-arylbenzothiazoles were formed directly after treatment with iron(III) triflimide and NBS. From mechanistic and control experiments, we showed that while the aromatic ring of *N*-arylbenzamides undergoes iron-catalyzed halogenation, followed by cyclization, for *N*-arylthiobenzamides halogenation occurs at the sulfur atom, followed by electrophilic aromatic substitution and cyclization (Scheme 15c). This mechanism is similar to the Jacobsen-Hugerschoff cyclization of thiobenzamides using either potassium ferricyanide or bromine.[37,38] Although more restrictive in scope than previous one-pot processes, biologically active compounds, such as an affinity agent of the amyloid-beta protein in Alzheimer's disease could be prepared using these one-pot processes.



Scheme 15 (a) One-pot synthesis of 2-arylbenzoxazoles. (b) One-pot synthesis of 2-arylbenzothiazoles. (c) Proposed cyclization of *N*-arylthiobenzamides.

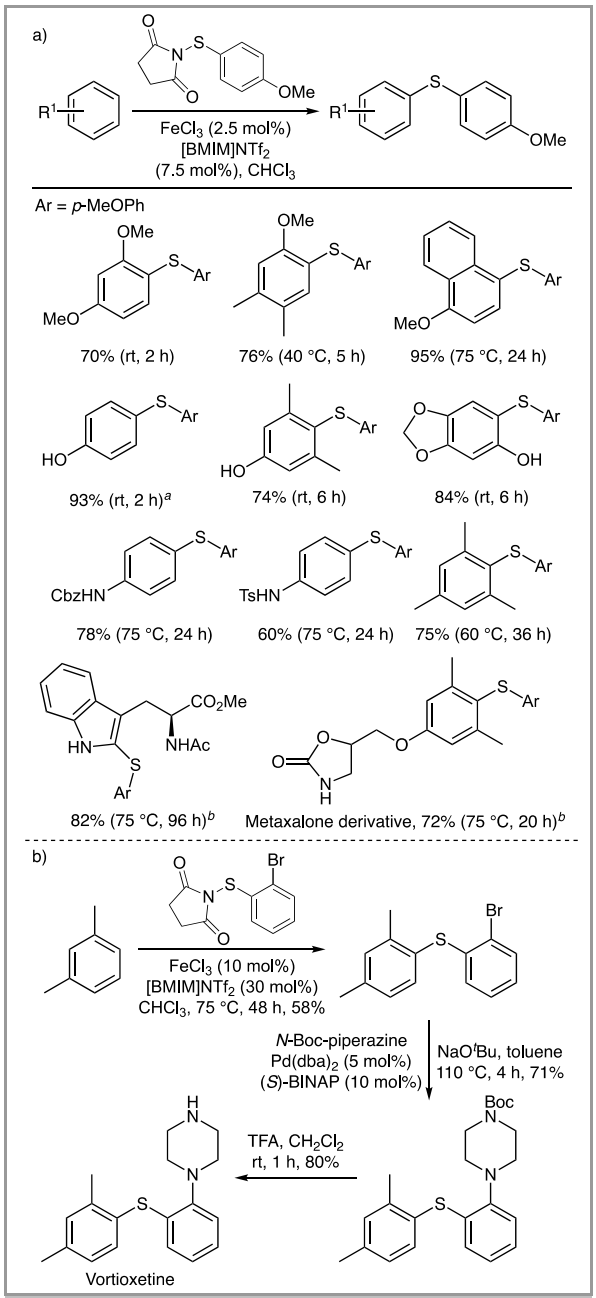
5 Iron(III)-Catalyzed Thioarylation of Arenes

