# An unusual stepwise mechanism for the bromination of arenes by a hypervalent iodine reagent

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Dedicated to Prof. Dr. Antonio Otero on the occasion of his retirement

ABSTRACT: A mild, metal-free bromination method of arenes has been developed using the combination of bis(trifluoroacetoxy)iodobencene and trimethylsilyl bromide. *In situ* formation of dibromo(phenyl)-λ3-iodane ($PhIBr_2$) is proposed as reactive intermediate. This methodology using PIFA-TMSBr has been applied with success to a great number of substrates (25 examples). The treatment of mono-substituted activated arenes led to *para* brominated products (**2u-z**) in excellent 83-96% yields. DFT calculations indicate a stepwise mechanism involving a double bromine addition followed by a type II dyotropic reaction with concomitant re-aromatization of the six-membered ring.

**Introduction**

Aryl bromides are useful intermediates in the production of pharmaceuticals, agrochemicals, and organic semiconductors.[1] Additionally, they have found widespread usefulness in metal-catalyzed cross-coupling reactions, as well as classical precursors for organometallic reagents.[2,3] Although electrophilic aromatic bromination was discovered in the 19$^{th}$ century, it is still the most common synthetic methodology for the preparation of aryl bromides. Classically, it has been driven using $Br_2$ and HOBr in presence or absence of catalyst.[4] In 1997, Majetich's group showed that bromodimethylsulfonium bromide was a milder and more selective reagent than $Br_2$.[5] Many reagents have been used including NBS,[6] 1,3-

dibromomethylhydantoin,[7] benzyltrimethylammonium tribromide,[8] pyridinium bromide perbromide,[9] and $NaBrO_3$[10] among others.

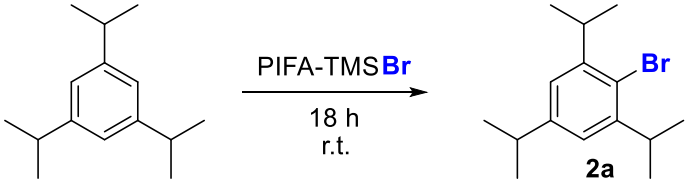
The use of hypervalent reagents for the aromatic bromination is of current interest. In a seminal work, Evans and Brandt described the use of $PhI(OAc)_2$ (PIDA)-TMSBr system at 0°C for the bromination of a few 1,4-dimethoxynaphthalenes.[11] In 1999, Togo and collaborators obtained the monobromination of 1,3,5-triisopropylbenzene mixing 1-(*p*-chlorobenzenesulfonyloxy)benziodoxolone with LiBr.[12] Huang's group described the use of PIDA, $CuBr_2$ and $NH_2SO_3H$ for the bromination of quinolines.[13] Rao's group[14] reported the PIDA/NaBr-mediated bromination of indoles, and Solorio-Alvarado[15] reported the electrophilic bromination of phenols and phenol-ethers by the PIDA–$AlBr_3$ system. Very recently, the use of PIDA and strong HBr or bromide salts was described.[16] Particularly, the use of $PhIBr_2$, **1,** (Scheme 3) is scarcely reported. In 1985, it was used by Macdonald and Narasimhan[17] for the nucleophilic substitution of alkyl iodides via oxidative ligand transfer; and by Cui and coworkers[18] for the *anti* addition of bromine to a double bond in one step of the synthesis of 24-methylenecholest-4-en-3β,6α-diol. No references regarding its preparation could be found.

In our previous studies,[19] the mixture of $PhI(OTFA)_2$ (PIFA) and TMSCl resulted in an excellent combination for the chlorination of a great variety of arenes in high yields, even when working at a multigram scale. Moreover, we confirmed the *in-situ* formation of $PhICl_2$ as reactive species. These results suggested us that we should test the combination PIFA-TMSBr in the bromination of arenes. To the best of our knowledge, the mixture PIFA-TMSBr has never been explored before.

