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Regioselective Iodination of Chlorinated Aromatic Compounds Using Silver Salts

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Abstract

The iodination of chlorinated aromatic compounds using Ag_2SO_4/I_2, $AgSbF_6/I_2$, $AgBF_4/I_2$ and $AgPF_6/I_2$ offers access to iodoarenes that are valuable intermediates in organic synthesis. Specifically, iodination of phenols, anisoles and anilines with a 3,5-dichloro substitution pattern preferentially yielded the *ortho*, *para* and *para* iodinated product, respectively. In the case of chlorobenzene and 3-chlorotoluene, $AgSbF_6/I_2$, $AgBF_4/I_2$ and $AgPF_6/I_2$, but not Ag_2SO_4/I_2, selectively introduced the iodine in *para* position to the chlorine substituent.

Keywords

Phenol; anisole; aniline; chlorobenzene; 3-chlorotoluene; non-coordinating ions; silver sulfate; silver hexafluoroantimonate; silver tetrafluoroborate; silver hexafluorophosphate

1. Introduction

The iodoarene moiety is an important structural motif in biologically active molecules (e.g. thyroid hormone) and a synthetic intermediate for a variety of fine chemistry products (e.g. isovanillyl sweeteners[1]), radiopharmaceuticals,[2] environmental contaminants[3,4] and numerous bioactive compounds, such as camptothecin,[5] cephalosporin derivatives,[6] dehydrotubifoline,[7] morphine,[8] sangliferine A,[9] ecteinascidine,[10] and berkelic acid methyl ester.[11] One example of a prescription drug synthesized from an iodoarene intermediate is galanthamine, an acetylcholinesterase inhibitor for the symptomatic treatment of senile dementia of Alzheimer patients.[12] The usefulness of iodoarenes as synthetic intermediates is

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partly due to the fact that the iodo substituent can undergo a multitude of transition metal-catalyzed cross-coupling reactions.[13,14]

In particular the electrophilic iodination of phenols, anisoles and anilines provides straightforward access to a range of valuable iodoarene intermediates.[15,16] A variety of iodine atom donating reagents, such as *N*-iodosuccinimide/*p*-toluenesulfonic acid[17] and iodine monochloride (ICl),[18] have been used successfully for the iodination of aromatic compounds. In addition, elemental iodine (I_2) is a particularly attractive source of iodine atoms.[15,16] Iodination reactions using I_2 require activation by protons, metal ions or a suitable solvent and trapping of the hydriodic acid formed during the reaction to prevent cleavage of carbon-iodide bonds. Finally, oxidative activation strategies have been employed to generate reactive iodonium species or to oxidize the released iodide to iodine, thus allowing a stochiometric use of the iodine atoms present in the reaction.[15,16] Most iodination reagents give good-to-excellent yields of iodinated phenols, anisoles and anilines and display a high *para* regioselectivity. In *para*-substituted aromatic compounds, iodination typically results in mono- or even di-iodination in *ortho* positions.

Iodinated phenols, anisoles and anilines with chlorine substituents in the *meta* position are of interest as starting materials for a variety of drug molecules[19–21] and environmental contaminants.[3,4] These compounds are frequently synthesized via the reduction of a suitable nitrobenzene followed by a Sandmeyer reaction to introduce the iodo substituent.[3,4,22–24] Although a direct iodination of a suitable chlorinated precursor would greatly improve access to these building blocks, the regioselectivity of the iodination of chlorinated aromatic compounds has been poorly characterized. For example, 3,5-dichloro-2-iodophenol, a starting material for the synthesis of heat shock protein-90 (HSP-90) inhibitors, can only be synthesized in moderate yield by iodination of 3,5-dichlorophenol with NaH/I_2.[19] 2,5-Dichloro-4-iodophenol, a precursor of cephalosporin derivatives with activity against methicillin-resistant *Staphylococcus aureus*, was synthesized from 2,5-dichlorophenol with Ag_2SO_4/I_2.[6] Several chlorinated iodo- and diiodoanilines have been prepared by iodination of the corresponding chlorinated aniline with iodine monochloride.[20,21,25,26] For example, 2-iodo-3,4-dichloroaniline, a starting material for preparation of indolyl substituted benzoic acids for the treatment of urinary tract disorders, has been synthesized by ICl/AcOH in only 35% yield.[26]

One reason for the lack of direct iodination procedures for chlorinated aromatic compounds is the challenging separation of different iodinated regioisomers (Scheme 1) and the formation of by-products resulting from dehalogenation, polysubstitution and other side-reactions, which considerably complicates the product isolation and purification. Here, we systematically investigate the regioselective iodination of a series of chlorinated phenols, anisoles, anilines and other aromatic compounds using a series of iodination reagents, with a special emphasis on iodination reactions using I_2 and silver salts with non-coordinating anions.

2. Results and discussion

2.1. Exploratory iodination of phenol (*1a*), 3,5-dichlorophenol (*1b*) and 3,5-dichloroanisole (*1c*)

2.1.1. Conventional iodination reagents—The iodination of phenol (**1a**) with different iodination reagents has been investigated extensively and typically results in good yields and *para* selectivity.[15] Building on published iodination approaches for **1a**, this study initially investigated the regioselectivity of the iodination of 3,5-dichlorophenol **1b** (Table 1). The corresponding iodides **2b** and **3b** are useful starting materials for the synthesis of HSP-90 inhibitors[19] or metabolites of polychlorinated biphenyls (PCBs).[3,4] Iodination with I_2 in ethanol resulted in complete conversion of **1b** within 16 hours and displayed *ortho* selectivity; however, the yield of the *ortho* iodinated product **2b** was only 16% (entry 1–1). *N*-Iodosuccinimide (NIS)/*p*-toluenesulfonic acid (PTSA) as the iodine atom donating reagent[17] resulted in almost complete conversion of **1b** within 24 h, with a **3b: 2b** ratio of approximately 3: 1 (entry 1–2). A more pronounced regioselectivity has been reported previously for the iodination of phenol (**1a**) with NIS/PTSA (**3a: 2a** > 14: 1).[17]

Although nearly complete conversion was observed within 24 h for the iodination of **1b** with benzyltrimethylammonium dichloroiodinate (BTMACl_2I)/$ZnCl_2$[3] at room temperature, the total yield of iodides **2b** and **3b** was poor and no diiodinated products were detected (entry 1–3). BTMACl_2I/$ZnCl_2$[3] at 90 °C also resulted in almost complete conversion of **1b** and the formation of essentially a 1:1 mixture of **2b** and **3b** (entry 1–4). Only 4% conversion and no regioselectivity was observed when **1b** was iodinated CAN/I_2 in acetonitrile (entry 1–5).[27,28] In contrast, the iodination of phenol with CAN/I_2 has been reported to give 70% yield of the 2- and 4-iodinated products, with a ratio of **2a: 3a** of 7: 3.[28] Overall, the yields and/or regioselectivity with the conventional iodination reagents were unsatisfactory (yields < 41%), with only NIS/PTSA resulting in a reasonable yield of **3b** (57%).