Having developed one-pot processes for the preparation of a range of benzannulated heterocycles based on an iron(III) triflimide-catalyzed halogenation, we have more recently begun to investigate other types of arene functionalization using this general approach. The importance of aryl thioethers have led to a variety of methods for formation of aryl C–S bonds. These have included the use of Lewis acids such as trifluoroacetic acid to activate *N*-(arylthio)succinimides for the thiolation of arenes.[39] A combined Lewis base and Brönsted acid activation of *N*-(arylthio)succinimides for thioarylation has also been reported.[40] Based on this work, we believed that iron(III) triflimide would serve as an effective Lewis acid catalyst for thiolation of arenes. Initial work investigated the thioarylation of anisole with *N*-(4-methoxyphenylthio)succinimide, which was easily prepared by the reaction of NCS with 4-methoxybenzene thiol.[41] Following an optimization study, we found that the reaction could be performed with low catalyst loadings of $Fe(NTf_2)_3$ (2.5 mol%) and after a reaction time of 2 hours gave the diaryl thioether in 90% yield (Scheme 16a). As observed with the iron(III)-catalyzed halogenation reactions, kinetic studies showed that the use of $Fe(NTf_2)_3$ resulted in a faster reaction that using $FeCl_3$ (Scheme 16b). More significantly, the shape of the conversion graphs was found to be sigmoidal, indicating that the reaction was autocatalytic. Similar autocatalysis was observed by Gustafson and co-workers in their TFA-promoted thioarylation reaction.[40] Indeed, when we added a catalytic amount of the product, bis(4-methoxyphenyl)sulfane (10 mol%) to the reaction, no induction period was observed. We proposed that the product can act as a Lewis base forming a reactive cationic disulfide with the *N*-(arylthio)succinimide, leading to an accelerated reaction (see Scheme 19b). The acceleration of the iron(III)-catalyzed thioarylation reaction using Lewis bases was used by us in later work, where more hindered and less reactive *N*-(arylthio)succinimides resulted in very slow reactions.



Scheme 16 (a) Iron(III)-catalyzed thioarylation of anisole. (b) Conversion graphs for the thioarylation of anisole with *N*-(4-methoxyphenylthio)succinimide.

The scope of the optimised iron(III) triflimide-catalyzed thioarylation reaction was explored.[41] We found that the method was general for a wide range of electron-rich arenes, including anisoles, phenols and protected anilines and, gave the thioarylated products in high yields, under mild conditions as single regioisomers (Scheme 17a). Electron-rich heterocycles were also substrates for the reaction, and this allowed the efficient thioarylation of more functionalized compounds such as tryptophan. The method was used for the late-stage derivatization of drug molecules, as shown with the efficient thioarylation of the pain-relief medicine, metaxalone.[42] The synthetic utility of the iron(III)-catalyzed thioarylation was also demonstrated with the use of this transformation as the key step in new syntheses of the antibiotic, dapsone[43] and the antidepressant, vortioxetine (Scheme 17b).[44] The synthesis of vortioxetine showed that using a less activated arene (*meta*-xylene) and an electron-deficient, *ortho*-substituted *N*-(arylthio)succinimide, this reaction was still effective, giving the coupled product in 58% yield.

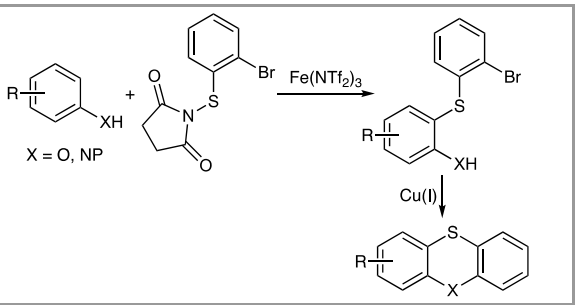


Scheme 17 Scope and applications of the iron(III)-catalyzed thioarylation of electron-rich (hetero)arenes. [a]Done using $FeCl_3$ (5 mol%) and $[BMIM]NTf_2$ (15 mol%). [b]Done using $FeCl_3$ (10 mol%) and $[BMIM]NTf_2$ (30 mol%).

6 Synthesis of Phenoxathiins and Phenothiazines using Lewis Acid and Lewis Base Catalysis

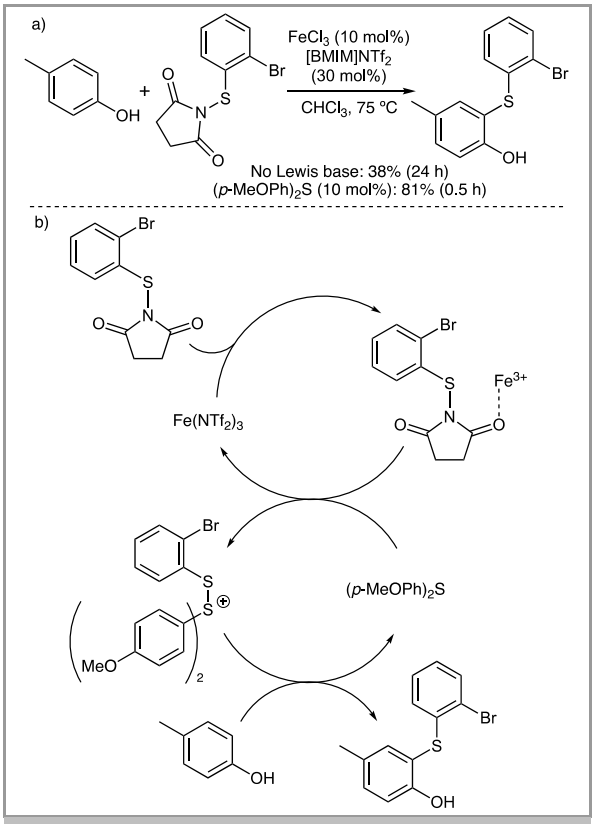
The synthesis of vortioxetine demonstrated that functionalized *N*-(arylthio)succinimides could be used for iron(III)-catalyzed thioarylations and then subjected to further reactions. While the