**Results and discussion**

1,3,5-Triisopropylbenzene was selected as a model. Using the mixture PIFA-TMSBr (1:1.5 equiv) in dry dichloromethane (Table 1, entry 1) compound **2a** was isolated (78% yield). Better yield (90%) was obtained with 2 equiv. of TMSBr (Table 1, entry 2), presumably due to the full generation of $PhIBr_2$. Further equivalents of TMSBr (Table 1, entry 3) did not enhance the yield. We noticed worst results when the reaction was done in open air and/or with no dried solvent (Table 1, entries 4-6), probably due slow degradation of reagents. The use of other solvents such as DMF, toluene and THF did not improve the reaction yield (Table 1, entries 6 and 8). The change of PIFA to PIDA gave lower yield (Table 1, entries 2 *vs* 9).

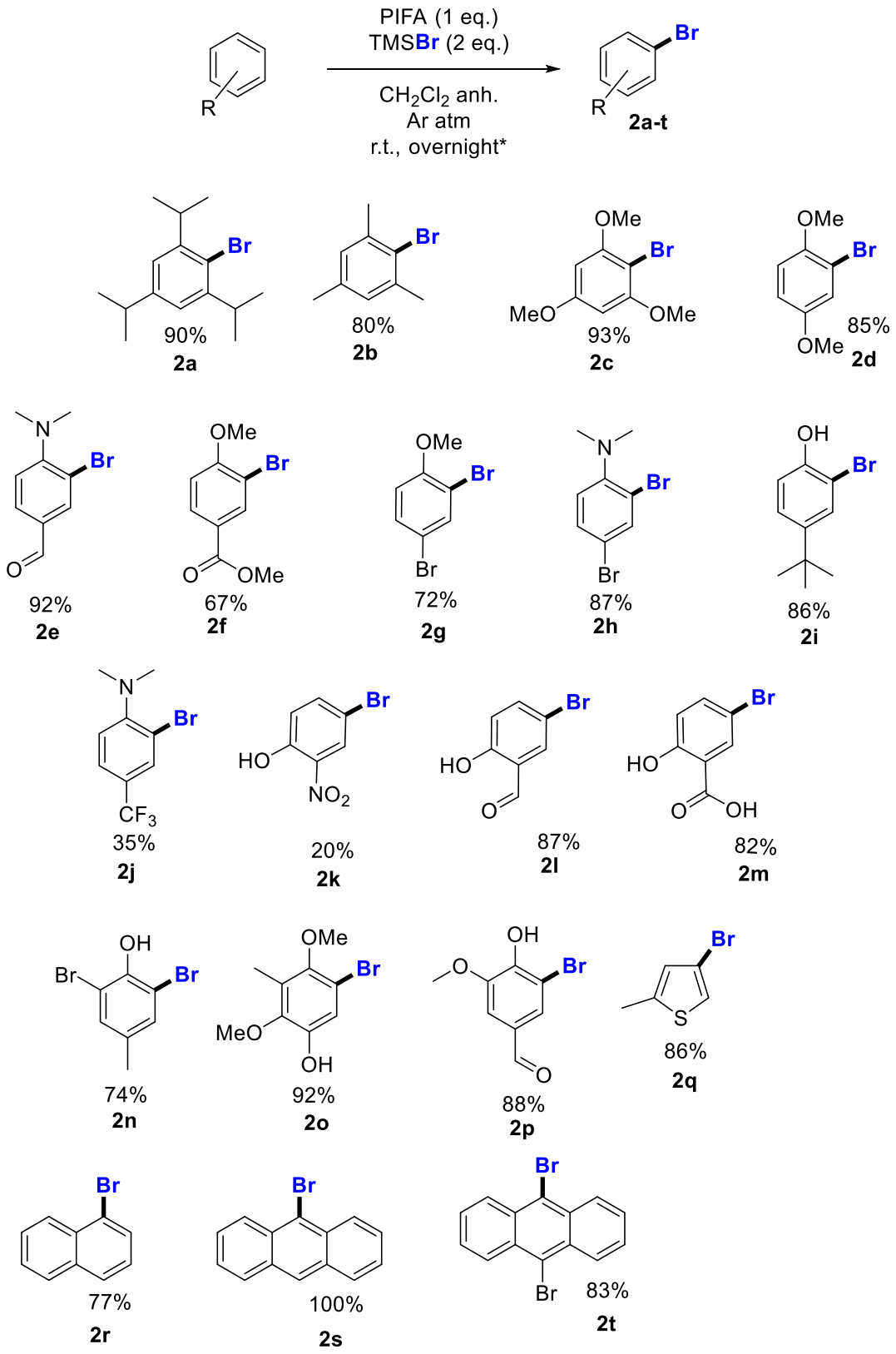
**Table 1.** Optimization of the reaction of 1,3,5-triisopropylbenzene and PIFA-TMSBr




