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Review

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Iodine(III)-mediated oxidative halogenation and catalytic nitration using simple aluminum salts. The full account

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In memory of Kevin, wherever you are in your last destination

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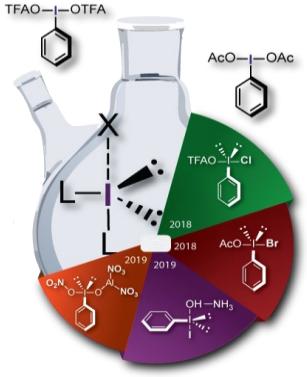
Abstract

Aromatic functionalization mediated or catalyzed by iodine(III) reagents represents an important approach in contemporary organic synthesis. This review provides a systematic analysis of methodologies for the introduction of chlorine, bromine, iodine, and nitro groups into aromatic compounds using aluminum or ammonium salts as halogen sources in combination with hypervalent iodine(III) reagents. The role of these salts in the presence of iodine(III) species is discussed, highlighting their contribution to efficient and selective aromatic functionalization. Reported mechanistic studies, including theoretical DFT calculations, are reviewed, offering insight into plausible reaction pathways for iodine(III)-mediated chlorination and bromination processes. In addition, recent advances in the catalytic introduction of nitro groups under mild, non-acidic conditions are summarized. Overall, this review emphasizes the utility of hypervalent iodine(III) compounds as practical and more sustainable alternatives to conventional aromatic functionalization methods.



Keywords: Iodine(III) Reagents, Aluminum Salts, Aromatic Halogenation, Catalytic Nitration.

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1. Introduction

Over the science history, organic chemistry has played a key role in the discovery of novel drugs that contribute to the quality life´s improvement, mainly for attending public health diseases such as drug resistance, [1-4] cancer,[5-9] diabetes,[10-11] Parkinson, pain, inflammation [12-14] or mycoses [15-16] among some of the most representatives; through the development of new synthetic methodologies. These new procedures, involve the use of metal-catalyzed [17-22] as well as metal-free [23-32] strategies. Concerning metal-free protocols, the use of iodine(III) reagents have been used among others, for introducing halogens in aromatic systems.[33-38] These oxidative functionalization commonly required the use of a halide salt, usually having Na^+, K^+ or NH_4^+ as cations, that after their interaction with iodine(III) reagents generates a halide synthon for an electrophilic aromatic substitution SEAr. Herein, we review the full account developed in our laboratories which involve a new strategy that uses aluminum salts and led to the chlorination, bromination and catalytic nitration of phenols, anilines and different heterocycles, under open flask, green, efficient and mild reaction conditions.

2. Scope of the review

This account is focused to briefly describe the discovery and development of the unique and efficient synergic combination of different iodine(III) reagents and aluminum salts, which transfer the halogen or anion present as a cationic synthons, to different aromatic rings, giving as result, the corresponding electrophilic substitution. This concept was applied to the stoichiometric chlorination, bromination and to the catalytic nitration of phenols and anilines mainly. Fo the case of the iodination reaction, ammonium iodide was used instead of the aluminum one.

3. Oxidative Chlorination: The PIFA-$AlCl_3$ system

Chlorinated compounds, commonly found in various chemical fields, are prevalent in natural products,[39-43] agrochemicals,[44] synthetic intermediates,[45] and materials science.[46] Particularly, chlorophenols are a highly relevant group due to their industrial and pharmacological use (Figure 1).

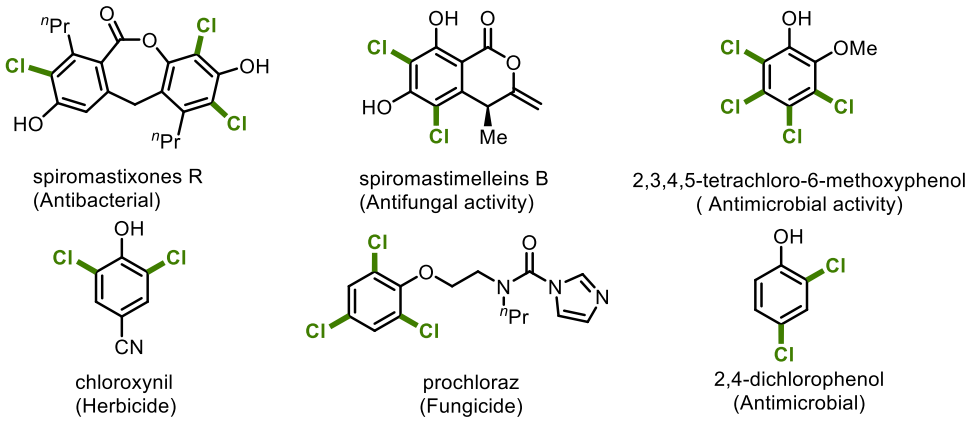
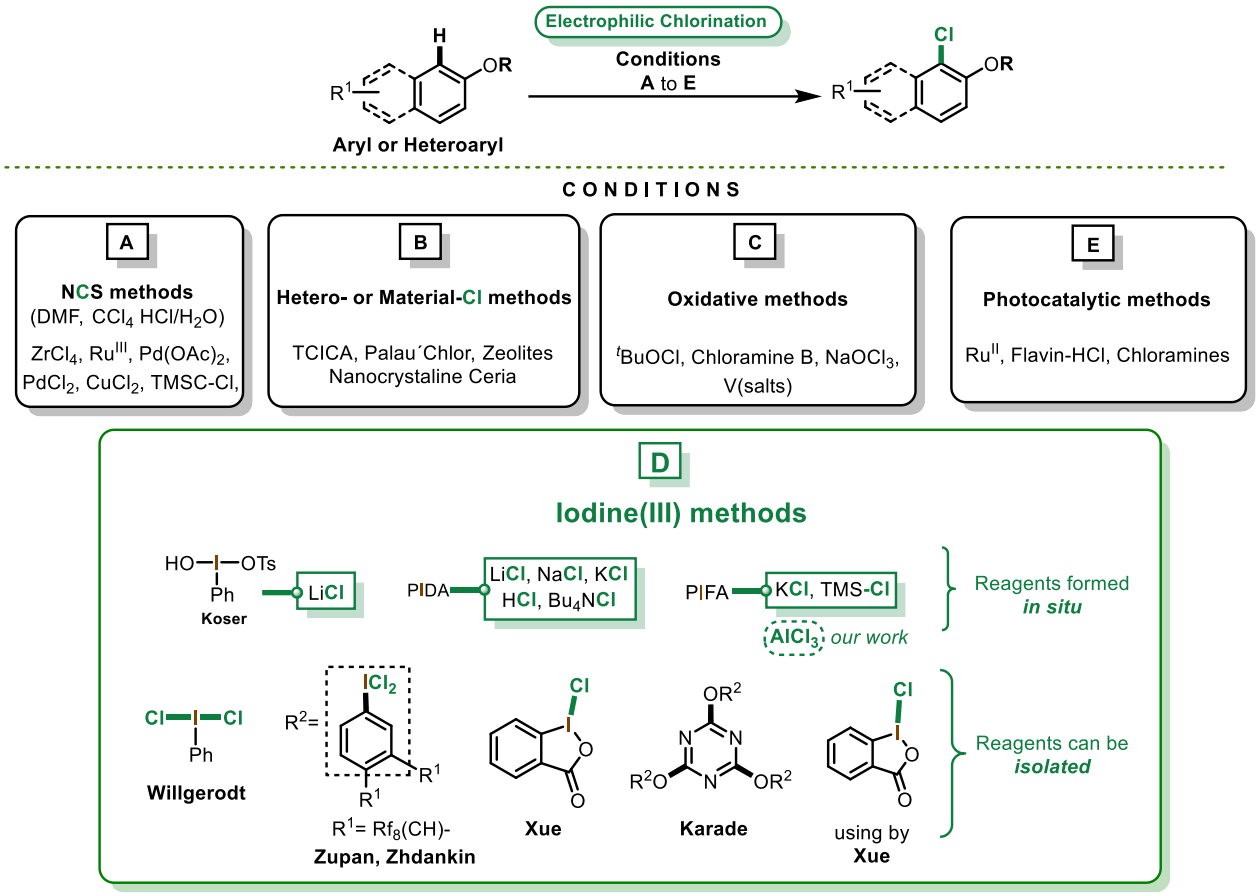


Figure 1. Relevance of the chlorophenolic core.

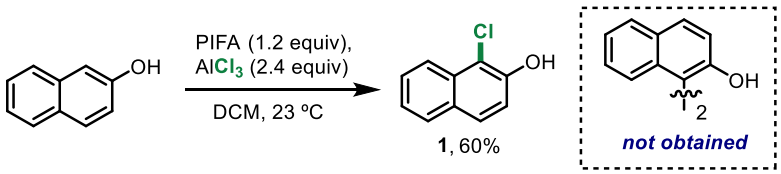
Regarding protocols for introducing the chlorine atom in aromatic systems, plenty of strategies have been described. While chlorine gas is typically used for their synthesis in industry, despite its associated hazards,[47-49] academic research often utilizes alternatives such as *N*-chlorosuccinimide in different solvents (e.g., DMF,[50] CCl_4,[51] HCl/H_2O[52]), usually activated by Lewis bases,[53] Brønsted acids,[54] Lewis acids (both metallic and non-metallic)[55-61] or oxidants.[62-63] To achieve milder reaction conditions, reagents like TCICA, DCDMH, and $TMPH/SO_2Cl_2$,[64-66] as well as heterogeneous catalysts such as zeolites[67-68] and nanocrystalline ceria[69] have been employed. More recently, new methods utilizing Palau'Chlor®[70] and strong oxidants such as ^{t}BuOCl,[71] chloramine B,[72] $NaOCl_3/HCl/AcOH$,[73] or vanadium-based systems[74,75] have been developed. Additionally, photocatalytic approaches using flavin hydrochloride[76] and reactions mediated by chloramines or Ru^{III} complexes[77] have been also investigated. Finally, chlorination with hypervalent iodine(III) reagents have been described by the use of Wilgerodt Reagent ($PhICl_2$).[78] Other protocols combine Koser´s reagent, PIDA or PIFA with chloride salts, usually having Na^+, K^+, or NH_4^+ as ionic pair.[79-82] Also, isolable iodine(III)-based reagents containing the I^{III}-Cl bond was followed by the Zupan and Zhdankin[84-84] work and later developed by Karade[85] and Xue,[86] represents another much less toxic, green and easy to handle alternative (Scheme 1).



Scheme 1. Representative procedures for the aromatic chlorination.

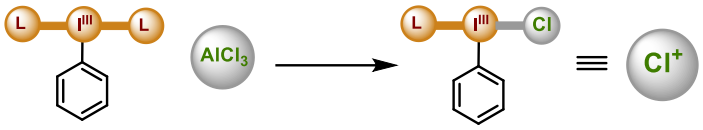
Within this context, we described our development on the oxidative aromatic halogenation using aluminum salts and commercially available iodine(III) reagents, which were serendipitously discovered.

Oxidative aromatic dimerization mediated by iodine(III) reagents has been described under PIFA-BF_3 (1:1) conditions.[87] In 2017, during our studies focused on the nitrogen-based total synthesis of naturally occurring compounds[4-7] including ningalins,[2] we needed to use the aforementioned protocol for the 2-naphthol dimerization. Unfortunately, in such period and due to the low financial support of the Mexican government to the science, we didn´t have $BF_3{\cdot}Et_2O$ in our chemical stock. Then, we decided to use aluminum trichloride instead. The analysis of the obtained product revealed the chlorine atom introduction in the starting material. Thus, we realized that the only source of chlorine atoms was the aluminum salt which was introduced in an umpolung fashion at the C1 of 2-naphthtol to get **1** in 60% yield. This serendipitous discovery started the synergic combination of iodine(III) reagents with aluminum salts[23] (Eq. 1).



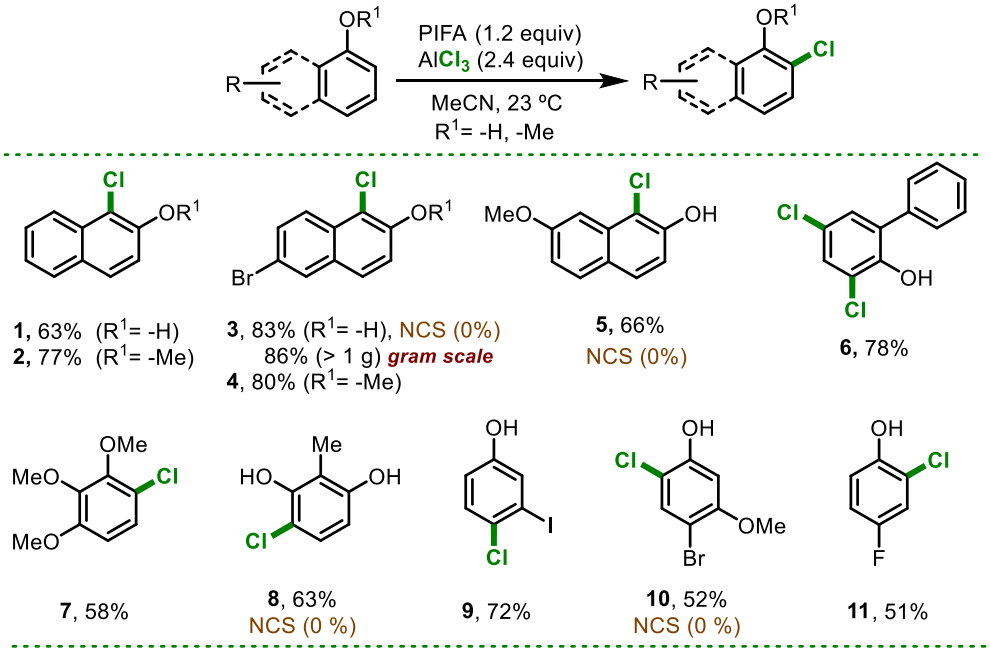
(**1**)

Regarding this new reactivity found, we hypothesized that the oxidation of the chloride coming from the aluminum salt, had place once this make a bond with iodine(III) center of the reagent, making plausibly a "Cl^{+}" synthon that was introduced via a common SEAr (Scheme 2).