product of this reaction underwent an intermolecular coupling, we proposed that the use of a pendant nucleophile such as a phenol or aniline would result in an intramolecular cyclization and the synthesis of phenoxathiins and phenothiazines, respectively (Scheme 18). In a similar manner to our previous work, we believed a copper-mediated Ullmann-Goldberg reaction would facilitate the cyclization step.



Scheme 18 Proposed synthesis of phenoxathiins and phenothiazines.

Using *para*-substituted phenols that would direct thioarylation to the *ortho*-position, we began by developing an iron-catalyzed thioarylation with *N*-(2-bromophenylthio)succinimide.[45] Using similar catalyst loadings and reaction conditions to the vortioxetine synthesis, we found that thioarylation of *p*-cresol required a reaction time of 24 h and gave the product in 38% yield (Scheme 19a). To improve this process, we used the previous observation that Lewis bases could accelerate the reaction. Therefore, a catalytic amount of bis(4-methoxyphenyl)sulfane (10 mol%) was added to the reaction, resulting in a significant improvement of both the reaction time (0.5 h) and yield (81%).

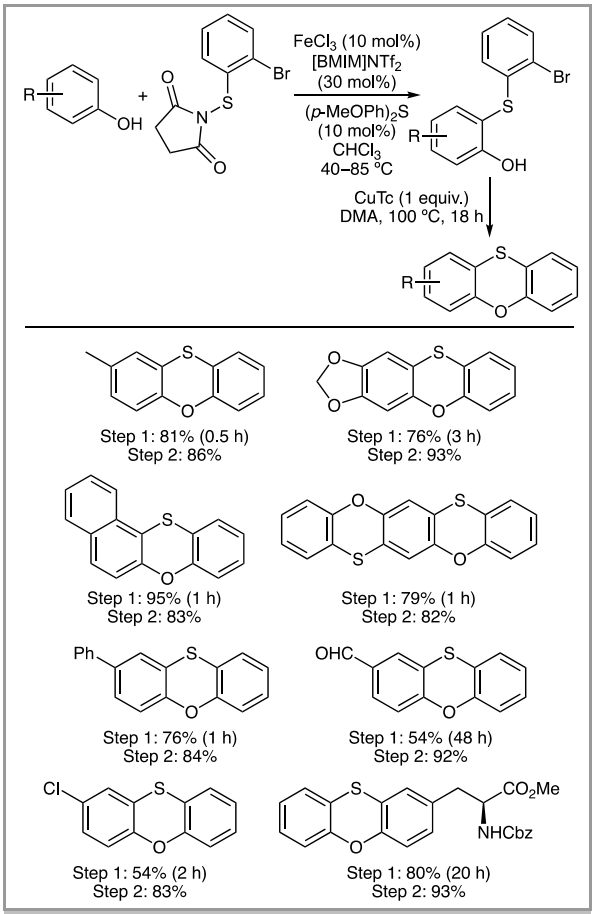


Scheme 19 (a) Development of *ortho*-thioarylation of cresol. (b) Proposed mechanism for the Lewis base accelerated thioarylation reaction.

To account for the observed acceleration of the reaction a mechanism was proposed (Scheme 19b).[45] Control experiments showed that without the presence of iron triflimide, the Lewis base could not promote the reaction. Based on this, we believe that the iron(III) Lewis acid initially activates *N*-(2-bromophenylthio)succinimide, which then reacts with the Lewis base, bis(4-methoxyphenyl)sulfane. Formation of a more reactive cationic disulfide (compared to the iron-activated succinimide) results in a faster thiolation reaction with the arene.