2.1.2. Iodinations of 3,5-dichlorophenol 1b using Ag_2SO_4/I_2 and related silver reagents—

Considering the poor yield and regioselectivity of more conventional iodination reagents (Table 1, entries 1–1 to 1–5), a series of silver salt/I_2 reagents was studied as iodination reagents for **1b**. Silver salts, such as Ag_2SO_4/I_2[6,29–31] and $Ag(OCOCF_3)/I_2$[32,33], have been used extensively for the iodination of aromatic compounds. They activate I_2 by forming insoluble silver iodide, thus generating an electrophilic iodine species. The reactive iodine species appears to be identical in many of these reactions and is thought to react with the respective aromatic compound via a σ-complex.[34] As shown in Table 1, only a small percentage of **1b** was iodinated with Ag_2SO_4/I_2 in acetonitrile (entry 1–6), whereas complete or almost complete conversion of **1b** was observed with all other silver salts investigated (entries 1–7 to 1–10). However, several reagents displayed poor yields, possibly due to the high reactivity of the respective reagent (entries 1–7 and 1–8).

β-Cyclodextrin has been shown to improve the regioselectivity of bromination reactions in organic solvents due to complexation of the aromatic phenol or aniline,[35,36] but to decrease the *ortho*-to-*para* ratio for the *ortho*-iodination of phenol (**1a**) in aqueous solution.[37] In this study, β-cyclodextrin had no advantageous effect on the regioselectivity of the iodination of **1b** with Ag_2SO_4/I_2 in DMSO/DCM (entry 1–8). Iodination of **1b** with Ag_2SO_4/I_2 in *n*-hexane resulted in good yields (total yield of **2b** + **3b** is 90%), but displayed poor regioselectivity (**2b: 3b** ~ 1: 1; entry 1–9). The iodination with $Ag(OCOCF_3)/I_2$ in ethanol resulted in an almost complete conversion of **1b** and gave unsatisfactory yields after 16 hours, with a 7-times higher yield of the *ortho* iodinated product **2b** (entry 1–10).

2.1.3. Iodination of 3,5-dichloroanisole 1c using Ag_2SO_4/I_2—

The iodination of 3,5-dichloroanisole (**1c**) was investigated as a structural analog to 3,5-dichlorophenol (**1b**) (Table 2). The structures of the iodination products **3c** and **4c** were confirmed by crystal structure analysis to ensure a correct interpretation of the product ratios (Figure S1). The iodination of **1c** with NIS/PTSA, which gave the best iodination results with phenol **1b**, yielded the 4-substituted product **3c** in 68% yield (complete conversion) (entry 2-1). However, considerable quantities of **2c** and **4c** were also formed (**2c: 3c** ~ 1: 5 and **4c: 3c** ~ 1: 23). Subsequent experiments investigated the yield and regioselectivity of the iodination of anisole **1c** with Ag_2SO_4/I_2 in different solvents. Iodination of **1c** in DCM resulted in poor yields of **2c** and **3c**, possibly due to the formation of multi-iodinated products, and limited regioselectivity (entry 2–2). While the yields of the iodination reaction in hexane were excellent (87% total yield), the regioselectivity was relatively poor, with **3c** being the major product (entry 2–3). This is comparable with the iodination of **1b** in hexane, which also resulted in poor regioselectivity (entry 1–9). Significantly improved *para* regioselectivity was observed for reactions performed in acetonitrile (entries 2–4 and 2–5). In particular iodination with 1.5 equivalents Ag_2SO_4 and 1.1 equivalents I_2 gave **3c** in 65% yield, with **2c: 3c** ~ 1: 16 (complete conversion) (entry 2–4). Increasing the molar ratios of Ag_2SO_4 and I_2 gave a somewhat lower yield of **3c** and a decreased regioselectivity (**2c: 3c** ~ 1: 12) (entry 2–5). A reasonable *para* selectivity was also observed in DMSO; however, the yields of **3c** were only moderate (35% yield; 94% conversion) (entry 2–6).

2.2. Iodination with silver salt with non-coordinating anions and I_2 (AgX/I_2)

Since neither the conventional nor the silver-based iodination reagents offered a clear advantage for the regioselective iodination of phenol **1b** or anisole **1c** (Tables 1 and 2), the present study investigated the hypothesis that anions with different ligand binding strength may modulate the reactivity and, thus, regioselectivity of silver salt/I_2 reagents. In particular non-coordinating anions SbF_6^-, BF_4^- and PF_6^- are of interest in this context because their ligand binding strengths decrease in the order $SbF_6^- > BF_4^- > PF_6^-$.[38] Although $AgBF_4/I_2$ has been used for the synthesis of iodoarenes from aryltrimethylsilanes, this reagent has not been investigated for the direct electrophilic iodination of aromatic compounds.[39,40] Furthermore, several other iodinating reagents, such as bis(sym-collidine)iodine(I) hexafluorophosphate[41] or $HgO/HBF_4/I_2$ on SiO_3,[42] contain non-coordinating anions. However, to the best of our knowledge iodination reactions with I_2 and $AgSbF_6$, $AgBF_4$ or $AgPF_6$ have not been employed in aromatic iodination reactions.

2.2.1. Iodination of phenol 1a and 3,5-dichorophenol 1b with AgX/I_2—As

mentioned above, the iodination of phenol (**1a**) with a range of reagents, for example KI/H_2O_2/AcOH,[43] KI/$KClO_3$/HCl,[44] CAN/I_2,[28] $NaBO_3{\cdot}4H_2O/I_2$ in ionic liquids,[45] $H_5PV_2Mo_{10}O_{40}$ polyoxometalate/I_2,[46] ICl/DDQ/ferrocenium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate[47] or NIS/PTSA,[17] typically results in good yields and *para* selectivity; however, *ortho* iodination of **1a** reportedly occurs with a number of silver salts and iodine, for example Ag_2SO_4/I_2 and $AgNO_3/I_2$ in DCM.[48] In this study, conversion of 79% and 100% were observed for iodinations of **1a** with $AgSbF_6/I_2$ and $AgBF_4/I_2$, respectively, and the yields of **2a** and **3a** were poor (Table 3; entries 3-1 and 3-2). One possible explanation for the poor yields is the formation of poly-iodinated and other byproducts that cannot be detected by GC-MS. An intriguing observation is that the *para* substituted product **3a** was formed in 46% yield (91% conversion) with $AgPF_6/I_2$ (entry 3–3). This suggests that the side reactions responsible for the low yield with $AgSbF_6/I_2$ and $AgBF_4/I_2$ did not play a role in the iodination of **1a** with $AgPF_6/I_2$, possibly due to its lower reactivity. However, this reagent does not offer an apparent advantage compared to conventional iodination reagents.

Compared to **1a**, significantly improved yields and regioselectivities were observed for iodinations of **1b** with Ag_2SO_4/I_2, $AgSbF_6/I_2$, $AgBF_4/I_2$ and $AgPF_6/I_2$ in DCM (Table 3). These reactions gave moderate-to-good yields of the *ortho* product **2b** (Table 3, entries 3–4 to 3–7). Iodination of **1b** with Ag_2SO_4/I_2 in DCM gave **2b** in 53% yield (entry 3–4). In contrast, iodination of 2,5-dichlorophenol under comparable conditions has been reported to yield the corresponding *para* substituted product, 2,5-dichloro-4-iodophenol, in 86% yield.[6] $AgBF_4/I_2$ was the most reactive reagent among the silver salts investigated, with complete conversion of **1b** after only 1 h (entry 3–6). The highest **2b: 3b** ratio was obtained with $AgSbF_6/I_2$, which afforded **2b** in 82% yield (entry 3–5). In this reaction, only traces of the *para* product **3b** were detected by GC-MS. A relatively poor regioselectivity was observed for $AgPF_6/I_2$, with a **2b: 3b** ratio of approximately 6: 1. The opposite regioselectivity was observed for NIS/PTSA, with **2b: 3b** ~ 1: 3 (entry 1–2).