Scheme 2. Hypothesis for the aluminum trichloride oxidation by iodine(III) reagents to get chloronium synthons.

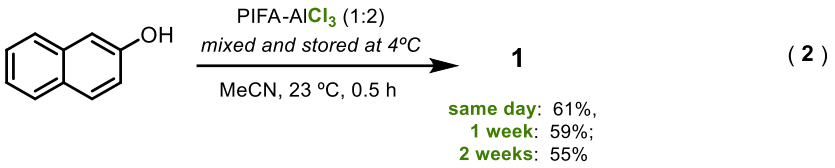
We considered this discovery a good alternative for introducing the chlorine atom in aryls, additionally not any single report about the combination of aluminum trichloride with iodine(III) reagents was described at such time. Then, we started an optimization of the reaction conditions. Initial assays were conducted at room temperature and open flask conditions, testing chlorinated solvents (DCM, DCE and $CHCl_3$) and acetonitrile. Both cases resulted in the full conversion, nevertheless, the use of acetonitrile lead to the better observed yields. Significantly, all the chlorinated solvents accelerated the process but yielding worse results. In this optimization, the iodine(III) reagents PIDA [(diacetoxyiodo)benzene] and PIFA [Bis(trifluoroacetoxy)iodo]benzene] were assayed, resulting PIFA the best oxidant. Other optimized aspect was the stoichiometry, in this case different Iodine(III) reagents and $AlCl_3$ ratios were tested. Herein, if a (1:1) ratio was tested the reaction proceeded slow and with a decreased yields compared against our optimal conditions PIFA-$AlCl_3$ (1.2:2.4). Thus, having the optimal chlorination conditions we proceeded to explore the scope of the reaction (Scheme 3). Importantly, the efficiency of the PIFA–$AlCl_3$ system was directly compared with *N*-chlorosuccinimide (NCS). As shown in Scheme 3, NCS failed to provide any detectable chlorinated products under the same reaction conditions, whereas the PIFA–$AlCl_3$ protocol afforded the desired chloro-naphthol derivatives in moderate to good yields. This comparison underscores the superior reactivity of the PIFA–$AlCl_3$ system for oxidative aromatic chlorination.



Scheme 3. Representative scope of the PIFA-$AlCl_3$ mediate oxidative aromatic chlorination of naphthols.

The reaction applied mainly to the chlorination of phenols and phenol-ethers, was successfully explored by testing different-in-nature derivatives. Accordingly, electron-neutral (**1**, **2**), electron-withdrawing (**3**, **4**, **9**-**11**) or electron-donating (**5**-**8**) aryls were successfully chlorinated in good to excellent yields (51-83%). This process was efficient even at gram scale obtaining excellent overall yields (86%).

Once explored the scope of our reaction, we attempted to isolate the chlorinating species of this developed protocol. For instance, a mixture of PIFA-$AlCl_3$ (1:2) was examined by ^1H NMR at different periods, however we only found iodobenzene as main product. Any identification by HRMS or isolation by column chromatography resulted unsuccessfully. Alternatively, we were able to evaluate the activity of this "*chlorinating mixture"* which was kept at 4 °C along two weeks, using the 2-napthol as model for testing the chlorination reaction. It was found a minor decrease of 6% yield compared to the best yield (Eq. 2).



(**2**)

With this experimentation we completed the initial forays in the combination of iodine(III) reagents and aluminum trichloride. Following the logical chemistry, we decided to explore if other anions present in the aluminum salts could be also oxidized and make halonium equivalents.

4. Oxidative Bromination: The PIDA-$AlBr_3$ system

Following the logic of our aromatic chlorination work using aluminum salts and iodine(III) reagents, we decided to explore the use of aluminum tribromide for carrying out the corresponding bromination under the same concept of reactivity. In this sense is important to highlight the relevance of the aromatic brominated aryls. Aryl bromides play a significant role in organic chemistry.[88] Likewise, they are frequently found in agrochemicals,[89-91] natural and pharmaceutical products as well as in the field of materials science[92-96] (Figure 2).

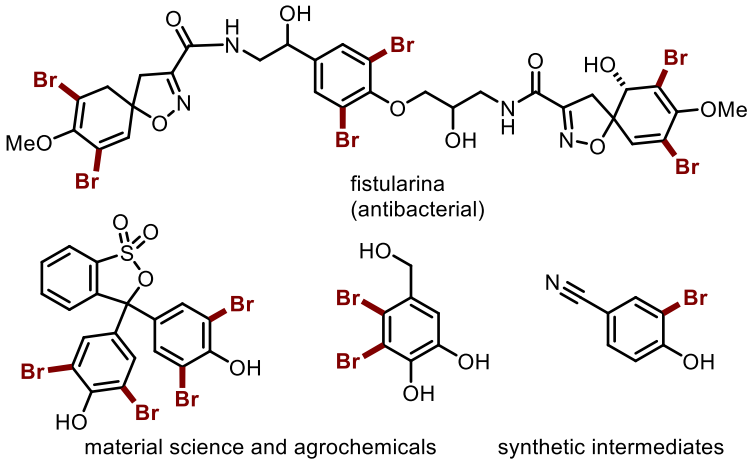
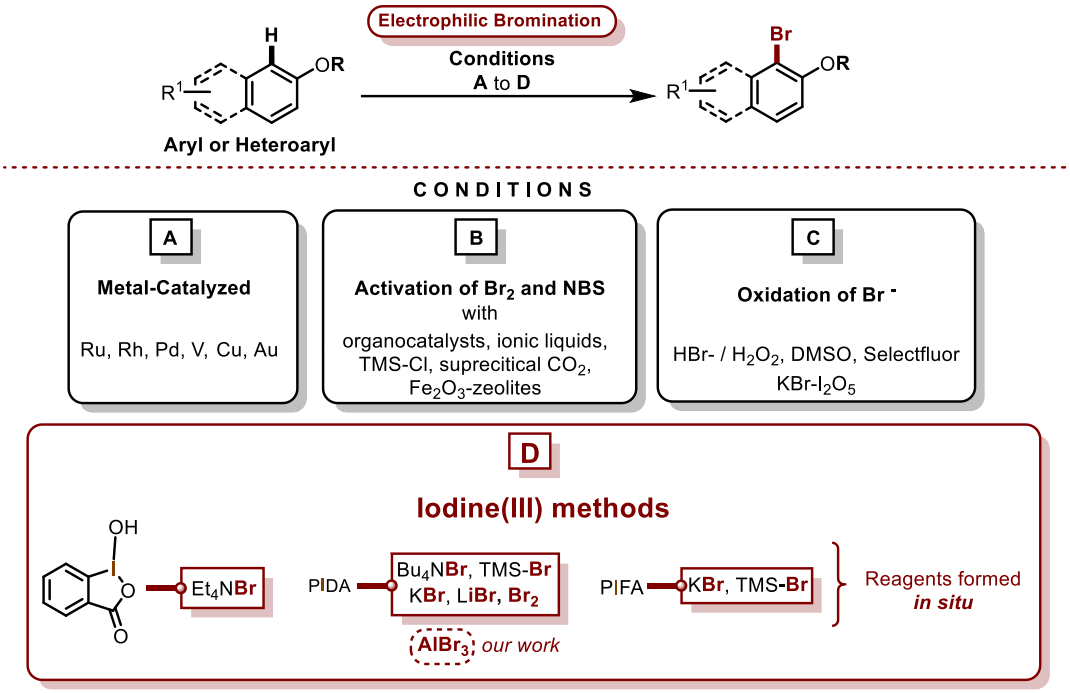


Figure 2. Relevance of the chlorophenolic core.

Furthermore, aryl bromides serve as essential components in C–C bond formation, either through metal-free processes or via well-known metal-catalyzed cross-coupling reactions such as Suzuki,[97] Stille,[98] and Negishi[99] couplings, as well as Mizoroki–Heck[100] olefination and Sonogashira alkynylation.[101]

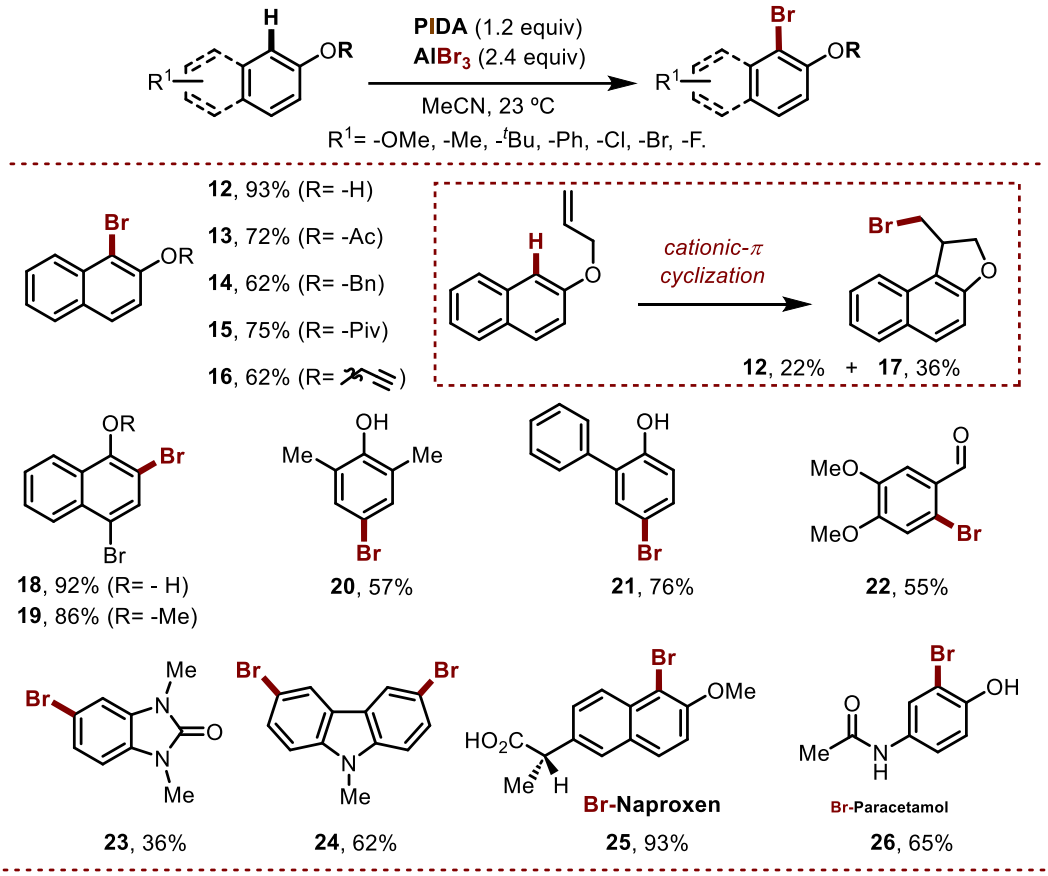
To date, numerous methodologies have been developed for the bromination of aromatic compounds. Among the most common are metal-catalyzed using transition metals such as Ru,[102] Rh,[103, 104] V,[105, 106] Cu,[107, 108] Pd,[109] or Au,[110] all of which have proven highly effective. In addition, bromination techniques involving Br_2 and NBS are often carried out using organocatalysts,[111] ionic liquids,[112, 113] TMSCl,[114] supercritical CO_2,[115] or Fe_2O_3-zeolite,[116] which can act as additives or as the reaction medium.

From the perspective of reagent-based approaches, the oxidation of bromide salts is a widely adopted strategy. Various oxidizing systems have been applied, including HBr-Selectfluor®,[117] HBr-H_2O_2,[1118] HBr-DMSO, [119] and KBr-I_2O_5.[120] On the other hand, particularly efficient, green and low-toxic bromination methods involves the oxidation of bromide salts using iodine(III) reagents. Noteworthy contributions in this area have been made by Evans,[121] Braddock,[122] Zhou,[123] and Cossio[124] (Scheme 4).



Scheme 4. Representative procedures for the aromatic bromination

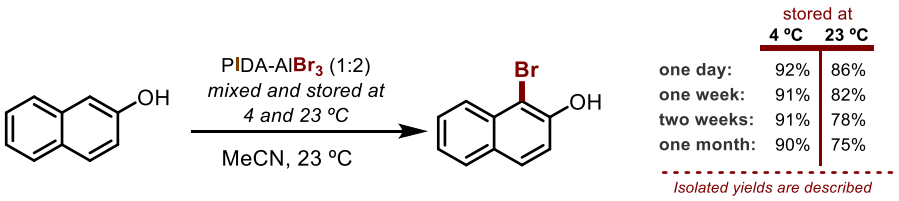
In the context of our synergic combination of I^{III}-$AlBr_3$,[24] the developed protocol reported in 2018 presents an accessible and effective method for electrophilic bromination of phenolic compounds, based on the oxidation of the bromide anion comming from $AlBr_3$ by an iodine(III) reagent. The referenced studies emphasize several advantages of this approach, such as ease of handling, rapid *in situ* formation of the brominating species, and a mild, non-toxic protocol that is straightforward to implement. Accordingly, we started with the identification of the ideal system for applying our concept, then, we combine PIFA-$AlBr_3$ (1.5:2.4) for the bromination of 2-naphthol as model. Thus, we got the corresponding 1-bromo-2-naphthol **12** in an excellent 84% yield. The following search testing PIDA-$AlBr_3$ (1.2:2.4) led to the formation of our desired product in a higher 93% yield. The triplicate of these experimentation confirmed stoichiometry as well as that for the oxidation of the bromide present in the aluminum tribromide, the best oxidant resulted PIDA. Once the new system for the oxidative aromatic bromination was identified, we proceeded to explore the scope of reaction (Scheme 5).



Scheme 5. Representative scope of the PIDA-$AlBr_3$ mediate oxidative aromatic bromintion of naphthols

In our method, we examined a wide range not only within the aromatic ring but also including the substituents attached to the oxygen. As a result, we discovered that groups such as acetyl, benzyl, pivaloyl, and propargyl were compatible, although the chemical yields varied from 93% to 62-75% (**12-16**). Plausibly due to the steric hindrance. Regarding the allyl group, we found an intriguing reactivity. The bromination process for 2-(allyloxy)naphthalene yielded two products: the anticipated brominated compound **12** in 22% yield and the naphthofuran **17**, which was obtained in 36% yield. The former is a product of the cationic-π bromocyclization facilitated by our reagent. This represents a significant characteristic that permits the utilization of our method in polyene bromocyclizations. Furthermore, the presence of methyl, phenyl or formyl groups (**20**-**22**) within the phenolic ring, as well as compounds like benzimidazolones **23**, carbazole **24**, and even therapeutically relevant substances such as naproxen **25** or paracetamol **26**, were effectively brominated with good to excellent yields. Similarly, limitations to this process imply electron neutral aryls such as benzene or toluene.