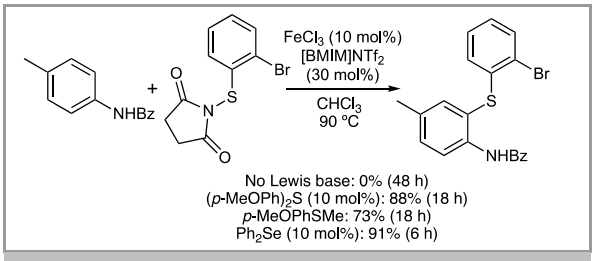
Using the combined Lewis acid and Lewis base catalyzed C–H thioarylation reaction, a two-step synthesis of phenoxathiins was developed (Scheme 20).[45] Thioarylation of electron-rich phenols was fast and efficient, while electron-poor analogues required longer reaction times and gave the product in moderate yields. The Ullmann-type cyclization step was then

performed using copper(I) thiophene-2-carboxylate as a stoichiometric reagent. For all substrates, standard conditions of 100 °C and 18 hours gave the phenoxathiin products in high yields. Attempts were made to combine both steps as a one-pot process, but the difference in solubility of reagents from each reaction meant this was not possible. The two-step process was applicable for bi-directional synthesis with hydroquinone, for the preparation of 5,12-dioxa-7,14-dithiapentacene and biomolecules with phenolic groups such as tyrosine and estradiol.



Scheme 20 Two-step synthesis of phenoxathiins.

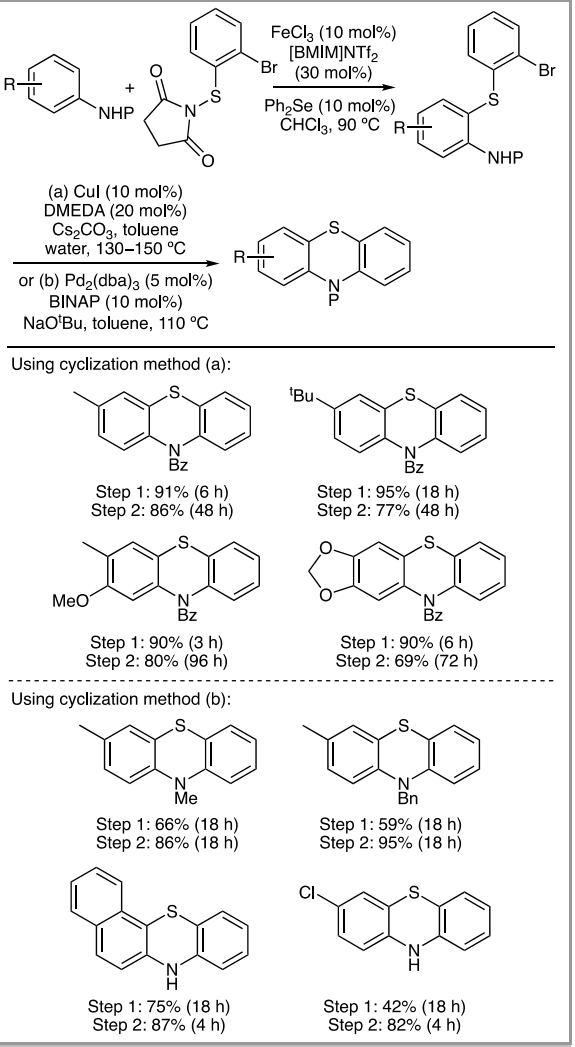
With the success of the Lewis base-accelerated iron(III)-catalyzed thioarylation of phenols for the synthesis of phenoxathiins, we applied this to anilines for the preparation of phenothiazines. The development of this process was investigated using benzoyl protected *p*-toluidine (Scheme 21).[46] Attempted thioarylation using iron(III) triflimide at 10 mol% loading and a 90 °C reaction temperature showed no reaction after 48 hours. Based on our previous study, several Lewis bases were screened to promote and accelerate the transformation. Bis(4-methoxyphenyl)sulfane was again shown to be effective, generating the product in 88% yield. However, completion of the reaction required 18 hours. Other sulfanes gave similar results, while Lewis bases such as diarylthioureas and triphenylphosphine sulfide showed no conversion. Commercially available diphenyl selenide was shown to be the optimal Lewis base. This gave the product in an excellent 91% yield, requiring only a 6 hour reaction time.



Scheme 21 Development of Lewis acid and Lewis base catalyzed thioarylation of *N*-benzoyl protected *p*-toluidine.