2.2.2. Iodination of anilines 1d-g with AgX/I_2—The iodination of aniline (**1d**) with Ag_2SO_4/I_2 in ethanol has been reported to result in the formation of **3d** in 46% yield.[31] Similarly, the direct iodination of aniline (**1d**) with different reagents, for example KI/H_2O_2/AcOH,[43] KI/$KClO_3$/HCl,[44] KI/KIO_3/HCl,[49] CAN/I_2,[28] $NaBO_3·4H_2O/I_2$ in ionic liquids,[45] $H_5PV_2Mo_{10}O_{40}$ polyoxometalate/I_2,[46] ICl/DDQ/ferrocenium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate[47] or bis(sym-collidine)iodine(I) hexafluorophosphate,[41] yields **3d** as the major product. The only reported selective synthesis of **2d** (46% yield) by direct iodination of **1d** employs Ag_2SO_4/I_2 in 1,2-ethanediol as iodinating reagent.[50] In this study, the iodination of aniline (**1d**) with $AgSbF_6/I_2$ and $AgPF_6/I_2$ resulted in the formation of 4-iodoaniline (**3d**) in 25% (57% conversion) and 22% (69% conversion) yield, respectively (Table 4, entries 4-1). While no 2- and 3-iodoanilines were detected with either reagent, significant amounts of a diiodo- and, in the case of $AgSbF_6/I_2$, a triiodo-aniline were detected by GC-MS. Therefore, $AgSbF_6/I_2$ and $AgPF_6/I_2$ do not offer a more straightforward access to *para* iodinated aniline **3d**.

2,5-Dichloroaniline (**1e**) was iodinated in *para* position to yield **3e** in 47% (84% conversion) with Ag_2SO_4/I_2 and 59% (83% conversion) with $AgSbF_6/I_2$ (entries 4-2a). Small quantities of diiodoaniline **4e** were detected by GC-MS with both reagents. Under similar reaction conditions, $AgBF_4/I_2$ and $AgPF_6/I_2$ gave only poor yields of **3e** plus small quantities of the diiodoaniline **4e**, which suggests that both reagents may be too reactive for the selective mono-iodination of **1e**.

Ag_2SO_4/I_2 also appeared to be a good iodination reagent for 3,4-dichloroaniline (**1f**), resulting in the formation of a 77% yield of 4,5-dichloro-2-iodoaniline (**3f**) (entries 4-3a). The other reagents investigated gave poor conversions of approximately 50% and overall yields of the possible mono- and di-iodination ≤ 16%. In the case of **1f**, the order of the addition of the starting material and I_2 did not alter the percent conversion or the regioselectivity of the reaction (entries 4-3a versus 4-3b), a finding that most likely applies to this type of iodination reaction in general.

All four reagents showed some *para* selectivity for the iodination of 3,5-dichloroaniline (**1g**), which is the structural analog of 3,5-dichlorophenol (**1b**) and 2,5-dichloroanisole (**1c**). However, only Ag_2SO_4/I_2 resulted in a good conversion (87%) and a reasonable yield (66%) of **3g** (entries 4–4). According to GC-MS analysis, all four iodination reagents resulted in the formation of two diiodinated anilines. Compared to the other three reagents, iodination with Ag_2SO_4/I_2 appeared to yield a larger amount of diiodinated products.

2,5-Dichloroaniline (**1e**) was selected to investigate the potential role of β-cyclodextrin on the yield and selectivity of the iodination reactions (entries 4-2b). Addition of β-cyclodextrin has been shown to improve the regioselectivity of bromination reactions in CCl_4.[35,36] Iodination of **1e** resulted in improved yields of the *para* iodinated aniline **3e** for all reagents, with exception of $AgSbF_6/I_2$ (entries 4-2a versus 4-2b). However, the yield of the diiodoaniline **4e** also increased, thus resulting in less favorable ratios of **3e: 4e** for all reagents. The only exception was the reaction with Ag_2SO_4/I_2/β-cyclodextrin in methanol, where **3e** was the major product with a yield of ~94% (99% conversion). These reaction conditions suggest that the iodination of chlorinated anilines in the presence of β-cyclodextrin may offer an excellent access to iodinated anilines, such as **3e**, especially if the reaction is performed in a protic solvent. These observations are in contrast to the fact that the addition of β-cyclodextrin (see entry 1–8) did not offer an obvious advantage compared to other silver salts/I_2 reagents investigated for the iodination of **1b** (Table 1). This is most likely due to the different reaction conditions employed.

Overall, Ag_2SO_4/I_2 and $AgSbF_6/I_2$ appeared to be the best reagents for the iodination of chlorinated anilines by providing a reasonable regioselectivity; however, the yields are typically moderate. One possible explanation for the relatively moderate yields of the iodination of anilines **1e–g** is the use of DCM as solvent. Significantly better yields have been reported for the iodination of various chloro and nitro anilines with Ag_2SO_4/I_2 in ethanol[31] and 1,2-ethanediol.[50] However, the regioselectivity of reactions using ethanol as solvent are relatively poor.[31] For example, iodination of 3-nitroaniline with Ag_2SO_4/I_2 in ethanol has a reported yield 90% of the corresponding 4- and 6-iodinated anilines in a 3: 1 ratio.[31] In the present study, iodination of **1e–g** typically occurred with much more pronounced regioselectivity, with product ratios frequently > 20: 1 (entries 4-2 to 4–4). This improved regioselectivity of iodination reactions with silver salts/I_2 in non-polar solvents may be advantageous compared to the higher yielding reactions in protic solvents.

2.2.3. Iodination of miscellaneous aromatic compounds with AgX/I_2—In addition to chlorinated phenols, anisoles and anilines **1**, the present study also investigated the iodination of several other aromatic compounds with the four silver salt/I_2 reagents (Tables 5 and 6). Chlorobenzene (**1h**), a deactivated aromatic compound, did not react with Ag_2SO_4/I_2 (Table 5; entry 5-1). $AgSbF_6/I_2$ and $AgPF_6/I_2$ iodinated **1h** preferentially in the *para* position; however the conversion was relatively low for both reagents (entries 5-2 and 5-4). The best iodination results were obtained with $AgBF_4/I_2$, which yielded the *para* iodinated product **3h** in 87% (93% conversion) (entry 5-3). Only traces of a diiodinated chlorobenzene were detected in the case of $AgSbF_6/I_2$ and $AgBF_4/I_2$. The largest relative amount of the diiodinated product was observed with $AgBF_4/I_2$. The iodination of chlorobenzene with other silver salts/I_2, such as AgOTf/I_2, has been reported to yield **3h** only in moderate yield.[33,51] In contrast, several other conventional reagents have given good-to-excellent yields of **3h**;[52–56] however, the respective reaction conditions required the use of concentrated sulfuric acid (e.g., NaI/conc. H_2SO_4 at 60 °C[52]), strong oxidizers (e.g., NaI/oxone in water,[53] $NaI/H_2O_2/CeCl_3{\cdot}7H_2O$[54] or $NaI/Ce(OH)_3O_2H$/SDS[55]) or elemental fluorine[56]. Therefore, $AgBF_4/I_2$ may offer a mild approach to *para* iodinated chlorobenzenes.