Conversely, various efforts to separate or characterize the active brominating species did not succeed. Nevertheless, the "*brominating mix: PIDA-$AlBr_3$*" was assessed over a month. In this situation, the mixture remained active only if stored at 4°C after that period (Eq. 3).

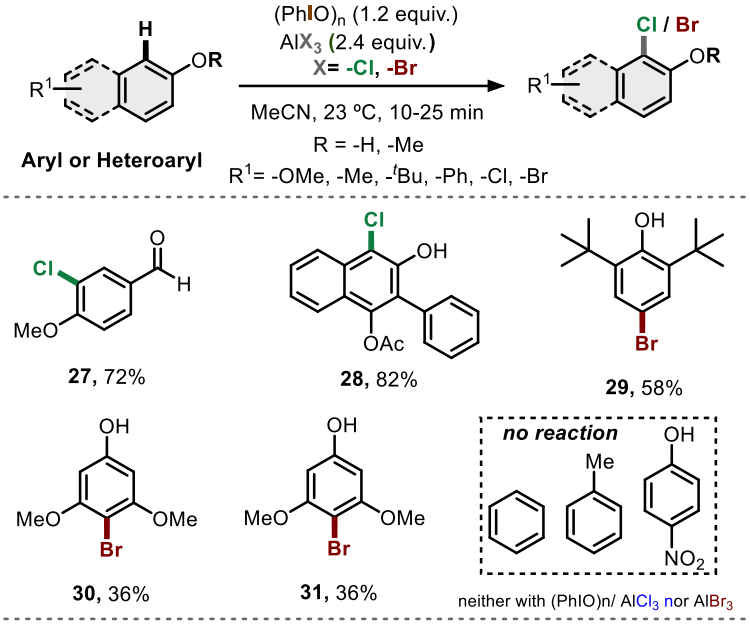


(**3**)

In such a way we completed the oxidative aromatic bromination under the synergic combination of PIDA reagents and aluminum tribromide. Then we started to explore different iodine(III) reagents that could be useful for combining with aluminum salts.

5. Chlorination and Bromination Processes Using The $(PhIO)_n$-AlX_3 (X= Cl, Br) System

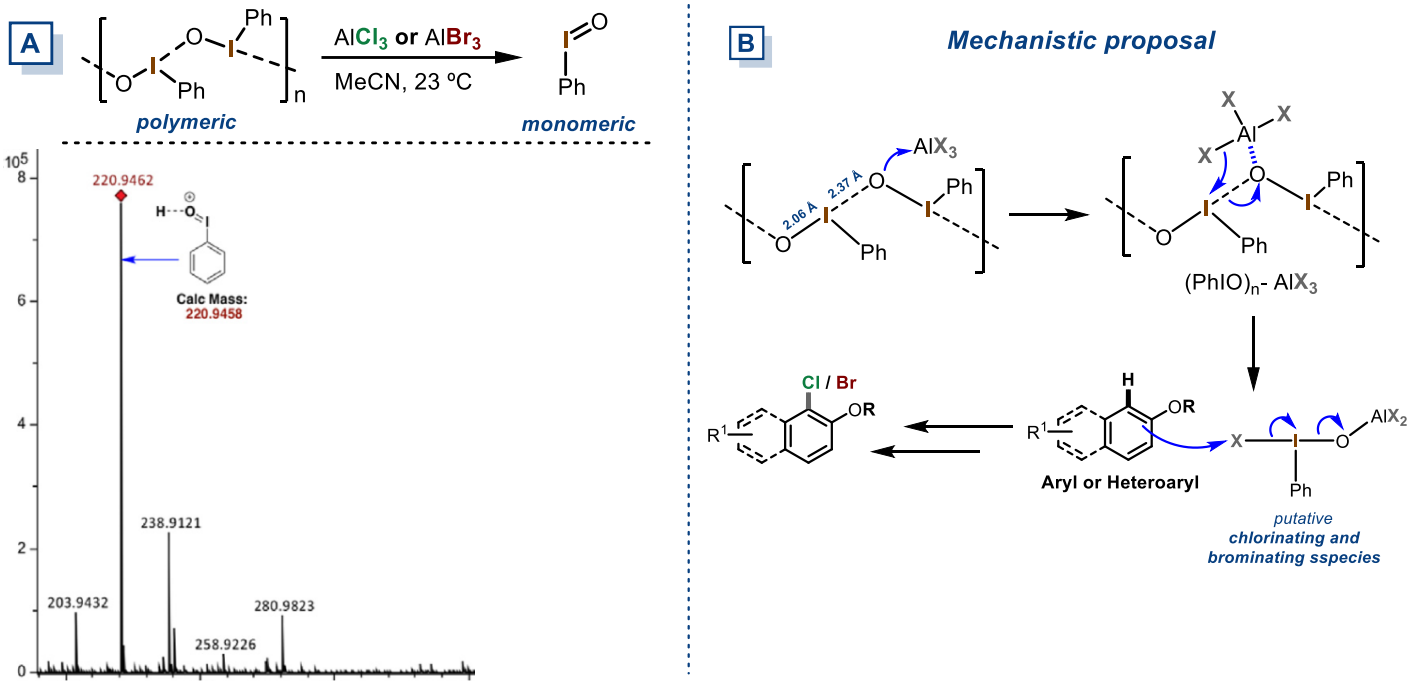
Several Iodine(III) reagents of common use such as PIDA, PIFA, IBX or $(PhIO)_n$ have been broadly described. We turned our attention in the polymeric iodosylbenzene due to its potential use in catalytic reactions, according to preliminary results obtained by our research group in 2018. An important point we considered was the iodosylbenzene nature which has been described as a polymer and whose X-ray structure has been reported.[125] Is known, iodosylbenzene is an insoluble compound that depolymerize by dissolving in methanol[126] or in presence of Brønsed[127] or Lewis acids.[128] Having all of these precedents in mind, we decided to start the reactivity exploration by mixing $(PhIO)_n$-AlX_3 (X= Cl, Br) looking for the chlorination and bromination of naphthols and naphthol-ethers.[27] To our delight, we found the expected reactivity and as consequence, the chlorination and bromination of the 2-naphthol that was used as model. The previously obtained compounds **1** and **12** in 94 and 98% yield respectively were identified as product of this rection. These results are slightly better than those obtained by using PIFA or PIDA. Regarding the stoichiometry used, we easily discover that the same ratio for I^{III}-AlX_3 (1.2:2.4) was still our best choice for the process (Scheme 6).



Scheme 6. Representative scope of the $(PhIO)_n$ / -$AlCl_3$, -$AlBr_3$ mediate oxidative aromatic chlorination and bromination of phenols.

In similar fashion several phenolic derivatives (**1**, **2**, **3**, **4**, **5**, **12**, **24**-**26**) previously described[23, 24] were chlorinated and brominated with particularly excellent yields and remarkably short times. Several other aromatics having the formyl, aryl naphthalene, *tert*-butyl or methoxylated derivatives (**27**-**31**) were successfully functionalized. Once explored the scope we carried out some mechanistic studies. The NMR experiments did not provide any significant information. However, we proposed that the reaction should started by the depolymerization of the iodosylbenzene. As described, this can be possible by interaction with Brønsed[127] or Lewis acids.[128] Accordingly, we hypothesized that the depolymerization process should started by the interaction of $(PhIO)_n$ with the aluminum salt which is a strong Lewis acid. This could generate monomeric subunits of iodosylbenzene that acted as the main iodine(III) species. To demonstrate this postulate, we combine $(PhIO)_n$-AlX_3 (X= Cl, Br) in acetonitrile and proceeded to analyze by HRMS. Gratifyingly, we found the molecular peak corresponding the PhIO indicating without any doubt the depolymerization. Worth mentioning this is the only report with feasible evidence of the iodosylbenzene depolymerization by a Lewis acid interaction, displaying a dual role as

depolymerizing reagent as well as the halogen source (Scheme 7A). Also, based upon this evidence we envisioned a reaction mechanism starting by coordination of polymer with Al**X₃** to yield the corresponding adduct $(PhIO)_n$-Al**X₃**, then the transfer of **X**$^-$ to the iodine(III) center led to the putative halogenating active species which reacted with the aryl or heteroaryl phenol to finally yield the chlorinated or brominated product (Scheme 7B).



Scheme 7. A) Depolymerization of $(PhIO)_n$ by interaction with AlX_3 (X= Cl, Br) for the HRMS molecular peak identification of PhIO monomer. B) Mechanistic proposal for the chlorination and bromination of naphthols using the system $(PhIO)_n$-AlX_3.

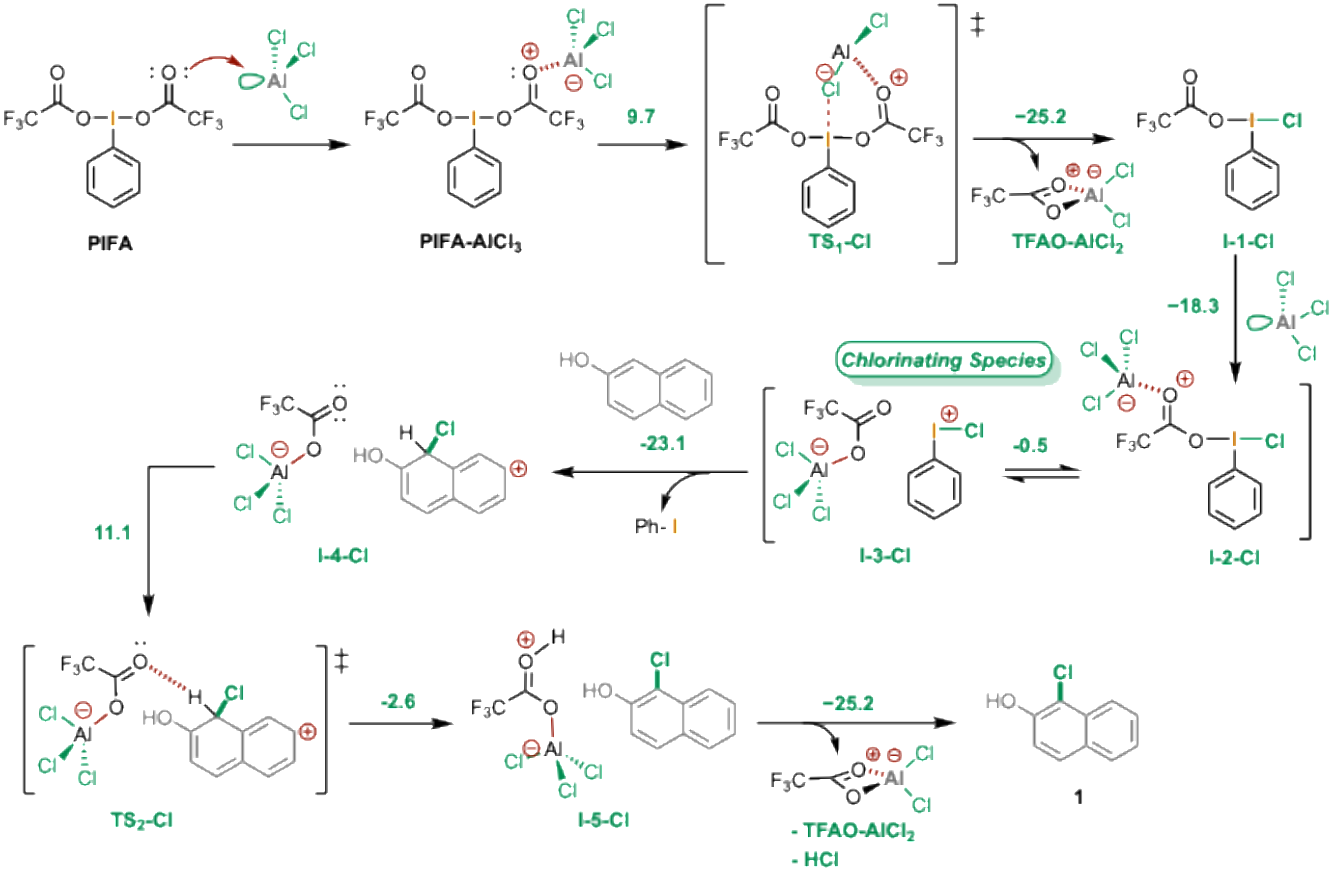
With these preliminary results and due to the impossibility to get by NMR spectroscopy additional information, we conducted DFT calculations to investigate the reaction mechanism for the chlorination and bromination processes using PIFA and PIDA with AlX_3 (X= Cl, Br) salts.

6. DFT Calculations for the Chlorination and Bromination Processes

The chlorination and bromination using the PIFA-$AlCl_3$ as well as the PIDA-$AlBr_3$ systems were theoretically studied.[129] Some important considerations for these calculations are the following. Equilibrium geometry of reagents and products, the stationary points, and transition-state structures were optimized by density functional theory (DFT) calculations employing the software Gaussian 16.[130]

The ω-B97XD functional[131] was selected for this study due it accounts for dispersion interactions using a range-separated approach—applying 22% Hartree–Fock exchange at short range and 100% at long range. This method accurately captures both thermochemical properties and noncovalent interactions. To identify the critical points on the potential energy surface for the different chlorination and bromination pathways explored, bromine and iodine atoms were described using an updated version of the LANL2DZ basis set and effective core potential, known as LANL08(d), which includes d-type polarization functions. All other atoms (such as H, C, O, F, Al, etc.) were modeled with the 6-31G(d) basis set. Geometry optimizations were performed without any imposed symmetry constraints. The resulting stationary points were confirmed through analytical frequency calculations: structures corresponding to energy minima (e.g., reactants, intermediates, products) showed only positive

harmonic frequencies, while transition states exhibited a single imaginary frequency. These frequency calculations also provided zero-point energy, thermal, and entropy corrections, which were added to the electronic energy to yield the Gibbs free energy at 298 K and 1 atm. All computations were initially carried out in the gas phase. Solvent effects were later introduced using the polarizable continuum model (PCM) through the SMD (solvent model density) method, based on Truhlar's model,[132-136] with MeCN (acetonitrile) as the solvent. To enhance the accuracy of single-point energy calculations, a mixed triple-ζ quality basis set was employed: 6-311G(d,p) with polarization for all atoms except Br and I, which continued to be described using the LANL08d relativistic pseudopotential [41–43]. Thus, the overall computational approach can be summarized as: (SMD: MeCN) ω-B97XD/(6-311G(d,p), LANL08d)//ω-B97XD/6-31G(d), LANL08d (Scheme 8).