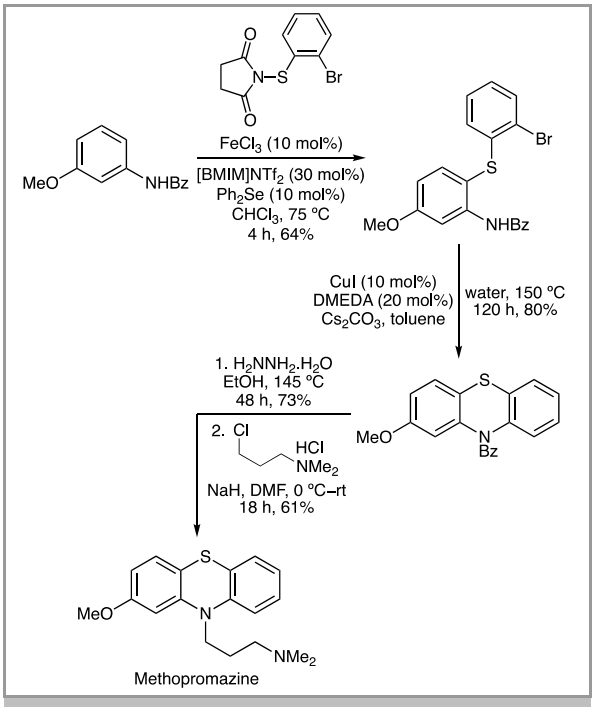
Using the diphenyl selenide accelerated thioarylation reaction, a two-pot process was developed for the synthesis of phenothiazines (Scheme 22).[46] For electron-rich anilines, *N*-protection was necessary to avoid competing *N*-thioarylation. Under the optimised conditions, clean and high yielding thioarylation reactions were observed. Anilines with electron-deficient substituents or extended conjugation did not require *N*-protection and underwent thioarylation directly. For this class, clean arene thioarylation was observed and gave the products in moderate to high yield. For the cyclization step, we found that catalytic processes were possible. For benzoyl protected anilines, an Ullmann-Goldberg

coupling using copper(I) iodide and DMEDA gave the corresponding phenothiazines. While the reactions were generally high yielding, forcing conditions (130–150 °C) and long reaction times were necessary (48–96 h). For unprotected or *N*-alkyl analogues, cyclization using a palladium-catalyzed Buchwald-Hartwig reaction gave the best results.[47] As well as high yields under slightly milder conditions, the reaction times, particularly for unprotected anilines were found to be much shorter (4 h).



Scheme 22 Two-step synthesis of phenothiazines.

An application of the two-step approach for the preparation of phenothiazines was demonstrated with a short synthesis of the neuroleptic agent, methopromazine.[46,48] Thioarylation of *N*-benzoyl protected 3-methoxyaniline using the dual Lewis acid and Lewis base procedure gave the *ortho*-substituted product in 64% yield. Using a slightly lower reaction temperature (75 °C) than the standard conditions of 90 °C allowed controlled mono-thioarylation at the *para*-position to the methoxy group. Copper(I)-catalyzed cyclisation again required forcing conditions and a long reaction time but gave the corresponding phenothiazine in 80% yield. Removal of the benzoyl protecting group using hydrazine, followed by alkylation of the amine with the hydrochloride salt of 3-dimethylaminopropyl chloride completed the four-step synthesis of methopromazine.



Scheme 23 Total synthesis of methopromazine.

7 Conclusions

Arenes are important as synthetic intermediates and as key structural components of pharmaceutical agents and materials. Therefore, selective functionalization of aromatic compounds is of vital importance in organic chemistry.

While many methods have been developed, traditional reactions tend to involve harsh conditions. In our programme of research, we have utilized a super Lewis acid, iron triflimide for the activation of *N*-functionalized succinimides for the subsequent electrophilic aromatic substitution of electron-rich arenes. Under relatively mild conditions, this has allowed the regioselective formation of carbon-halogen and carbon-sulfur bonds and, in combination with copper-catalyzed Ullmann-Goldberg reactions, also the generation of carbon-nitrogen and carbon-oxygen bonds. The iron-catalyzed halogenation and copper-catalyzed C–N or C–O coupling has been developed as a one-pot process and, using intramolecular nucleophiles, this has led to a general approach for the synthesis of a range of benzannulated heterocycles, which we have used for the preparation of natural products and drug compounds. Current work is investigating further applications of super Lewis acids for arene functionalization.

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Conflict of Interest

The authors declare no conflict of interest.

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