Similar to chlorobenzene (**1h**), iodination of 3-chlorotoluene (**1i**) with Ag_2SO_4/I_2 only yielded traces of iodinated products (Table 6, entry 6-1). In contrast, the other three reagents resulted in the formation of good yields of 5-chloro-2-iodotoluene (**4i**), with yields > 90 being observed for $AgSbF_6/I_2$ (entries 6-2 to 6-4). In comparison, the only other reported direct iodination of **1i** with $KI/NaNO_3$ result in a mixture of **3i** and **4i**.[57] Although the present study does not provide a clear rank order for the different silver salt/I_2 reagents, the iodination experiments with **1h** and **1i** demonstrate that, as expected, the iodination reagents with the non-coordinating anions SbF_6^-, BF_4^- and PF_6^- are more reactive compared to Ag_2SO_4/I_2, with $AgBF_4/I_2$ being the most reactive iodination reagent. One possible explanation for this observation is that there are fewer interactions between the reactive iodonium intermediate and the respective anion, which results in a more electrophilic iodinating species.

2.3. Synthesis of hydroxylated polychlorinated biphenyls

Selected hydroxylated metabolites of two PCB congeners were synthesized to demonstrate the usefulness of the iodination reactions described above. In short, the respective iodoanisoles **2c** or **3c** were synthesized by iodination of **1b** with $BTMACl_2I/ZnCl_2/AcOH$ at room temperature (25% yield) followed by methylation with dimethyl sulfate (99% yield) or directly from **1c** with Ag_2SO_4/I_2 (44% yield), respectively, and coupled with the respective benzene boronic acid **5** to yield the desired methoxylated PCB **6** (Scheme 2). Subsequent demethylation with BBr_3 in DCM yielded the desired hydroxylated PCB metabolite **7**. The structure of the two PCB derivatives **6a** and **6b** was verified by crystal structure analysis, thus providing additional evidence for the structure of the respective iodoanisoles **2c** and **3c** (Figure S2).

3. Conclusion

Although the iodination of phenol (**1a**) and aniline (**1d**) typically proceeds with good yield and regioselectivity, conventional iodination reagents do not necessarily allow a convenient and regioselective iodination of chlorinated phenols, anisoles and anilines **1**. The present study demonstrates that iodination reactions with Ag_2SO_4/I_2 and AgX/I_2, where X is a non-cooordinating anion SbF_6^-, BF_4^- or PF_6^-, provides a convenient access to selected iodoarenes. Specifically, the iodination of 3,5-dichlorophenol (**1b**) with Ag_2SO_4/I_2 and all three AgX/I_2 in DCM gave moderate-to-good yields of the *ortho* product **2b**. In contrast, iodination of the corresponding anisole **1c** with Ag_2SO_4/I_2 in acetonitrile yielded the *para* product **3c**. All silver salt/I_2 reagents iodinated the chlorinated anilines **1e–g** preferentially in *para* position, with Ag_2SO_4/I_2/β-cyclodextrin being the best reagent for this reaction. In the case of chlorobenzene (**1h**) and 3-chlorotoluene (**1i**), the three AgX/I_2 reagents, but not Ag_2SO_4/I_2, yielded iodinated products in good yields and regioselectivity. These findings suggest that silver salt-based iodination reagents may offer straightforward access to select iodinated aromatic compounds. In particular, the three AgX/I_2 systems may offer access to iodinated intermediates that are difficult to synthesize with other reagents, including Ag_2SO_4/I_2.

4. Experimental

All chemicals were purchased from commercial suppliers and used without further purification. Column chromatography was carried out on silica gel (100–200 mesh) from Sorbent Technologies (Atlanta, GA, USA). Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. NMR spectra were measured at room temperature on a Bruker Avance-300 or a Bruker Avance DRX-400 spectrometer in the University of Iowa Central NMR Research Facility (Iowa City, IA, USA) using $CDCl_3$ as solvent. Chemical shifts are reported in parts per million relative to $CDCl_3$ (^1H, δ 7.24; ^{13}C, δ 77.00). GC-MS analysis of all compounds was performed in the electron impact (EI) mode on an Agilent 6890N Gas Chromatograph coupled with an Agilent 5975 Mass Selective Detector (Agilent Technologies, CA, USA) using a HP-1 (Methyl Silicone Gum) column (Hewlett Packard, PA, USA). The following conditions were used for the GC-MS analysis: injector: 250 °C, starting temperature: 50 °C, final temperature: 250 °C, heating rate: 20 °C/min, hold 5 min. For all compounds investigated, the retention time followed the order *ortho* < *para* iodinated product. Only the isotopic ion with the lowest mass is reported for all fragments observed in the MS spectra. HRMS were recorded by the High Resolution Mass Spectrometry Facility of the University of California Riverside (Riverside, CA, USA).

4.1. General procedure for the iodination of chlorinated benzene derivatives *1a–i*

The respective silver salt (0.32 g, 1 mmol) and iodine (0.25 g, 1 mmol) were typically added to a stirred solution of the benzene derivative **1a–i** (1 mmol) in dichloromethane (3 mL). The reaction mixture was allowed to stir at room temperature for approximately 16 h (see Tables 1–6). The reaction mixture was cooled with ice-cold water, quenched with an aqueous solution of sodium metabisulfite (0.2 mL) and, in the case of anilines, 2 M NaOH (0.2 mL). The mixture was filtered through Celite® and the residue was washed with dichloromethane (3 × 3 mL). The combined filtrate was washed with aq. sodium bicarbonate (3 mL), water (3 mL) and brine (3 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was redissolved in dichloromethane (10 mL) and the percent conversion of the starting material and the yields of the iodination products were determined by GC-MS using diethylene glycol di-*n*-butyl ether as internal standard. The relative response factor for the respective analyte (RRF_A) was calculated from a calibration standard containing known amounts of the internal standard and the respective analytes using the formula $RRF_A = A_{IS} \cdot M_A/(A_A \cdot M_{IS})$, where A_{IS} is the peak area of the internal standard, A_A is the area of an analyte (i.e., starting material or iodination product), M_A is the mass of the analyte and M_{IS} is the mass of the internal standard. The mass of the analyte in the reaction mixture was determined as $M_A = (RRF_A \cdot M_{IS} \cdot A_A)/A_{IS}$. All samples were analyzed at least in duplicate. The iodination products of selected reactions were separated by column chromatography to obtain milligram quantities for their characterization and use as analytical standards. In the case of **3g**, the isolated quantities were not sufficient for ^{13}C NMR analysis.

4.1.1. 3,5-Dichloro-2-iodophenol 2b[19]—White solid; Mp: 81–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 7.07 (m, 1 H), 6.90 (m, 1 H), 5.69 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 156.9, 139.0, 135.9, 121.6, 113.4, 89.0; mass spectrum *m/z* (relative abundance %): 288 ($M^{\cdot+}$, 60), 252 (10), 133 (10), 97 (10), 62 (10); HRMS *m/z* : calculated for $C_6H_2OCl_2I$ [M-H] 286.8533; Found 286.8533.

4.1.2. 3,5-Dichloro-4-iodophenol 3b—White solid; Mp: 134–135 °C (hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 6.92 (s, 2 H), 5.17 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm 156.1, 140.8, 115.2, 92.6; mass spectrum *m/z* (relative abundance%): 288 ($M^{\cdot+}$, 80), 133 (10), 97 (10); HRMS *m/z*: calculated for $C_6H_2OCl_2I$ [M-H] 286.8533; Found 286.8532.