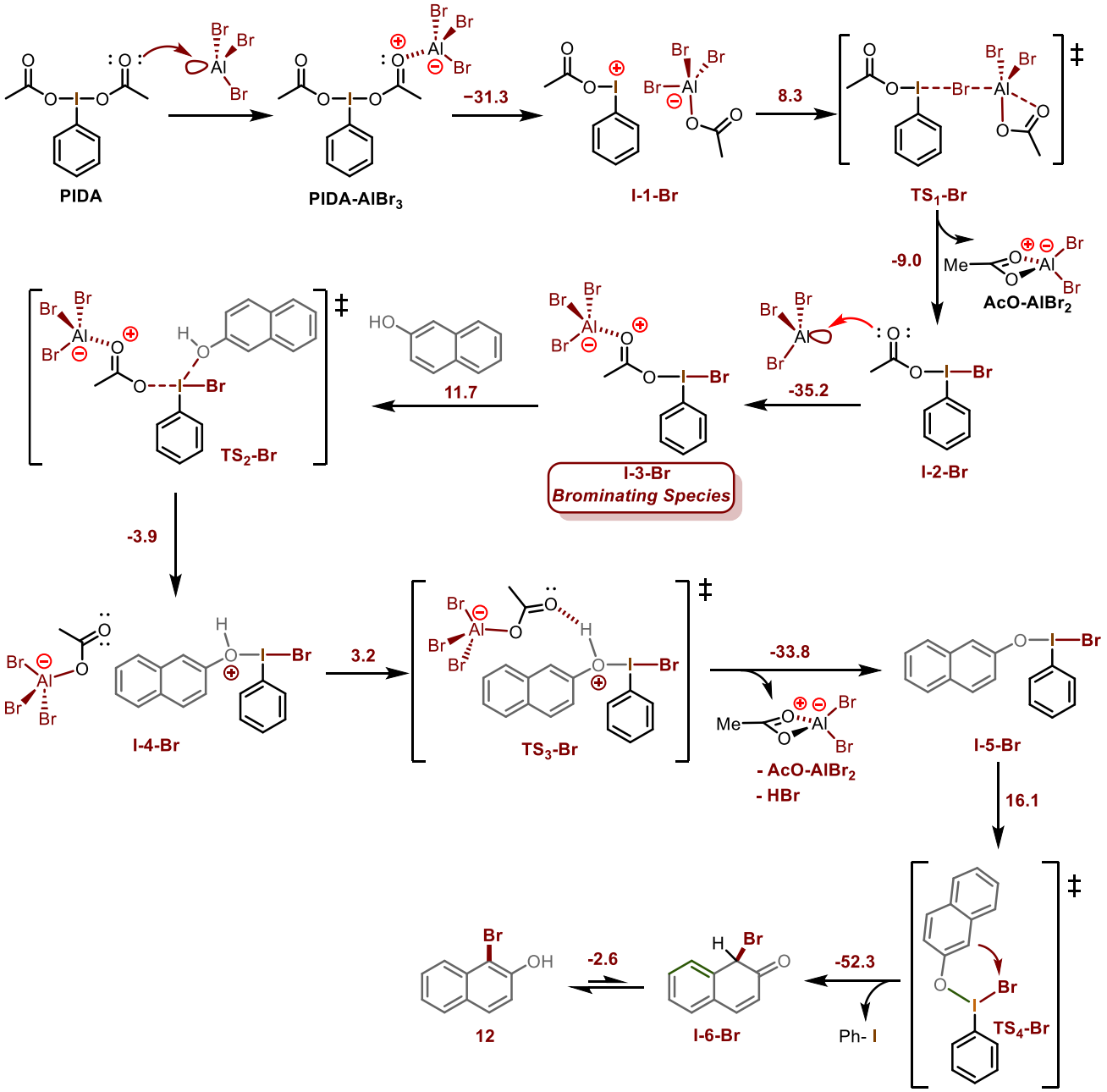


Scheme 8. Reaction mechanism for the chlorination of 2-naphthol using the PIFA-$AlCl_3$ system, DFT-calculated at the (SMD:acetonitrile)ωB97X-D/def2-tzvpp//ωB97X-D/def2-svpp level. ΔG values in green color are given in kcal·mol^{-1}.

The proposed mechanism for the chlorination reaction begins with the coordination of an oxygen atom from PIFA to aluminum chloride, forming a highly exergonic **PIFA–$AlCl_3$** complex. This adduct is used as the reference point at 0 kcal·mol^{-1}. A chlorine atom is then transferred from aluminum to the hypervalent iodine(III) center via a six-membered transition state labeled as **TS_1–Cl**, with an associated activation free energy ($\Delta G^{‡}$) of 9.7 kcal·mol^{-1}. Following, a tetracoordinate **TFAO–$AlCl_2$** salt is released, leading to the formation of intermediate **I-1–Cl** (ΔG = −25.2 kcal·mol^{-1}), which features the key Cl–I^{III} bond. This occurs through a formal ligand exchange between TFAO and Cl. The Cl–I bond in this structure measures 2.46 Å, with the halogen occupying the equatorial position of the iodine center. Subsequently, a second equivalent of $AlCl_3$ binds to the TFAO ligand, forming the active chlorinating species **I-2–Cl** (ΔG = −18.3 kcal·mol^{-1}). This species exists in equilibrium with the ion pair **I-3–Cl** (ΔG = −0.5 kcal·mol^{-1}). The small energy gap between these two states highlights their spontaneous interconversion, a phenomenon only observed in the presence of two equivalents of the Lewis acid. Upon introducing 2-naphthol, the chlorine is barrierless incorporated into the phenolic, forming the non-

aromatic intermediate **I-4–Cl** (ΔG = −23.1 kcal·mol^{-1}). Aromatization then occurred with assistance from TFAO–$AlCl_2$ via **TS_2–Cl** ($\Delta G^{‡}$ = 11.1 kcal/mol), involving hydrogen transfer from the non-aromatic intermediate to TFAO–$AlCl_3$. Overcoming the barrier in **TS_2–Cl** results in the formation of the 1-chloro-2-naphthol adduct **I-5–Cl**, complexed with TFA–OH–$AlCl_2$ (ΔG = −2.6 kcal/mol). This intermediate then spontaneously yields the final product, 1-chloro-2-naphthol **1**, alongside the regeneration of TFAO–$AlCl_2$, in a strongly exergonic step (ΔG = −44.2 kcal·mol^{-1}) (Scheme 7).

Regarding the bromination reaction using the PIDA-$AlBr_3$ system, the reaction follows a stepwise mechanism (Scheme 9).



Scheme 9. Reaction mechanism for the bromination of 2-naphthol using the PIDA-$AlBr_3$ system, DFT-calculated at the (SMD:acetonitrile)ωB97X-D/def2-tzvpp//ωB97X-D/def2-svpp level. ΔG values in red color are given in kcal·mol^{-1}.

This begins with aluminum bromide coordinating to an acetate ligand in PIDA, to get the PIDA–$AlBr_3$ complex through a strongly exergonic process. As in the previous case, the Gibbs free energy at this stage is set to 0 kcal·mol^{-1} for reference. Subsequently, the PIDA–$AlBr_3$ adduct undergoes ionization, producing the ion pair **I-1–Br** (ΔG = −31.3 kcal·mol^{-1}) in a thermodynamically favorable step. Next, an intramolecular SN2 reaction occurs, in which the aluminum-based anion transfers a bromine atom to the electrophilic iodine(III) center via the transition state **TS_1–Br**. This transition state has a reasonable activation energy of 8.3 kcal kcal·mol^{-1}. The bond distances for **I–Br** and **Br–Al** are 3.15 Å and 2.78 Å, respectively, with an **I–Br–Al** bond angle of 93.1°, which is characteristic of the typical T-shaped geometry seen in hypervalent iodine(III) species. This step results in the release of the **$AcO–AlBr_2$** salt and generates the intermediate **I-2–Br** (ΔG = −9 kcal·mol^{-1}), which contains the essential **Br–I^{III}** bond, measured at 2.65 Å. At this point, a favorable ligand exchange between AcO^- and Br^- occurs, releasing 35.2 kcal·mol^{-1} of energy. Then, a second equivalent of aluminum bromide coordinates to an acetate ligand, forming the active brominating species **Br–I(Ph)–OAc–$AlBr_3$** (**I-3–Br**). The next step involves the addition of 2-naphthol to the iodine(III) center, facilitating the release of the Br_3Al–OAc ligand via transition state **TS_2–Br** ($\Delta G^‡$ = 11.7 kcal·mol^{-1}), producing the protonated intermediate **I-4–Br**. Deprotonation assisted by the released **Br_3Al–OAc**, follows. This leads to the formation of the **$AcO–AlBr_2$** salt through **TS_3–Br**, and results in the *trans* intermediate **I-5–Br**, which includes a **Br–I(Ph)–O–naphthyl** bond measuring 2.14 Å. In the final key step, bromination takes place through isomerization of **I-5–Br** to the *cis* transition state **TS4–Br** ($\Delta G^‡$ = 16.1 kcal·mol^{-1}), yielding the non-aromatic intermediate **I-6–Br** in a highly exergonic process (ΔG = −52.3 kcal·mol^{-1}). Lastly, **I-6–Br** undergoes spontaneous aromatization, leading to the experimentally observed 1-bromo-2-naphthol **12**, which is 2.6 kcal/mol more stable than **I-6–Br** (Scheme 8).

7. Oxidative Iodination: The $(PhIO)_n$-NH_4I system

Aromatic compounds containing iodine atoms, play a significant role in organic chemistry.[137] Iodinated arenes are particularly important due to their natural occurrence[138, 139] and their presence in pharmaceuticals,[140] hormones,[141] antifungal[142] and antibacterial agents.[143] Aryl iodides are also of great interest as they serve as precursors for the synthesis of hypervalent iodine(V)[144] and iodine(III)[145] regents. Additionally, they are excellent substrates for carbon–carbon bond-forming reactions such as Suzuki, Stille, Sonogashira alkynylation, and Mizoroki–Heck olefination (Figure 3). [146]

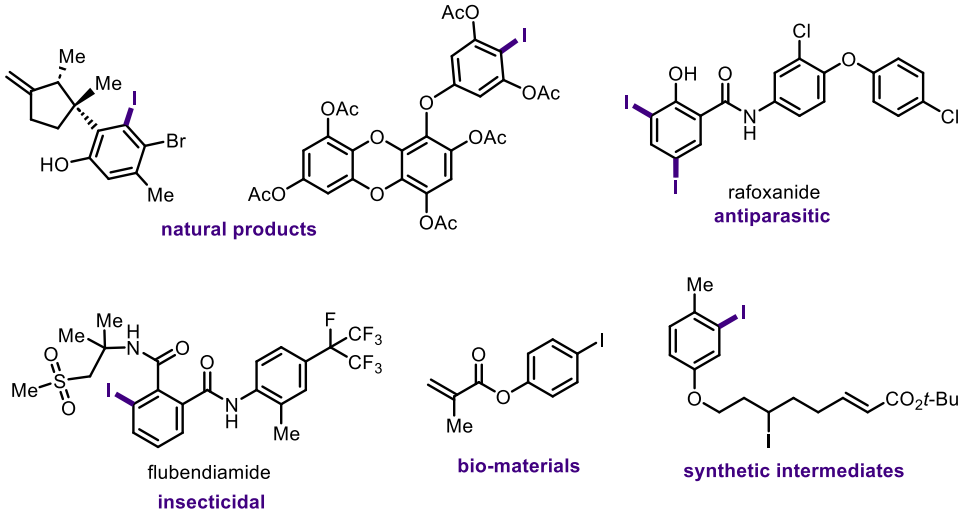
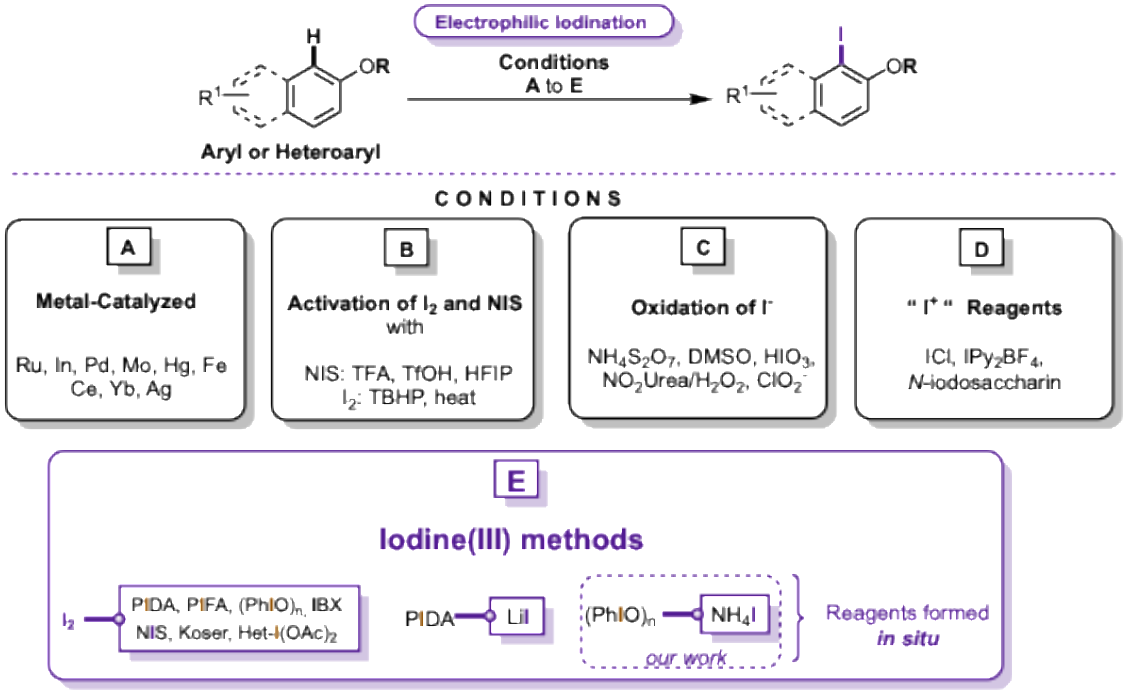