| Entry | Solvent[a] | Equivalents TMSBr | Yield **2a** (%) |
|---|---|---|---|
| 1 | $CH_2Cl_2$ | 1.5 | 78 |
| 2 | $CH_2Cl_2$ | 2.0 | 90 |
| 3 | $CH_2Cl_2$ | 3.0 | 89 |
| 4 | $CH_2Cl_2$[b] | 2.0 | *n.d.* |
| 5 | $CH_2Cl_2$[c] | 2.0 | *n.d.* |
| 6 | DMF | 2.0 | 86 |
| 7 | PhMe | 2.0 | 64 |
| 8 | THF | 2.0 | 77 |
| 9[d] | $CH_2Cl_2$ | 2.0 | 81 |

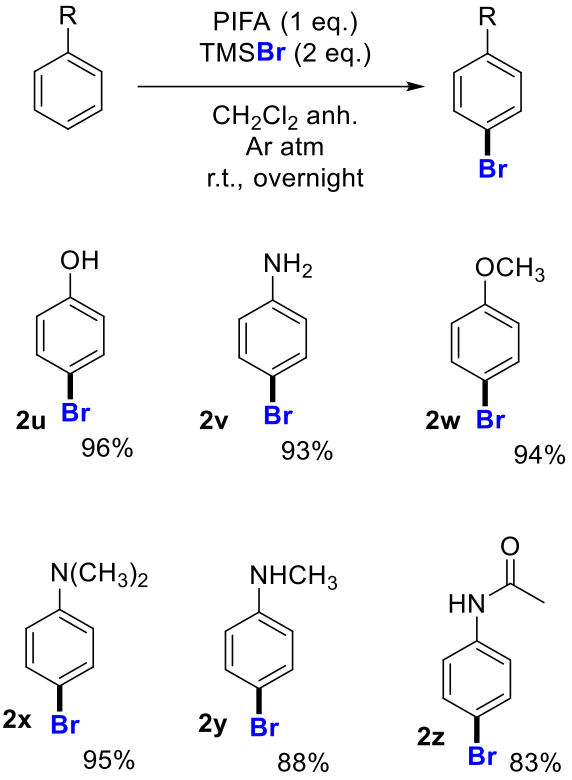
[a] Anhydrous solvent [b] Dry solvent and open-air reaction. [c] Wet solvent and open-air reaction. [d] Using PIDA-TMSBr.

After screening the reaction conditions, we followed to examine the substrate scope (Scheme 1). We first performed the reaction with trisubstituted symmetrical arenes. Compounds **2a-c** were prepared in high yields (80-93%). The highest yield (93%) was obtained for the strongly activated **2c**. Otherwise, deactivated arenes, such as 1,3,5-tribromobenzene or 4-trifluoromethylacetophenone did not react. Next, 1,4-disubstituted arenes were tested. As expected, those aromatics which possess almost one strong electron-donating group (-$OCH_3$, -OH, -$N(CH_3)_2$), furnished the reaction in good to high yields (**2d-2i:** 67-92%). The bromination of *p*-trifluorodimethylaniline and 2-nitrophenol was achieved in low yields, in agreement with the presence of a strong electron-withdrawing group. Moreover, two salicyl derivatives afforded **2l** (87%) and **2m** (82%) in excellent yields. Other phenols and phenolethers were assayed yielding excellent results. Especially fast bromination reactions (less than 5 minutes) were obtained for **2c,d,o,q**. Some nitrogen-based heterocycles such as pyrrole and indole, gave rise to complex crude reactions. In turn, excellent performance was found for naphthalene, anthracene and 9-bromoanthracene. The reaction conditions were tolerant with a large list of functional groups including easily oxidable aldehydes.