4.1.3. 3,5-Dichloro-2-iodoanisole 2c—White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 7.12 (d, *J* = 2.1 Hz, 1 H), 6.67 (d, *J* = 2.1 Hz, 1 H), 3.88 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm 160.2, 140.3, 135.5, 121.6, 109.4, 89.1, 57.0; mass spectrum *m/z* (relative abundance %): 302 ($M^{\cdot+}$, 60), 287 (10), 259 (10), 160 (20), 97 (10); HRMS *m/z*: calculated for $C_7H_5OCl_2I$ [M] 301.8757; Found 301.8760.

4.1.4. 3,5-Dichloro-4-iodoanisole 3c[3,58]—White solid; Mp: 49–50 °C (Lit.: 62 °C[58]); ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 6.94 (s, 2 H), 3.78 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm 160.2, 140.7, 113.8, 92.1, 55.8; mass spectrum *m/z* (relative abundance %): 302 ($M^{\cdot+}$, 60), 287 (10), 259 (10), 160 (10), 97 (10); HRMS *m/z*: calculated for $C_7H_5OCl_2I$ [M] 301.8757; Found 301.8763.

4.1.5. 3,5-Dichloro-2,4-diiodoanisole 4c—White solid; Mp: 143–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 6.85 (s, 1 H), 3.89 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 160.0, 144.5, 140.8, 109.3, 91.6, 88.5, 57.2; mass spectrum *m/z* (relative abundance %): 428 ($M^{\cdot+}$, 70), 413 (15), 286 (15); HRMS *m/z*: calculated for $C_7H_4OCl_2I_2$ [M] 427.7723; Found 427.7718.

4.1.6. 3,6-Dichloro-2-iodoaniline 2e[23]—Brown solid; Mp: 98 °C (Lit.: 68 °C[23]); ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 7.16 (d, *J* = 8.4 Hz, 1 H), 6.80 (d, *J* = 8.4 Hz, 1 H), 4.77 (*br* s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 145.2, 137.7, 129.4, 118.3, 115.3, 87.9; mass spectrum *m/z* (relative abundance %): 287 ($M^{\cdot+}$, 60), 160 (20), 1245 (20); HRMS *m/z*: calculated for $C_6H_4NCl_2I$ [M] 286.8766; Found 286.8770.

4.1.7. 2,5-Dichloro-4-iodoaniline 3e[23]—Brown solid; Mp: 53 °C (Lit.: 57 °C[23]); ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 7.59 (s, 1 H), 6.82 (s, 1 H), 4.11 (*br* s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 143.7, 138.9, 137.1, 118.1, 115.3, 81.6; mass spectrum *m/z* (relative abundance %): 287 ($M^{\cdot+}$, 50), 160 (20), 135 (10), 124 (10), 97 (10); HRMS *m/z*: calculated for $C_6H_5NCl_2I$ [M+H] 287.8838; Found 287.8826.

4.1.8. 3,6-Dichloro-2,4-diiodoaniline 4e[25]—Brown solid; Mp: 110 °C (Lit.: 111–112 °C[25]); ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 7.71 (s, 1 H), 4.82 (*br* s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 145.4, 140.7, 138.6, 115.8, 86.0, 79.0; mass spectrum *m/z* (relative abundance %): 413 ($M^{\cdot+}$, 70), 286 (20), 159 (10); HRMS *m/z*: calculated for $C_6H_4NCl_2I_2$ [M+H] 413.7805; Found 413.7787.

4.1.9. 3,4-Dichloro-2-iodoaniline 2f[26]—Brown solid; Mp: 40 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 7.20 (d, J = 8.8 Hz, 1 H), 6.58 (d, J = 8.8 Hz, 1 H), 4.31 (*br* s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 147.7, 136.7, 130.1, 120.4, 112.9, 88.8; mass spectrum *m/z* (relative abundance %): 287 ($M^{\cdot+}$, 70), 160 (15), 124 (15); HRMS *m/z*: calculated for $C_6H_5NCl_2I$ [M+H] 287.8838; Found 287.8836.

4.1.10. 4,5-Dichloro-2-iodoaniline 3f[20,21]—Brown solid; Mp: 67 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 7.64 (s, 1 H), 6.78 (s, 1 H), 4.12 (*br* s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 146.4, 139.0, 133.1, 121.5, 115.0, 81.0; mass spectrum *m/z* (relative abundance %): 287 ($M^{\cdot+}$, 60), 160 (20), 133 (20); HRMS *m/z*: calculated for $C_6H_5NCl_2I$ [M +H] 287.8838; Found 287.8830.

4.1.11. 3,4-Dichloro-2,6-diiodoaniline 4f[25]—Brown solid; Mp: 116 °C (Lit.: 120–121 °C[25]); ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 7.73 (s, 1 H), 4.85 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 147.1, 138.7, 137.3, 120.3, 86.2, 77.7; mass spectrum *m/z* (relative abundance %): 413 ($M^{\cdot+}$, 70), 286 (15), 159 (15); HRMS *m/z*: calculated for $C_6H_4NCl_2I_2$ ([M+H] 413.7805; Found 413.7785.

4.1.12. 3,5-Dichloro-2-iodoaniline 2g[24]—Brown solid; Mp: 46 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 6.84 (d, J = 2.4 Hz, 1 H), 6.57 (d, J = 2.4 Hz, 1 H), 4.39 (*br* s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 149.5, 139.8, 135.2, 118.5, 117.7, 85.8; mass spectrum *m/z* (relative abundance %): 287 ($M^{\cdot+}$, 70), 160 (15), 124 (15); HRMS *m/z*: calculated for $C_6H_5NCl_2I$ [M+H] 287.8838; Found 287.8833.

4.1.13. 3,5-Dichloro-4-iodoaniline 3g[22]—Brown solid; Mp: 143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 6.68 (s, 2 H), 3.76 (*br* s, 2 H); mass spectrum *m/z* (relative abundance %): 287 ($M^{\cdot+}$, 60), 160 (20), 133 (20); HRMS *m/z*: calculated for $C_6H_5NCl_2I$ [M+H] 287.8838; Found 287.8824.

4.1.14. 3,5-Dichloro-2,6-diiodoaniline and 3,5-dichloro-2,4-diiodoaniline 4g—Brown solid; Mp: 110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 6.78 (s, 1 H), 4.44 (*br* s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 149.1, 143.8, 140.3, 118.5, 111.74, 111.66, 86.2, 84.8; mass spectrum *m/z* (relative abundance %): 413 ($M^{\cdot+}$, 70), 286 (15), 159 (15); HRMS *m/z*: calculated for $C_6H_4NCl_2I_2$ [M+H] 413.7805; Found 413.7774.

4.2. Synthesis of PCB derivatives

4.2.1. Synthesis of 4,4′,6-trichloro-2-methoxybiphenyl 6a—A mixture of **2c** (0.45 g, 1.5 mmol), 4-chlorophenylboronic acid (**5a**) (0.47 g, 3.0 mmol), bis(dibenzylideneacetone) palladium (20 mg, 22.5 μmol), 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (DPDB) (40 mg, 0.1 mmol) and powdered K_3PO_4 (0.95 mg) in toluene (3.5 mL) were heated at 100 °C in a sealed tube under a nitrogen atmosphere as described previously.[4] The tube was allowed to cool to room temperature and the reaction mixture was passed through a Celite® bed. The residue was washed with dichloromethane (2 × 25 mL) and the combined filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with n-hexane as eluent and the pure compound was crystallized from methanol-dichloromethane to yield 4,4′,6-trichloro-2-methoxybiphenyl

(**6a**) as a colorless solid in 18% yield. Mp: 58–59 °C (chloroform-methanol); ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 7.41 (AAXX′ system, 2 H), 7.20 (AA′XX′ system, 2 H), 7.13 (d, J = 1.8 Hz, 1 H), 6.87 (d, J = 1.8 Hz, 1 H), 3.73 (s, 3 H, $-OCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 158.1, 134.7, 134.3, 133.7, 132.8, 131.7, 128.3, 127.3, 121.6, 110.2, 56.2; Anal. Calcd for $C_{13}H_9Cl_3O$: C, 54.30; H, 3.15; Found: C, 54.39; H, 3.13; mass spectrum m/z (relative abundance %): 286 ($M^{\cdot+}$, 100), 249 (6), 236 (82), 216 (20), 173 (40).