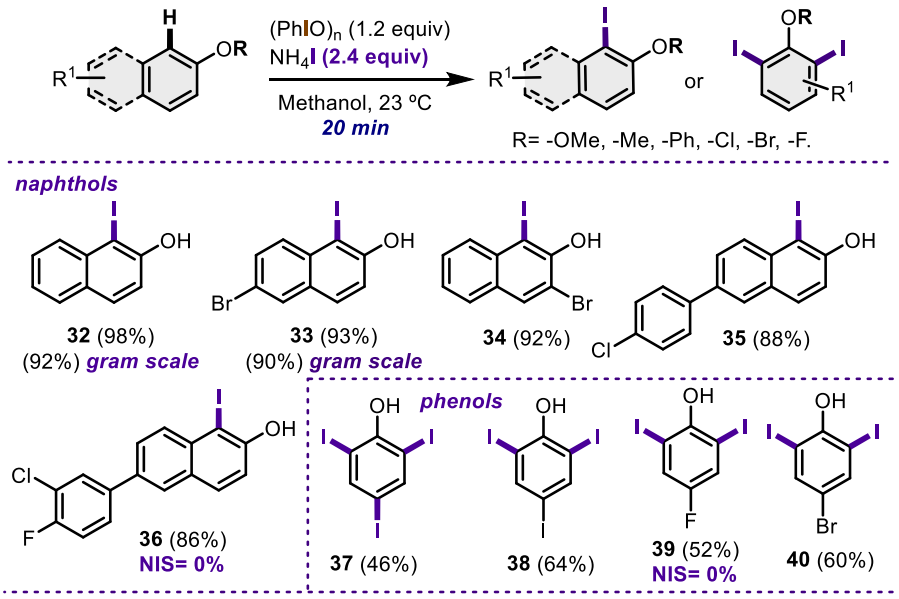
Figure 3. Relevance of the iodoarene core.

Various methods for the iodination of arenes have been reported in the literature. Among the most prominent are those involving transition metals like Ru,[147] In,[148] Pd,[149] Mo,[150] Hg,[151] Fe,[152] Ce,[153] Yb,[154] and Ag.[155] There are also metal-free approaches using I_2 with oxidants such as peroxodisulfate,[156] DMSO,[157] HIO_3,[158] urea–H_2O_2,[159] or NO_2.[160] Another strategy relies on the oxidation of iodide salts with systems like NH_4I/H_2O_2,[161] $NaI/NaClO_2$,[162] or $NaClO_2$/NaI/HCl.[163] Alternatively, iodination using electrophilic iodine (I^+) species is commonly carried out with reagents such as ICl,[164] *N*-iodosaccharin,[165] IPy_2BF_4,[166] and NIS in strongly acidic media like TFA, [167] TfOH,[168] or HFIP.[169] A more recent development includes radical iodination with I_2/TBHP.[170] A less explored yet promising route for the oxidative iodination of arenes and phenols involves the use of hypervalent iodine(V)[171] or iodine(III) reagents.[172] Iodine(III)-based methods typically proceed through the formation of a diaryliodonium intermediate, which then reacts with a metal iodide (commonly NaI) to undergo a thermally driven reductive elimination, yielding two different aryl iodides.[173] Most current methods for phenol iodination rely on costly transition metals or harsh oxidants, often leading to poor functional group compatibility. In this context, hypervalent iodine reagents present an attractive alternative. Nevertheless, existing iodine(III) iodination protocols face major drawbacks, including low selectivity,[171] polyhalogenation, the use of expensive precursors,[172] multistep synthesis, restriction to electron-rich arenes, limited applicability, and demanding conditions (high temperature, strong Lewis acids, or long reaction times) (Scheme 10).



Scheme 10. Representative procedures for the aromatic iodination of phenols.

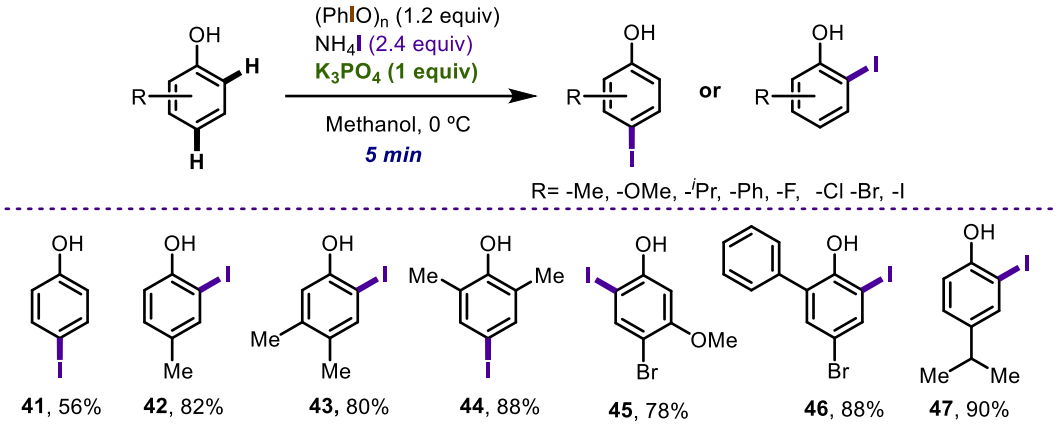
These limitations have hindered the development of an efficient iodine(III)-based iodination approach. Against this backdrop, we aimed to develop a systematic and efficient method for phenol iodination using hypervalent iodine(III) reagents. Inspired by our novel protocols for chlorination and bromination using PIFA, PIDA and the corresponding aluminum salts (AlX_3, X= Cl, Br) we initially propose the combination of the mentioned reagents with AlI_3. Unfortunately, after several attempts, this system only produced large amounts of molecular iodine along the full recovery of the starting material. The continuous search for a useful iodinating system led to the discovery of the iodosylbenzene $(PhIO)_n$ combined with ammonium iodide (NH_4I) as a cost-effective iodine source.[26] The stoichiometric and solvent optimization of this reagents combination showed that $(PhIO)_n$-NH_4I (1:2) in methanol by periods of 5-25 minutes were the best conditions. Then, we proceeded to explore the scope of the reaction (Scheme 11).



Scheme 11. Representative scope of the $(PhIO)_n$-NH_4I mediate oxidative aromatic iodination of phenols.

Different naphthols (**32**-**36**) were succesfully iodinated even some of them at gram scale with excellent yields (> 86%) and remarkably in short times. However, for the case of phenols, the polyiodination was a constant in every reaction, even for electro-poor aryls.

Then, we developed and improved a protocol for preventing the polyiodination of mono-annular phenolic aromatic systems, which is a common and undesired observed side-reaction. Accordingly, we considered the increasing acidity of the media generated after the aromatización process as result of the first iodination atom introduction, that acelerates the following iodination process. Then, the intorduction of more than one iodine atom in the phenolic ring was observed. To overcome this inconvenient and after several experiments we tested potasium tribasic phospate for buffering the reaction. To our delight, the addition of this salt succesfully controlled the polyiodination enabling the single iodine atom introduction. Next, we proceeded to identify the scope of this buffered reaction (Scheme 10).

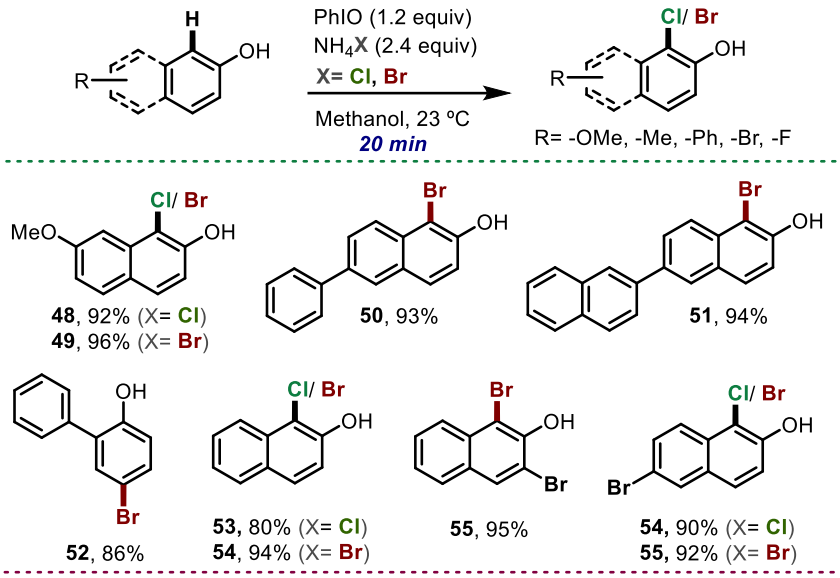


Scheme 10. Scope of the $(PhIO)_n$-NH_4I mediate the controlled mono-iodination of phenols buffered by K_3PO_4.

A representative amount of iodinated phenols are showed. Under optimized buffered conditions the controlled mono-iodination of several phenols was achieved. These include electron- neutral (**41**), -rich (**42**-**45**) or with bulky substituents (**46**, **47**) in modest to excellent yields (56-90%).

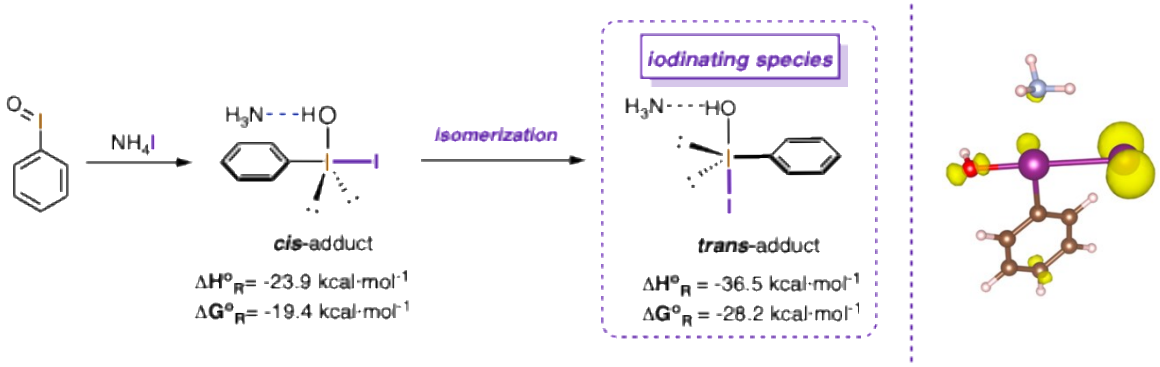
Following this strategy on the use of ammonium iodide, we envisioned that the corresponding ammonium chloride and -bromide would produce the corresponding chlorinated and brominated phenolic derivatives. Once

we test the aformentioned salts in combination with polymeric idosylbenzene, we obtained the chlorination and bromination products using the same stoichiometry, solvent and temperature previously identified for iodination process. Then, we demonstrate a brief scope (Scheme 11).



Scheme 11. Scope of the $(PhIO)_n$/-NH_4Cl, -NH_4Br mediated aromatic chlorination and bromination of phenols.

To conclude our work on the oxidative aromatic controlled mono- or diiodination of phenols, mechanistic studies using different radical scavengers such as TEMPO or DPPH were added to a model reaction. Then, the iodination of 2-naphthol under standard conditions, were we carried out. Not yield decreasing in any of both scavengers used was found. Also, theoretical studies to postulate a possible iodinating species was carried out. For instance, calculations considering the interaction of monomeric PhIO and ammonium iodide were conducted at the B3LYP/DGDZVP level. The enthalpy and Gibbs free energy for the reaction between PhIO and NH_4I were analyzed to assess the energetic stability of the resulting product. The calculated values strongly indicate that the *trans*-adduct[174] $PhII(OH)\cdot NH_3$ is the most likely active iodinating species. This hypervalent iodine(III) compound is formed through isomerization from its initially generated *cis*-adduct, which appears as the kinetic product. In contrast, the *trans*-$PhII(OH)\cdot NH_3$ represents the thermodynamically favored species. Additionally, Fukui function of this species was calculated showing the most electrophilic center which is yellow colored (Scheme 12).

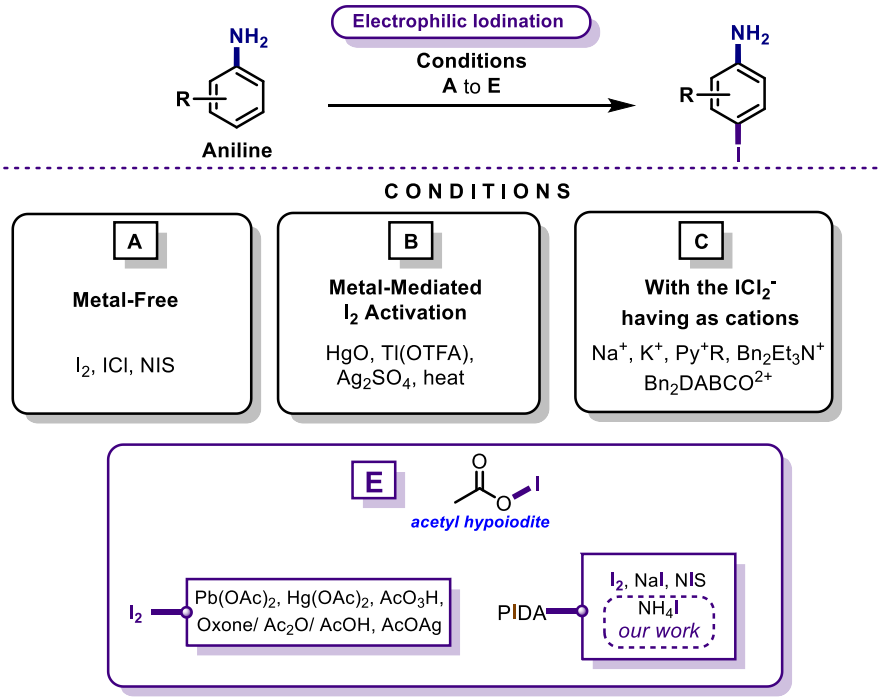


Scheme 12. DFT-calculated plausible iodinating species for the $(PhIO)_n$-NH_4I system and its Fukui function.