**Scheme 1.** Scope of the bromination of arenes using PIFA/TMSBr.*Especially fast bromination reactions (less than 5 minutes) were obtained for **2c**,**d**,**o**,**q**.

Then, we addressed our efforts to the problem of regioselectivity, given that efficient methodologies for the regioselective preparation of bromobenzenes are still required. Recently, Xia's group reported that the combination of Eosin Y with Selecfluor resulted in a regioselective *para*-brominating agent.[20] To our delight, we discovered that the treatment of mono-substituted activated arenes with PIFA/TMSBr led to *para* brominated products (**2u-z**) in excellent 83-96% yields (Scheme 2).



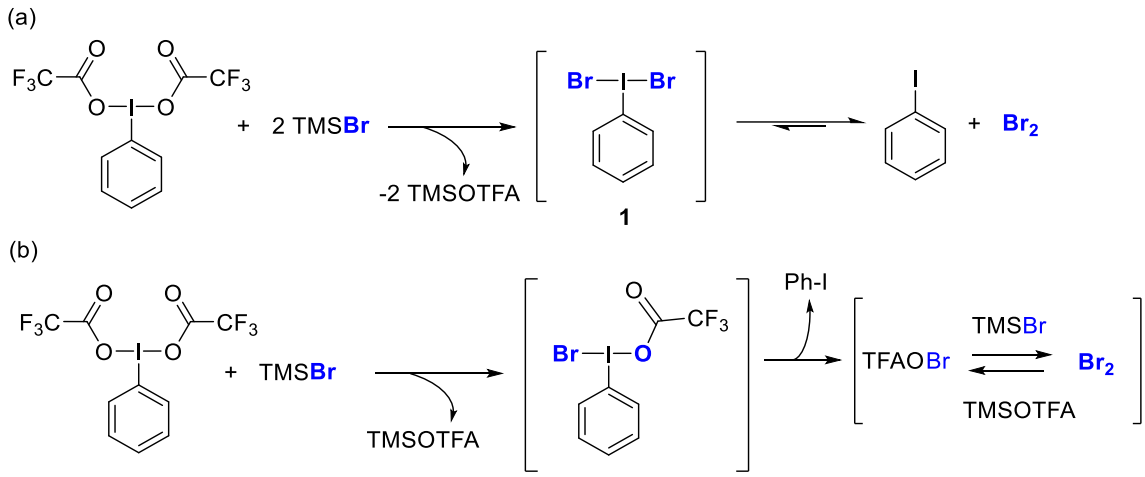

**Scheme 2.** Regioselective *para*-bromination in monosubstituted phenyl compounds.

To get insights into the mechanism, we performed a control experiment mixing 1 equivalent of PIFA and 2 equivalents of TMSBr (reaction conditions). $^{1}$H NMR analysis showed that after 5 minutes PIFA was consumed leading to the formation of 1 equiv. of PhI and 2 equiv. of $Me_3SiOCOCF_3$ (TMSOTFA, see SI). The unique signal in $^{19}$F NMR was assigned to this salt by comparison of with a commercial sample. The formation of two equivalents of TMSOTFA might be explained by the exchange of both OTFA ligands from PIFA by two bromine atoms, generating *in-situ* the $PhIBr_2$ which quickly reacts with the corresponding arene (Scheme 3 (a)). In its absence, **1** decomposes to PhI and $Br_2$. As OTFA is a better leaving ligand than OAc a more efficient formation of $PhIBr_2$ is expected. Other authors using PIDA and several inorganic halogen sources as $AlBr_3$, $ZnBr_2$ or HCl have proposed a non-symmetrical hypervalent iodine species as intermediate (PhI(OAc)X).[15,16] We have also proposed the formation of PhI(OTFA)Cl