4.2.2. 2,2′,5′,6-Tetrachloro-4-methoxybiphenyl 6b—Synthesized as described above by the Suzuki coupling of **3c** (0.50 g, 1.66 mmol) and 2,5-dichlorophenylboronic acid (**5b**) (0.48 g, 2.5 mmol) to afford **6b** as a colorless solid in 77% yield. Mp: 87 °C (chloroform-methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 7.41 (d, J = 8.8 Hz, 1 H), 7.32 (dd, J = 2.4 & 8.8 Hz, 1 H), 7.21 (d, J = 2.4 Hz, 1 H), 6.97 (s, 2 H), 3.84 (s, 3 H, $-OCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 159.9, 137.3, 135.2, 132.7, 132.4, 131.5, 130.5, 129.7, 128.2, 113.9, 55.8; Anal. Calcd for $C_{13}H_8Cl_4O$: C, 48.49; H, 2.48; Found: C, 48.73; H, 2.37; HRMS m/z: calculated for $C_{13}H_8OCl_4$ ($M^{\cdot+}$) 319.9324, found 319.9325.

4.2.3. 4,4′,6-Trichlorobiphenyl-2-ol 7a—BBr_3 (1.2 mL, 1.2 mmol, 1M solution in heptane) was added to a stirred solution of **6a** (70 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (5 mL) under a nitrogen atmosphere.[3] The reaction was stirred at room temperature for 5 days, quenched by pouring onto crushed ice and extracted with dichloromethane (5 mL). The organic layer was washed with 2 M NaOH solution (5 mL), the aqueous layer was acidified with 2 N HCl (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic layer was washed with water (25 mL), brine (25 mL), dried over (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using a hexane-chloroform gradient (100% to 90% hexane) to yield 4,4′,6-trichlorobiphenyl-2-ol (**7a**) as a colorless oil in 29% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 7.50 (AA′XX′ system, 2 H), 7.26 (AA′XX′ system, 2 H), 7.08 (d, J = 2.0 Hz, 1 H), 6.93 (d, J = 2.0 Hz, 1 H), 4.95 (s, 1 H, −OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 154.2, 135.4, 134.7, 134.3, 131.9, 130.8, 129.8, 124.9, 121.9, 114.8; mass spectrum m/z (relative abundance %): 272 ($M^{\cdot+}$, 47), 236 (18), 237 (38), 202 (100), 173 (42), 139 (46), 118 (27), 86 (82); HRMS m/z: calculated for $C_{12}H_6OCl_3$ [M-H] 270.9484, found 270.9481.

4.2.4. 2,2′,5′,6-Tetrachlorobiphenyl-4-ol 7b—Prepared from 2,2′,5′,6-tetrachloro-4-methoxybiphenyl (**6b**) (0.31 g, 1 mmol) as described above to afford **7b** as a colorless solid in 87% yield. Mp: 101 °C (chloroform-methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm 7.42 (d, J = 8.4 Hz, 1 H), 7.33 (dd, J = 2.4 & 8.4 Hz, 1 H), 7.21 (d, J = 2.4 Hz, 1 H), 6.94 (s, 2 H), 5.57 (s, 1 H, -OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm 156.0, 137.1, 135.3, 132.7, 132.4, 131.4, 130.5, 129.7, 128.5, 115.4; mass spectrum m/z (relative abundance %): 306 ($M^{\cdot+}$, 75), 270 (5), 235 (5); HRMS m/z: calculated for $C_{12}H_6OCl_4$ [M] 305.9167, found 305.9177.

4.3. X-ray crystal structure analysis

X-ray diffraction data were collected at 90.0(2) K on either a Nonius KappaCCD or a Bruker-Nonius X8 Proteum diffractometer with graded-multilayer focusing optics as described previously.[59] Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 827884 to 827887. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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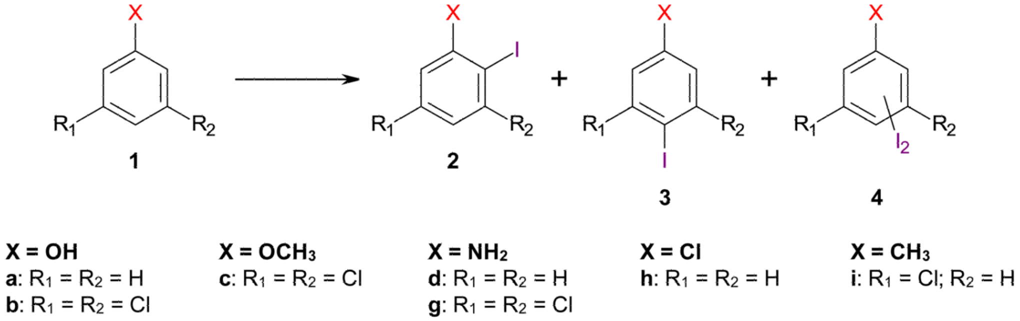
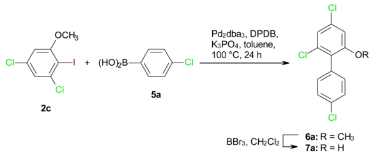
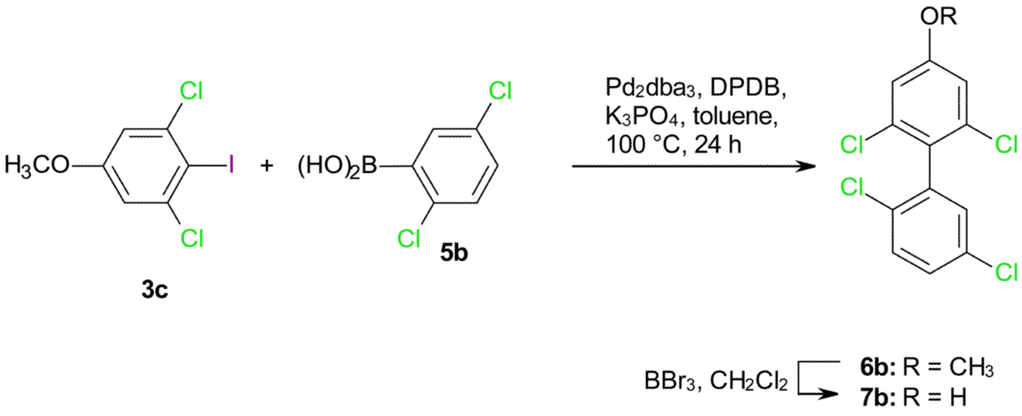


Scheme 1.

Regioselective iodination of chlorinated phenols, anisoles, anilines, chlorobenzenes and chlorotoluenes using different silver salts as iodination reagents.



Scheme 2.
Synthesis of hydroxylated polychlorinated biphenyl **7a** using the *ortho* iodinated 3,5-dichloroanisole **2c**.