This set of experiments described a novel reagent combination [$(PhIO)_n$-NH_4X (X= Cl, Br, I)] focused, explored and developed mainly for the iodination of phenols which was illustratively extended to the chlorination and bromination processes. At such point we turned our attention on a broad exploration of the iodosylbenzene as a valuable reagent for additional functional groups introduction as well as for the functionalization of other important aromatic aryls such as anilines.

8. Iodination of Anilines by *in situ* formed AcO-I

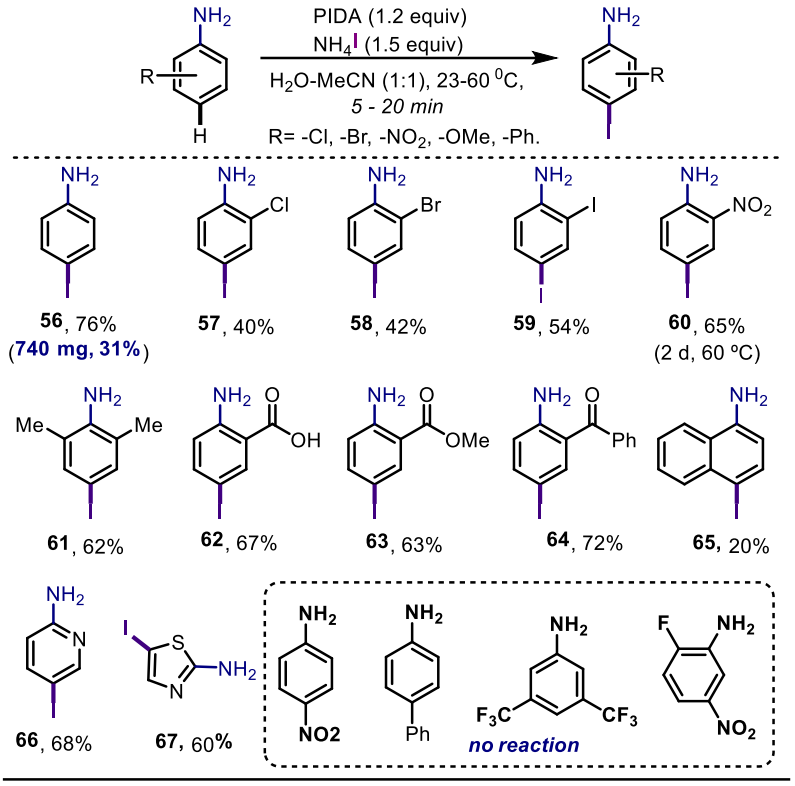
Electron-rich arenes, such as anilines, often require specific conditions for halogenation, since conventional methods using strong Lewis acids (e.g., Al or Fe metals) are not suitable when the nitrogen atom lacks electron-withdrawing substituents. Standard iodination procedures for anilines generally involve metal-based oxidants and are typically limited to a narrow range of *N*-substituted anilines.[175-180] Metal-free approaches utilize molecular iodine (I_2) in polar solvents,[181, 182] oxidant combinations,[183] ICl,[184] NIS,[185] or iodide oxidation using agents like $KClO_3$[186] or H_2O_2.[187] Additionally, the ICl_2^- ion has been used with various cations, including Na^+,[188] K^+,[189] Py^+R,[190] $Bn_2Et_3N^+$,[191] and Bn_2DABCO^{2+}.[192] Meanwhile, metal-mediated iodination methods for anilines have been confined to reagents such as HgO-,[193] $Tl(OTFA)_3$-,[194] and the Ag_2SO_4-I_2[195] systems. Additionally, a well know method for the direct iodination of non-nitrogen functionalized anilines, concern to the use of acetyl hypoiodite (AcO-I). In this regard several methods have been described for their synthesis such as the reaction of I_2 with various reagents, including $Pb(OAc)_2$,[196] $Hg(OAc)_2$,[197] AcO_3H,[198] Oxone/Ac_2O/AcOH,[199] AcOAg, and the AcOAg/ICl system.[200] Additionally, the generation of AcOI using iodine(III) reagents has been reported via the reaction of PIDA with I_2,[201] NaI,[202] NIS,[203] and regarding our work, NH_4I[31] (Shceme 13).



Scheme 13. Representative procedures for the aromatic iodination of *N-H* free anilines.

To get iodination of anilines we tested our previously described iodination method using iodosylbenzene and ammonium iodide in acetonitrile,[26] nevertheless, we couldn´t find any reaction. Then we assayed PIDA with the same iodide salt under (1:1.5) stoichiometry, surprisingly we isolated 46% yield of the exclusively *p*-iodoaniline

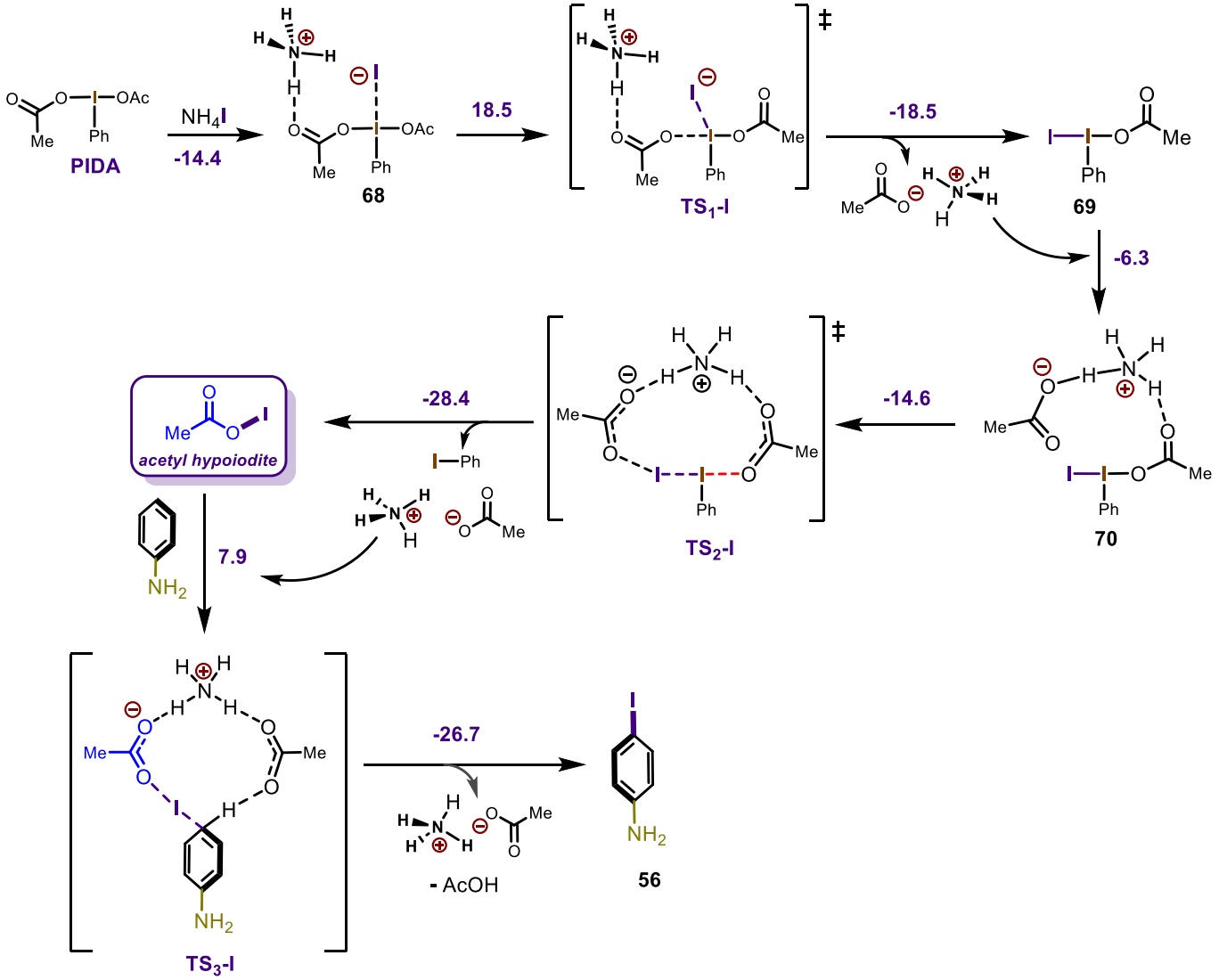
56. The optimization led to the use of MeCN-H_2O (1:1) as the best solvent mixture for the reaction. Other solvent such as methanol accelerated the process in such way that didn´t allow a productive reaction, and as consequence any isolable product was identified. Thus, once optimized the conditions we started a short scope exploration (Scheme 14).



Scheme 14. Scope of the PIDA-NH_4I mediated aromatic iodination of *N*-H free anilines.

Some *N*-H free neutral anilines as well as such containing electron-attracting groups like halogens and nitro group (**56**-**60**) were modestly iodinated (40-76%) even at gram scale. The alkyl and carbonyl groups including carboxylic acids, esters or ketones (**61**-**64**) could be iodinated in yields ranging from 62-72%. Other aryls containing the naphthyl, pyridyl and thiazolyl groups (**65**-**67**) were also iodinated under our conditions. Strong electron-attracting groups such as nitro and fluor, bis-trifluoromethyl or aniline with preinstalled *p*-substitution are the limitations of the protocol. Interestingly, this protocol only gave the *p*-iodination.

Next, we performed theoretical calculations to find a plausible reaction pathway (Scheme 15).

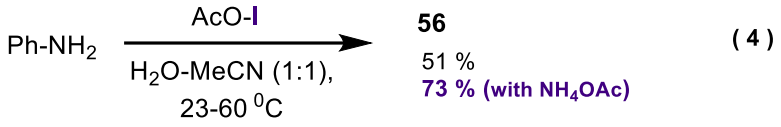


Scheme 15. DFT-calculations for the iodination reaction mechanism of aniline using PIDA-NH_4I in MeCN-H_2O (1:1). Calculations were carried out at the (SMD:acetonitrile)ωB97X-D/def2-SVPP level. ΔG values in purple color are given in kcal·mol^{-1}.

The proposed mechanism begins with the interaction between PIDA and ammonium iodide, resulting in intermediate **68** with an energy of –14.4 kcal/mol. Subsequently, the acetate group from PIDA, which is associated with the ammonium cation, dissociates via transition state **TS_1-I** (ΔG = +18.5 kcal/mol), yielding intermediate **69** without any net energy change (0.0 kcal/mol) relative to **68**. Then, NH_4OAc interacts with **69** to form adduct **70**, releasing –6.3 kcal/mol of energy (ΔG = –6.3 kcal/mol). In this adduct, the acetate ion displaces the iodine atom, a process favored by the geometry of **70**. The remaining acetate in **70** is released through transition state **TS_2-I** (ΔG = +14.6 kcal/mol), forming **AcO–I** and releasing –28.4 kcal/mol. The final step involves para-iodination of aniline, which has a reaction energy of +18.8 kcal/mol (ΔG_R = +18.8 kcal/mol). In this step, the transition state (**TS_3-I**) involves **AcO–I** interacting with ammonium acetate, requiring +7.9 kcal/mol (ΔG = +7.9 kcal/mol). The ammonium cation plays a key role by bridging both acetate groups through hydrogen bonding, which increases the electrophilicity of the iodine in **AcO–I** and facilitates both its formation and the subsequent halogenation reaction.

Ammonium acetate has been found to play a critical role in this transformation. To experimentally validate the key mechanistic steps, **AcO–I** was synthesized following established protocols.[31, 201-203] Subsequent iodination of aniline was performed using the generated acetyl hypoiodite under two different conditions: (i) in the absence of externally added ammonium acetate, and (ii) in the presence of one equivalent. The reaction without

ammonium acetate afforded a 51% yield, whereas the addition of one equivalent resulted in a significantly improved yield of 73%. This latter outcome closely aligns with the 76% yield observed under the standard reaction conditions. These findings provide strong experimental support for the mechanism proposed through DFT calculations (Eq. 4).



(4)

The remarkable highlights of this developed protocol consited in the new and really fast water-tollerant generation of acetyl hypoiodite in only 2 minutes by mixing PIDA and ammonium iodide.

Simultaneously, an unusual reactivity was identified by exploration of polymeric iodosylbenzene with aluminum nitrate to get a catalytic nitration of phenolic systems.