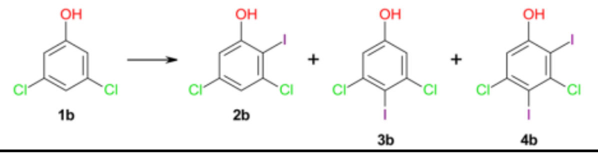


Scheme 3.

Synthesis of hydroxylated polychlorinated biphenyl **7a** using the *para* iodinated 3,5-dichloroanisole **3c**.

Table 1

Effect of iodinating reagents, solvents and temperature on the iodination of 3,5-dichlorophenol (**1b**).[*]



Entry	Reaction Conditions[a]	Reaction time (h)	Conversion (%)	Yield 2b (%)	Yield 3b (%)	Yield 4b (%)
1–1	I_2 (1.5 eq.), C_2H_5OH	16	100	16	1	T
1–2	*N*-Iodosuccinimide, PTSA, CH_3CN	24	< 100	18	57	T
1–3	$BTMACl_2I$, $ZnCl_2$, AcOH, RT[b]	24	< 100	5	4	nd
1–4	$BTMACl_2I$, $ZnCl_2$, AcOH, 90 °C[c]	2	< 100	46	39	T
1–5	CAN, I_2, CH_3CN	24	> 0	2	2	nd
1–6	Ag_2SO_4, I_2, CH_3CN[d]	16	> 0	11	3	T
1–7	Ag_2SO_4, I_2, DCM-MeOH-H_2O (1:1:1, *v*/*v*)[d]	2	100	9	2	T
1–8	Ag_2SO_4, I_2, β-cyclodextrin[e]	1	100	8	nd	nd
1–9	Ag_2SO_4, I_2, n-hexane[d]	16	< 100	49	41	T
1–10	$Ag(OCOCF_3)_2$, I_2, C_2H_5OH	16	< 100	28	4	T

[*] Percent conversion and yields were determined by GC-MS;

[a] one equivalent (eq.) of each key reagent was employed if not mentioned otherwise;

[b] $BTMACl_2I$ (1.5 eq.) and $ZnCl_2$ (1.5 eq.);

[c] $BTMACl_2I$ (1.1 eq.) and $ZnCl_2$ (1.5 eq.);

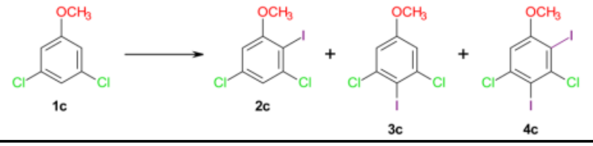
[d] I_2 (1.5 eq.) and Ag_2SO_4 (1.1 eq.);

[e] β-cyclodextrin in DMSO was added to a solution containing **1b** and Ag_2SO_4/I_2 (1 eq.: 1 eq.) in DCM (DMSO: DCM = 1: 1, *v*/*v*);

T = traces were detected by GC-MS; nd = not detected; $BTMACl_2I$ = benzyltrimethylammonium dichloroiodinate; RT = room temperature; PTSA = *p*-toluenesulfonic acid.

Table 2

Effect of solvents and molar ratio of the starting materials on the iodination of 3,5-dichloroanisole (**1c**) with Ag_2SO_4/I_2.*



Entry	Reaction Conditions	Reaction time (h)	Conversion (%)	Yield		
				2c (%)	3c (%)	4c (%)
2-1	NIS, PTSA, CH_3CN[a]	18	100	14	68	3
2–2	Ag_2SO_4, I_2, DCM[b]	60	100	4	7	9
2–3	Ag_2SO_4, I_2, *n*-hexane[b]	16	100	28	48	11
2–4	Ag_2SO_4, I_2, CH_3CN[c]	42	100	4	65	T
2–5	Ag_2SO_4, I_2, CH_3CN[d]	19	90	4	49	T
2–6	Ag_2SO_4, I_2, DMSO[a]	4	94	4	35	nd

[*] Percent conversion and yields were determined by GC-MS;

[a] (1.0 eq.) and Ag_2SO_4 (1.0 eq.);

[b] I_2 (1.5 eq.) and Ag_2SO_4 (1.1 eq.);

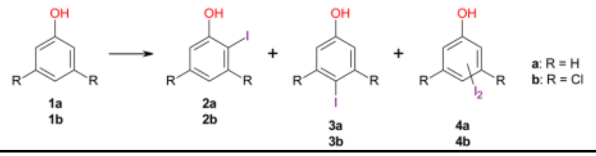
[c] I_2 (1.1 eq.) and Ag_2SO_4 (1.5 eq.);

[d] I_2 (2.0 eq.) and Ag_2SO_4 (2.0 eq.);

T = traces were detected by GC-MS; nd = not detected.

Table 3

Iodination of phenol (**1a**) and 3,5-dichlorophenol (**1b**) using different iodination reagents.[*]



Entry	Reaction Conditions[a]	Reaction time (h)	Conversion (%)	Yield		
				2 (%)	3 (%)	4 (%)
(A) Phenol (*1a*)						
3-1	$AgSbF_6$, I_2, DCM	23	79	2	1	T
3-2	$AgBF_4$, I_2, DCM	1.5	100	7	3	T
3–3	$AgPF_6$, I_2, DCM	23	91	4	46	T
(B) 3,5-Dichlorophenol (*1b*)						
3–4	Ag_2SO_4, I_2, DCM[b]	16	100	53	2	T
3–5	$AgSbF_6$, I_2, DCM	16	<100	82	T	nd
3–6	$AgBF_4$, I_2, DCM[c]	1	<100	>90	5	nd
3–7	$AgPF_6$, I_2, DCM	16	<100	57	10	nd

[*] Percent conversion and yields were determined by GC-MS;

[a] one equivalent (eq.) of each reagent was employed if not mentioned otherwise;

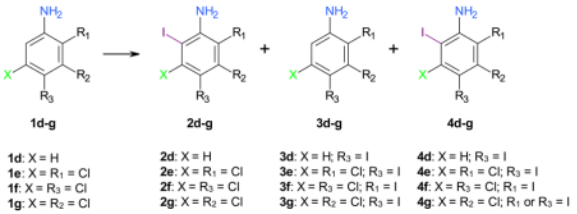
[b] I_2 (1.5 eq.) and Ag_2SO_4 (1.5 eq.);

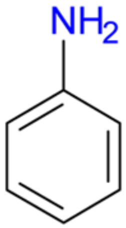
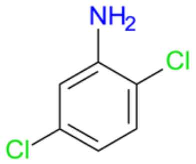
[c] I_2 (1.1 eq.) and Ag_2SO_4 (1.1 eq.);

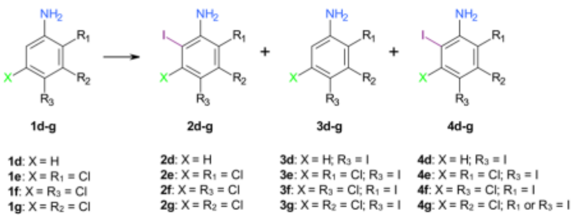
T = traces were detected by GC-MS; nd = not detected.

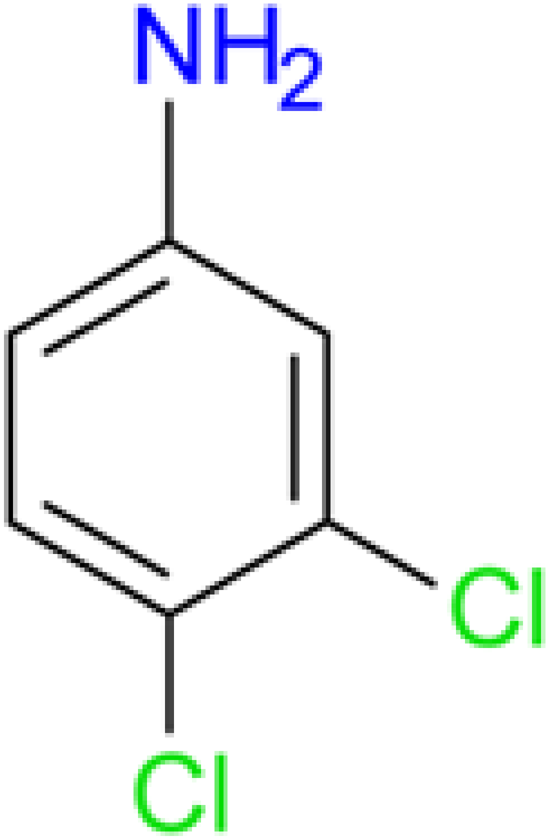
Table 4

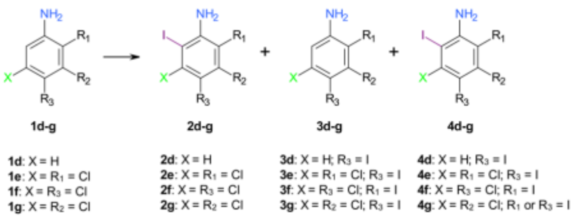
Percent conversion (C) and yields of mono and diiodinated products from selected chlorinated anilines using different iodination reagents (R_1 to R_3 = H if not mentioned otherwise).[*,#]

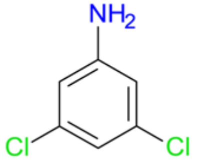


Entry	Starting Material 1		Reaction Time (t) and Reaction Conditions																			
			Ag_2SO_4, I_2, DCM					$AgSbF_6$, I_2, DCM					$AgBF_4$, I_2, DCM					$AgPF_6$, I_2, DCM				
			Time (h)	C	2	3	4	Time (h)	C	2	3	4	Time (h)	C	2	3	4	Time (h)	C	2	3	4
				Yield (%)					Yield (%)					Yield (%)					Yield (%)			
4-1		**d**						15	**57**	–[a]	25	T						15	**69**	–[a]	22	T
4-2a[b]			18	**84**	T	47	2	18	**83**	nd	59	3	18	**49**	T	22	1	18	**79**	T	14	2
4-2b[c]		**e**[d]	17[e]	**99**	3	~94	3	3	**76**	5	48	6	3	**88**	nd	55	7	3	**68**	1	48	9



Entry	Starting Material 1	Reaction Time (t) and Reaction Conditions																			
		Ag_2SO_4, I_2, DCM					$AgSbF_6$, I_2, DCM					$AgBF_4$, I_2, DCM					$AgPF_6$, I_2, DCM				
		Time (h)	C	2	3	4	Time (h)	C	2	3	4	Time (h)	C	2	3	4	Time (h)	C	2	3	4
			Yield (%)					Yield (%)					Yield (%)					Yield (%)			
4-3a[f]	 f[g]	17	**96**	8	77	8	17	**52**	5	6	5						15	**48**	1	T	1
4-3b[b]							15	**58**	2	9	5						15	**53**	3	6	5



Entry	Starting Material 1	Reaction Time (t) and Reaction Conditions																		
		Ag_2SO_4, I_2, DCM					$AgSbF_6$, I_2, DCM					$AgBF_4$, I_2, DCM					$AgPF_6$, I_2, DCM			
		Time (h)	C	2	3	4	Time (h)	C	2	3	4	Time (h)	C	2	3	4	Time (h)	C	2	3	4
			Yield (%)					Yield (%)					Yield (%)					Yield (%)			
4–4	 **g**	18	**87**	22	66	T	18	**65**	T	36	T	19	**56**	1	24	T	18	**59**	T	19	T

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[*] Percent conversion and yields were determined by GC-MS;

[a] no traces of 2- and 3-iodoaniline were detected by GC-MS;

[#] the reaction scheme for the iodination of aniline (**1d**) is shown in Scheme 1;

[b] the silver salt and I_2 were stirred for 30 minutes before addition of the respective starting material;

[c] the silver salt and β-cyclodextrin were stirred in the respective solvent for 30 minutes, followed by addition of I_2; the starting material was added after stirring for another 15 minutes;

[d] **2e** = 3,6-dichloro-2-iodoaniline; **3e** = 2,5-dichloro-4-iodoaniline; **4e** = 3,6-dichloro-2,4-diiodoaniline;

[e] methanol was used as reaction solvent;

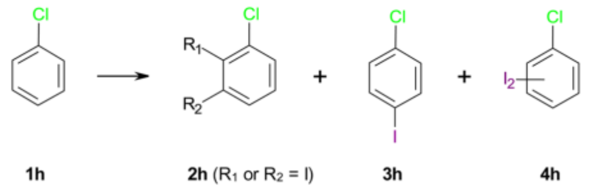
[f] the silver salt and the respective starting material were stirred for 30 minutes before addition of I_2;

[g] **2f** = 3,4-dichloro-2-iodoaniline; **3f** = 4,5-dichloro-2-iodoaniline; **4f** = 3,4-dichloro-2,6-diiodoaniline;

T = traces were detected by GC-MS; nd = not detected; ND = not determined, but considerable quantities were detected according to GC-MS.

Table 5

Iodination of chlorobenzene (**1h**) using different iodination reagents.[*]



Entry	Reaction Conditions[a]	Reaction time (h)	Conversion (%)	Yield		
				2h (%)	3h (%)	4h (%)
5-1	Ag_2SO_4, I_2, DCM	18	**0**	-	-	-
5-2	$AgSbF_6$, I_2, DCM	17	**73**	8[b]	59	T
5-3	$AgBF_4$, I_2, DCM	18	**93**	1[b]	87	T
5-4	$AgPF_6$, I_2, DCM	12	**56**	6[b]	47	-

[*] Percent conversion and yields were determined by GC-MS;

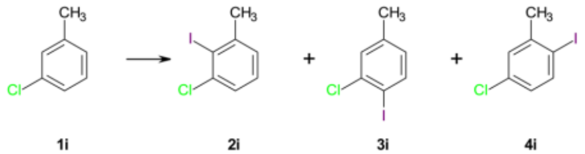
[a] one equivalent (eq.) of each reagent was employed;

[b] unidentified monoiodinated chlorobenzene; the yield was estimated using the relative response factor of the corresponding 4-chloro-iodobenzene;

T = traces were detected by GC-MS.

Table 6

Iodination of 3-chlorotoluene (**1i**) using different iodination reagents.[*]



Entry	Reaction Conditions^a	Reaction time (h)	Conversion (%)	Yield		
				2i (%)	3i (%)	4i (%)
6-1	Ag_2SO_4, I_2, DCM	16	**10**	-	2	8
6-2	$AgSbF_6$, I_2, DCM	16	**100**	3	7	>90
6-3	$AgBF_4$, I_2, DCM	16	**100**	3	8	70
6-4	$AgPF_6$, I_2, DCM	16	**100**	3	15	80

[*] Percent conversion and yields were determined by GC-MS;

[a] one equivalent (eq.) of each reagent was employed.