9. Catalytic Nitration: The $(PhIO)_n$-$Al(NO_3)_3$ system

Nitroarenes, particularly nitrated phenol derivatives, hold significant importance due to their wide-ranging applications.[204] They naturally occur in various sources[205] and are commonly found in antibiotics,[206] organic dyes,[207] explosives,[208] pesticides,[209] polymers,[210] the pharmaceutical industry,[211] solvents, [212] and serve as key intermediates in the synthesis of amine derivatives (Figure 4).[213]

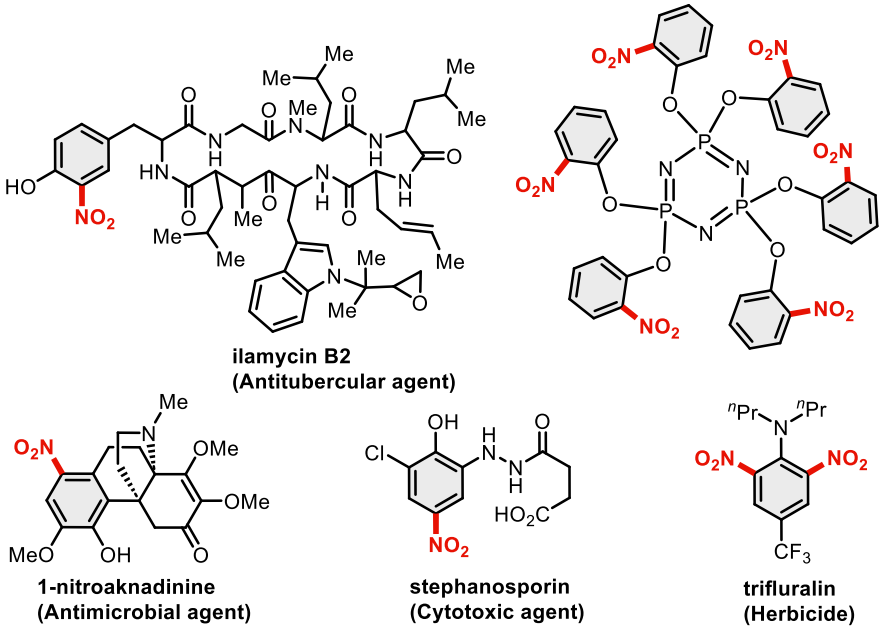


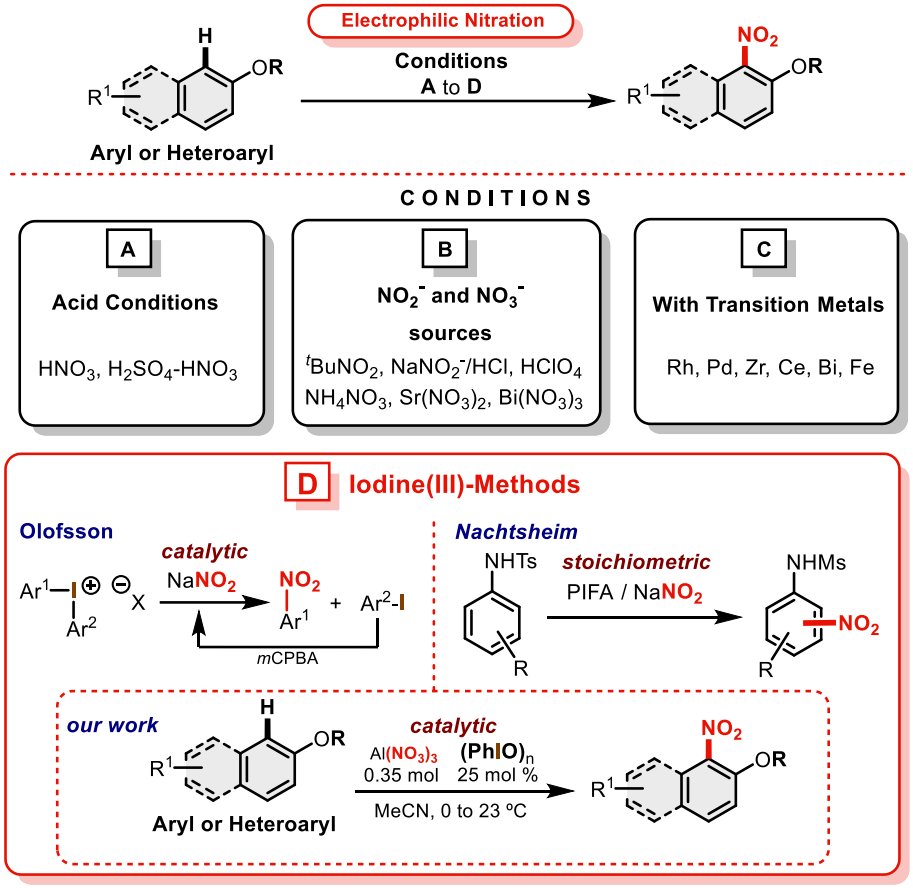
Figure 4. Relevance of nitrophenols and nitrorenes.

The nitration of aromatic compounds has been extensively investigated, and numerous methods for introducing nitro groups are currently available.[214] The classical approach involves the use of concentrated nitric acid,[212] often in combination with strong acids such as HNO_3-H_2SO_4 mixtures.[215-218] Milder alternatives include reagents like *tert*-butyl nitrite ($^tBuNO_2$)[219] or Crivello's reagent.[220] Sodium nitrite ($NaNO_2$) paired with various Brønsted acids also serves as a nitro source in several methods.[221-223] Additional nitro-containing systems applicable to arene nitration include melamine–NO_3,[224] TCT–$Zn(NO_3)_2$,[225] $[BnPh_3P^+][-S_2O_3^-]$–NO_3,[226] and combinations such as H_2SO_3 with $Sr(NO_3)_2$[227] or $Bi(NO_3)_3$.[228]

Transition metal-catalyzed nitration has also been explored using metals like rhodium,[229] palladium,[230] zirconium,[231] cerium,[232] bismuth, and iron.[233] However, these methods often face challenges such as limited functional group tolerance and harsh conditions. This has driven interest in hypervalent iodine(III) chemistry, which formed the basis of our research.

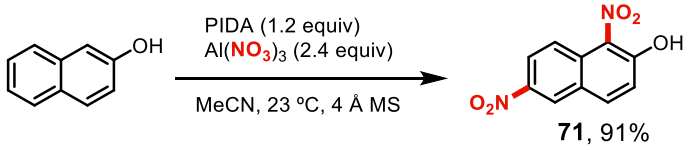
Recent work has demonstrated nitration using reagents like PIFA[234] or diaryliodonium salts.[235] Notably, Professor Olofsson[236] developed an *in situ* strategy for generating diaryliodonium salts followed by nitration.

Our motivation stems, from the need to develop milder, more selective nitration protocols. We aim to avoid Brønsted acids and harsh conditions by utilizing iodine(III) reagents in combination with aluminum salts. Our approach represents a novel contribution to the field, as it introduces catalytic conditions for arene nitration for the first time (Scheme 16).[25]



Scheme 16. Representative procedures for the aromatic nitration of phenols.

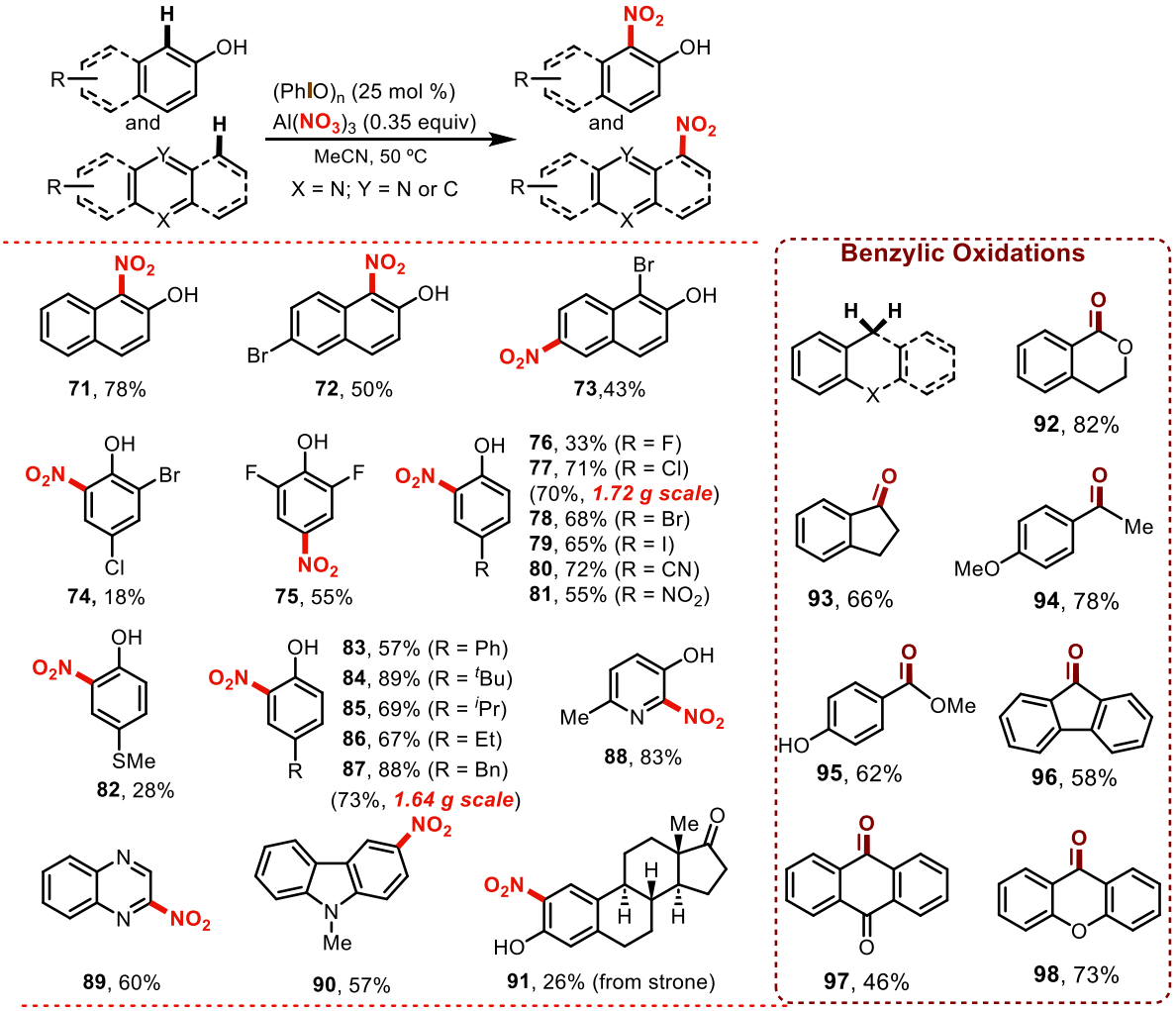
Inspired by our combination protocols of iodine(III)-reagents and aluminum salts for the chlorination and bromination and specifically the use of polymeric iodosylbenzene with these salts, we envisioned in 2018 the plausible nitration of phenols. Our preliminary exploration started by combining PIDA- $Al(NO_3)_3$ (1:2) using 2-naphthol as model. Surprisingly, we found the double nitration instead of the single one (Eq. 5).



(**5**)

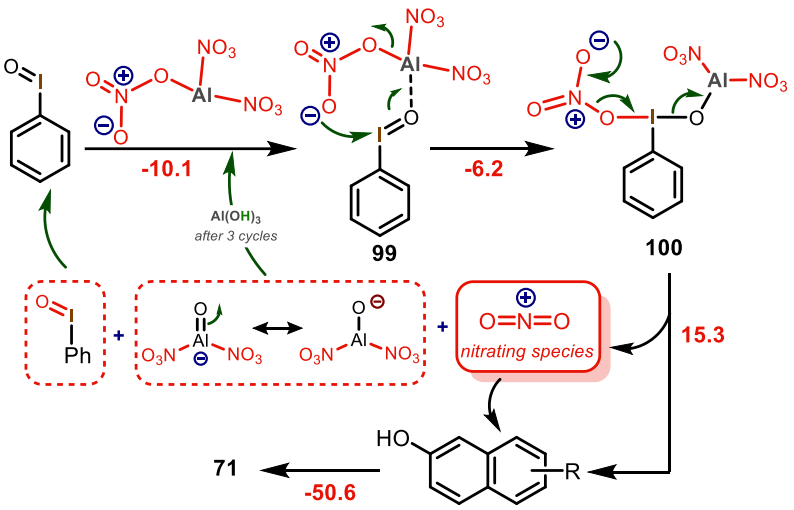
Several trials were carried out attempting to get the single nitration, nevertheless, just with the use of 0.5 equivalents of PIDA and 0.35 of aluminum nitrate it was possible to get 68% of single nitration of 2-napthol (**71**).

The use of sub-stoichiometric amounts of iodine(III) reagent led to the proposal that a *catalytic process* must be involved. Additionally, a mechanistic proposal considered to the iodosylbenzene as an active "by-product" which could be completed the reaction along several cycles. Then, we decided to use this polymeric reagent in combination with aluminum salts. To our delight we identified to the $(PhIO)_n$-$Al(NO_3)_3$ (0.25:0.35) in acetonitrile as optimal conditions. Consequently, we proceeded to identify the scope and limitations of this new nitrating process (Scheme 17).



Scheme 17. Scope of the $(PhIO)_n$-$Al(NO_3)_3$ catalyzed aromatic iodination of *N*-H free anilines.

Several naphthols (**71**-**73**), phenols (**74**-**87**), containing electron-withdrawing and electron-donating groups as well as different heterocycles such as pyridines **88**, quinoxalines **89**, carbazoles **90** and even steroids were successfully nitrated overall within excellent yields. As part of this scope exploration, we found that some aryls containing benzylic hydrogens surrounded to electron-rich groups were oxidized to get the corresponding carbonyl group to obtain ketones, esters and carboxylic acids (**92**-**98**).[28] An important point to highlight is the remarkably non-acidic conditions, that make a very mild protocol which proceed close to neutral medium. Next, we conducted some DFT calculations to identify a plausible reaction mechanism for the catalytic nitration process (Scheme 18).

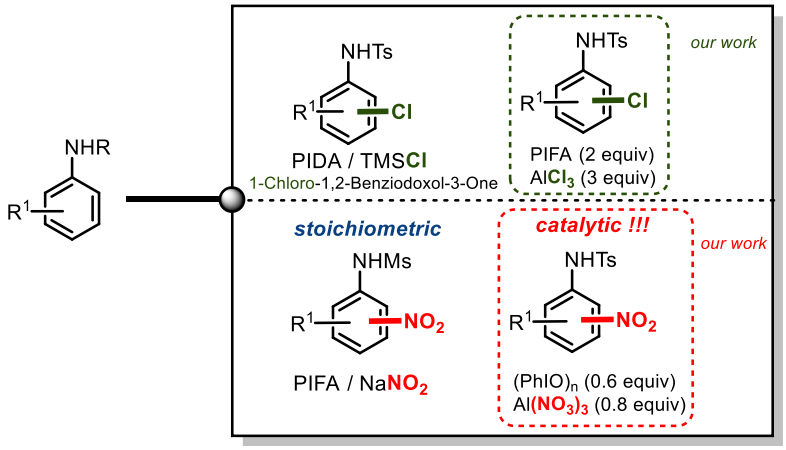


Scheme 18. DFT-calculations for the catalytic nitration of 2-naphthol using $(PhIO)_n$-$Al(NO_3)_3$ in MeCN. Calculations were carried out at the (SMD:MeCN)Mo8-HX/(LANLo8+f,6-311+G*) level. ΔG values in orange color are given in kcal·mol^{-1}.

The proposed mechanism begins with the coordination of a monomeric PhIO molecule to aluminum nitrate, forming intermediate **99** with a favorable free energy change of -10.1 kcal/mol. Subsequently, a nitrate group migrates from the aluminum atom to the iodine(III) center, resulting in intermediate **100**, which has an energy of -6.2 kcal/mol. This species then breaks apart on its own, generating the nitronium cation $\mathbf{NO_2^+}$ along with the regeneration of monomeric iodosylbenzene and the formation of mixed aluminum oxide species. This transformation requires an energy input of 15.3 kcal/mol. At this stage, the 2-naphthol reacts to form the nitrated product **71**, in a highly exergonic step that releases -50.6 kcal/mol. After three cycles of the reaction, the aluminum reagent is fully converted into $Al(OH)_3$.

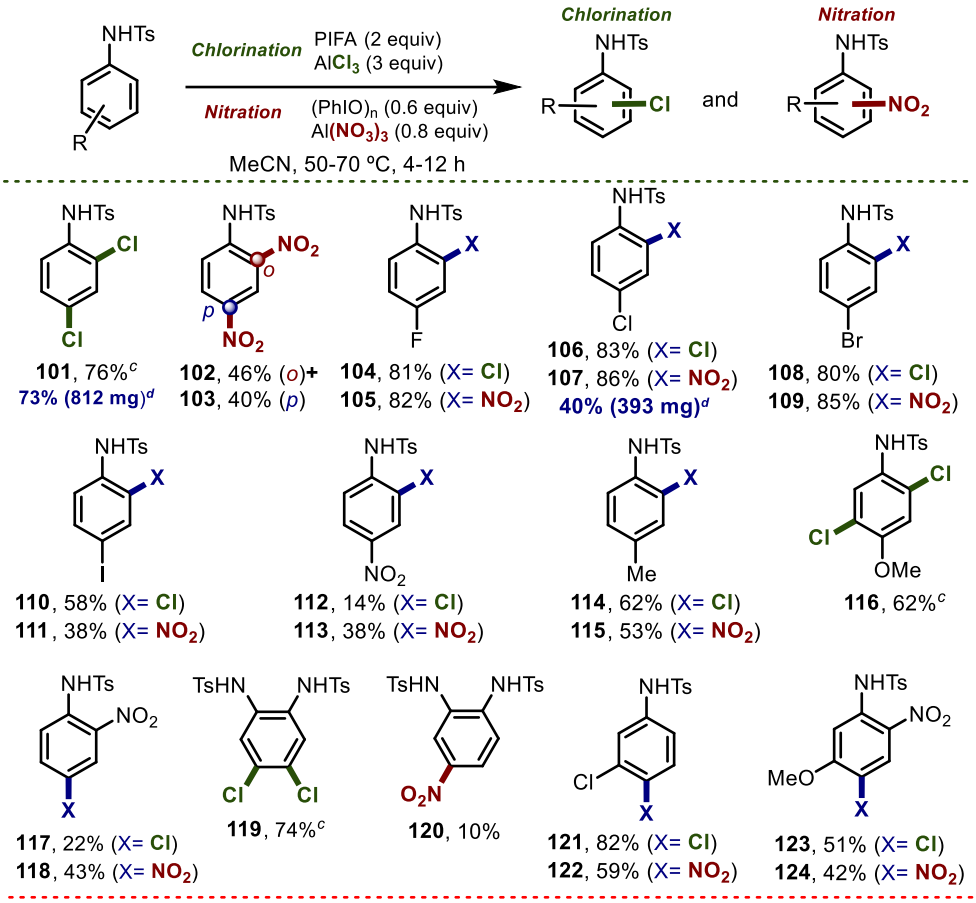
10. Catalytic Chlorination and Nitration of Anilines

The last contribution of this topic by our research group came in 2022.[30] Therein it was described the chlorination and nitration of anilines. In this contribution the nitrogen of the aniline must be functionalized in order the reaction proceed. After several assays, the tosyl group was the optimal for both processes. It is important mentioning that iodine(III)-based protocols for these processes are few considering this dense field of arene functionalization (Scheme 19).



Scheme 19. Iodine(III)-based methos for chlorination and nitration of anilines.

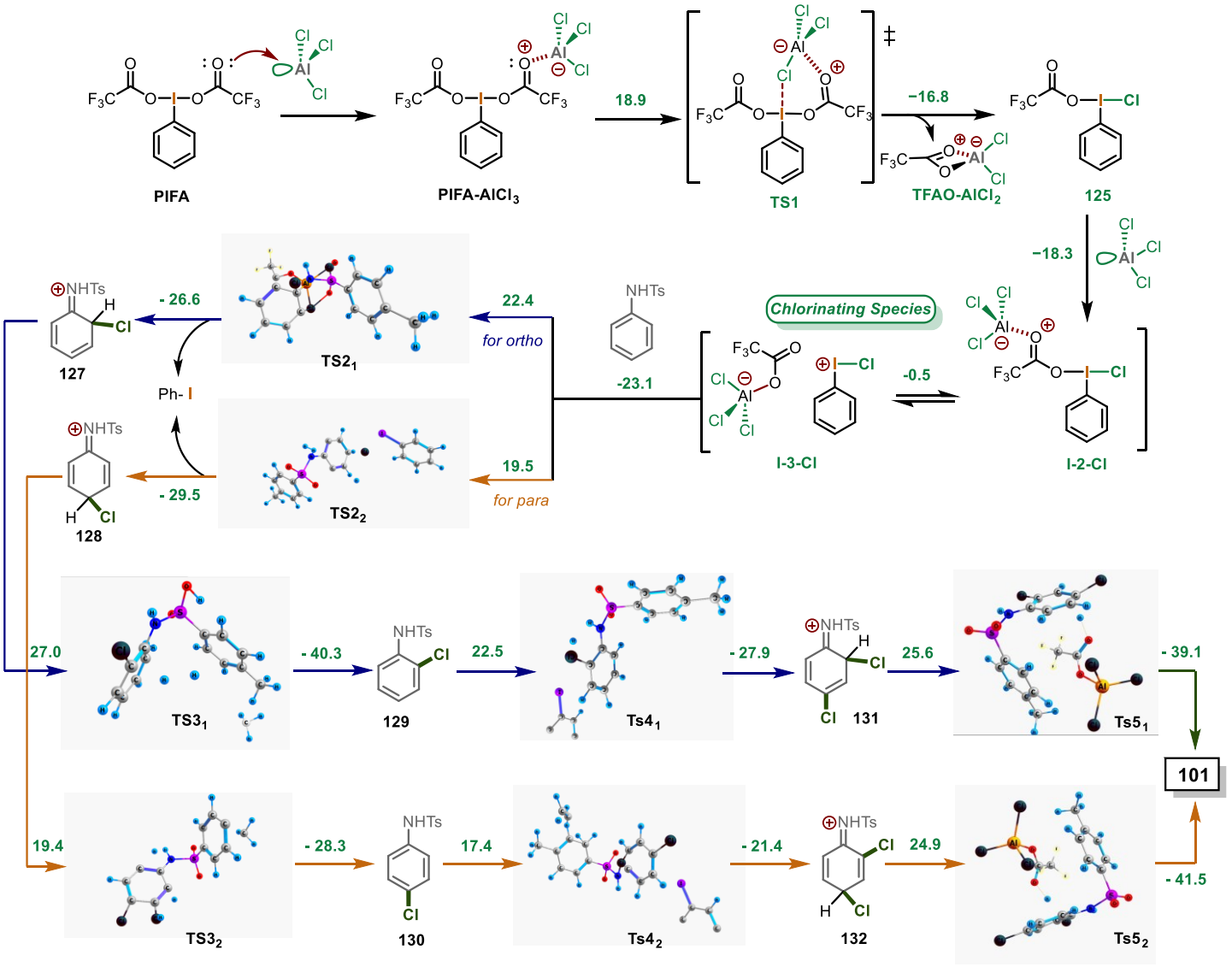
For the case of chlorination reaction, stoichiometric amounts of oxidant and aluminum salt was necessary for completing the reaction. On the other hand, the nitration proceeded in catalytic conditions using 60 mol% of polymeric iodosylbenzene and 0.8 equivalents of aluminum nitrate in acetonitrile at 50 °C. Using these optimized conditions, we explored the scope and limitations of this procedure (scheme 20).



Scheme 20. Scope of the chlorination and nitration of *N*-Tosyl anilines using the $(PhIO)_n$ / -$AlCl_3$, -$Al(NO_3)_3$, systems.

As illustrated, different *N*-tosyl anilines including the simplest one (**101**-**103**) as well as those *p*-substituted containing the full halogens family, the nitro group, alkyl and ether groups (**104**-**116**); also, anilines with *o*- (**117**-**120**), *m*- (**121**, **122**) and even tri-substituted anilines (**123**, **124**) were chlorinated and nitrated with variable yields ranging from low to excellent (10-86%). Important to mention is the low yields are selected and the very minor number of compounds obtained.

Next, we proceeded to explore the reaction mechanism by DFT calculations, to identify the most plausible reaction route which allowed the final product formation at the (SMD:acetonitrile)ωB97X-D/def2-tzvpp//ωB97X-D/def2-svpp level. We specifically focused on the chlorination processes. The study of the nitration by DFT calculations is currently under investigation in our laboratories (Scheme 21).



Scheme 21. DFT-calculations for the *o*- and *p*- chlorination of aniline using PIFA-$AlCl_3$ in MeCN. ΔG values in green color are given in kcal·mol^{-1}.

The process begins with thecoordination of a trifluoroacetate group from PIFA to $AlCl_3$. This interaction leads to the release of the acetate group while a chloride ion is simultaneously transferred to the iodine atom via the transition state **TS1** ($\Delta G^{‡}$ = 18.9 kcal·mol^{-1}), resulting in intermediate **125**, which is +2.1 kcal·mol^{-1} higher in energy than the starting materials (the trifluoroacetate becomes species C). **125** then binds to another $AlCl_3$ molecule, forming **126**, which is stabilized by 22.4 kcal·mol^{-1}. This complex then dissociates spontaneously into the ion pair **Cl(Ph)I**$^{+}$ and **$AlCl_3$·TFAO**$^{-}$, releasing 9.1 kcal·mol^{-1} and generating the active catalyst. At this stage, the reaction with *N*-tosyl aniline proceeds through electrophilic attack at either the *ortho* or *para* position. Both transition states were calculated: **$TS2_1$** (for *ortho*-chlorination) and **$TS2_2$** (for *para*-chlorination), with energy barriers of 22.4 and 19.5 kcal·mol^{-1}, respectively. The energy gap ($\Delta\Delta G^{‡}_2$ = 2.9 kcal·mol^{-1}) becomes even more evident when comparing intermediates **127** and **128** ($\Delta\Delta G_3$ = 5.8 kcal·mol^{-1}), although both steps are exergonic (releasing 4.2 and 10.0 kcal·mol^{-1}, respectively). Further along, species **$AlCl_3$·TFAO**$^{-}$ undergoes deprotonation via **$TS3_1$** ($\Delta G^{‡}_3$ = 27.0 kcal·mol^{-1}) or **$TS3_2$** ($\Delta G^{‡}_2$ = 19.4 kcal·mol^{-1}), showing the largest energy gap between the two paths ($\Delta\Delta G^{‡}_3$ = 13.4 kcal·mol^{-1}). These findings suggest that *para*-chlorination is significantly faster than *ortho*-

chlorination. The monochlorinated products **129** and **130** differ by only 1.4 kcal·mol^{-1}. In the second chlorination step, there's a reversal in intermediate stability, with **131** being 3.1 kcal·mol^{-1} more stable than **132**. Despite **TS4$_2$** being significantly faster than **TS4$_1$** ($\Delta\Delta G^{\ddagger}_4$ = 6.5 kcal·mol^{-1}), the subsequent deprotonation step through **TS5$_1$** has a lower energy barrier than **TS5$_2$** ($\Delta\Delta G^{\ddagger}_5$ = 2.4 kcal·mol^{-1}), leading to the final dichlorinated product. A comparison between **129→TS4$_1$** ($\Delta G^{\ddagger}$ = 22.5 kcal·mol^{-1}, *para* attack) and **130→TS5$_2$** ($\Delta G^{\ddagger}$ = 24.0 kcal·mol^{-1}, *ortho* attack) again shows a preference for para substitution. Nonetheless, this regioselectivity is primarily determined during the first chlorination step on the aniline ring.

This study completed our contribution to this area of the organic chemistry involving iodine(III) reagents and aluminum salts for the stoichiometric chlorination, bromination and catalytic nitration of phenols and anilines, which demonstrated the great versatility and unique reactivity of the development.[237]

11. Conclusions

In conclusion, the use of hypervalent iodine(III) compounds in combination with aluminum and ammonium salts has been discussed. This method allows for the electrophilic functionalization of aromatic and heteroaromatic compounds. The studies described above allow for catalytic halogenation and nitration under mild reaction conditions: non-Brønsted acidic, metal-free, and oxidant-free conditions. This represents an alternative to classical electrophilic aromatic substitution methods.

The dual role of inorganic salts, which act as a source of the halogen or nitro group and as modulators of the reactivity of the hypervalent iodine(III) center, allows for unique reactivity in the functionalization of derivatives of phenols, anilines, and heterocycles. Tolerance to different functional groups demonstrates the applicability of these methodologies; however, there are areas of opportunity in this field, such as the functionalization of more complex substrates and the extension to less activated aromatic systems.

We have also thoroughly discussed the experimental, mechanistic, and theoretical studies that support the importance of *in situ* generated iodine(III) species, which enable the formation of highly reactive electrophilic species. This allows for mild reaction conditions and good yields in functionalized systems. In this context, future efforts should focus on functionalization methodologies for arenes involving hypervalent iodine(III) reagents, emphasizing the application of these compounds in the synthesis of molecules of interest in pharmaceuticals, agrochemicals, and materials science.

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