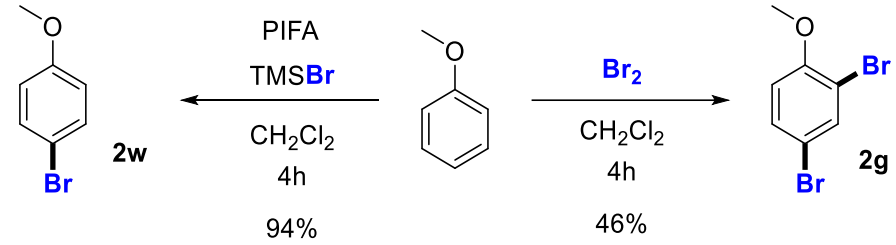
as reactive intermediate (detected by $^{1}H$ NMR) in the chlorination of arenes using PIFA and KCl.[19] In contrast, in this work using PIFA-TMSBr we could never detect the non-symmetrical hypervalent iodine PhI(OTFA)Br by spectroscopic techniques and we propose $PhIBr_2$ as reactive species. In the same way, when using PIFA-TMSCl, exchange of both OTFA ligands has been previously demonstrated.[19]

Moreover, It has been described that the non-symmetrical hypervalent iodine intermediate PhI(OTFA)Br, if formed, can evolve to give the $CF_3C(O)OBr$ (TFAOBr) salt (Scheme 3 (b)), a good brominating agent.[21] In our case TFAOBr could not be detected in $^{19}F$ NMR analysis of the mixture of 1 equivalent of PIFA and 2 equivalents of TMSBr (reaction conditions), which is an indirect probe that PhI(OTFA)Br is not formed.

A possible reaction pathway could be the direct bromination by the $Br_2$ generated from the reductive elimination of **1** (Scheme 3 (a)) as previously proposed by Evans.[11] Thus, we compared the evolution of the reaction of 1,3,5-trimethoxybenzene using $Br_2$ (1 equivalent) or PIFA-TMSBr as reagents. Both reactions were stopped after 5 minutes, obtaining **2c** in 45% (50% of 1,3,5-trimethoxybenzene recovered) and 88% yield, respectively. These results indicate that the proposed intermediate $PhIBr_2$ is more reactive than $Br_2$ under the same conditions. When we analyzed the bromination of anisole we observed that using $Br_2$ as reagent, 2,4-dibromoanisole, **2g**, was obtained in 46% yield in 4 hours. In contrast, using the PIFA-TMSBr mixture the bromination of anisole exclusively gave the *para* substitution in 94% yield (**2w**, Scheme 4). Thus, confirming that $Br_2$ is not the halogenating agent in our process. As mentioned before, Evans[11] proposed that $Br_2$ was responsible of the bromination of 1,4-dimethoxynapthalene on the bases of its slow disappearance of the reaction media (followed by UV-vis) when the arene was added. However, the same effect could be observed considering **1** as the reactive intermediate, due to the displacement of the equilibrium proposed in Scheme 3 (a). Finally, reagent $PhIBr_2$ (**1**) could not be isolated by mixing PIFA (1 equiv) and TMSBr (2 equiv) following the conditions previously reported to prepare $PhICl_2$.[19] Although di-acetoxy or di-chloro derivatives are stable, this is not the case for dibromoiodobenzene.[22] In fact, to stabilize I-Br bonds,[23] benziodoxoles were developed by C. Martin[22a] and D. C. Braddock.[22b]




**Scheme 3.** Possible reaction intermediates.




**Scheme 4.** Bromination in *para* or *ortho/para* positions.

In order to understand the main aspects that determine the regioselective bromination of these arenes, we performed Density Functional Theory[24] (DFT) based studies using the hybrid B3LYP functional[25] with the semiempirical D3 Grimme's correction.[26] Solvent effects were tackled by means of the Polarization Continuum (PCM) model.[27] All elements were computed with the 6-31+G* split valence basis set[28] including diffuse and polarization Gaussian functions, except in the case of iodine atoms, for which the LANL2DZ Effective Core Potential (ECP) and basis set were used.[29] All the calculations were carried out by means of the Gaussian 09 suite of programs.[30]

Interaction between methoxybenzene and $PhI(Br)_2$ led to a loose van der Waals reactive complex **RC1** (Figure 1). The profile of the Nucleus Independent Chemical Shift[31] (NICS) along the axis perpendicular to the average molecular plane of **RC1** shows a regular $\pi^2$-aromatic pattern,[32] slightly lower than that associated with methoxybenzene. However, in the zone between both reactants, the distortion of the NICS pattern indicates local diamagnetic shielding associated with the lone pairs of the hypervalent iodine atom. At closer distances between both

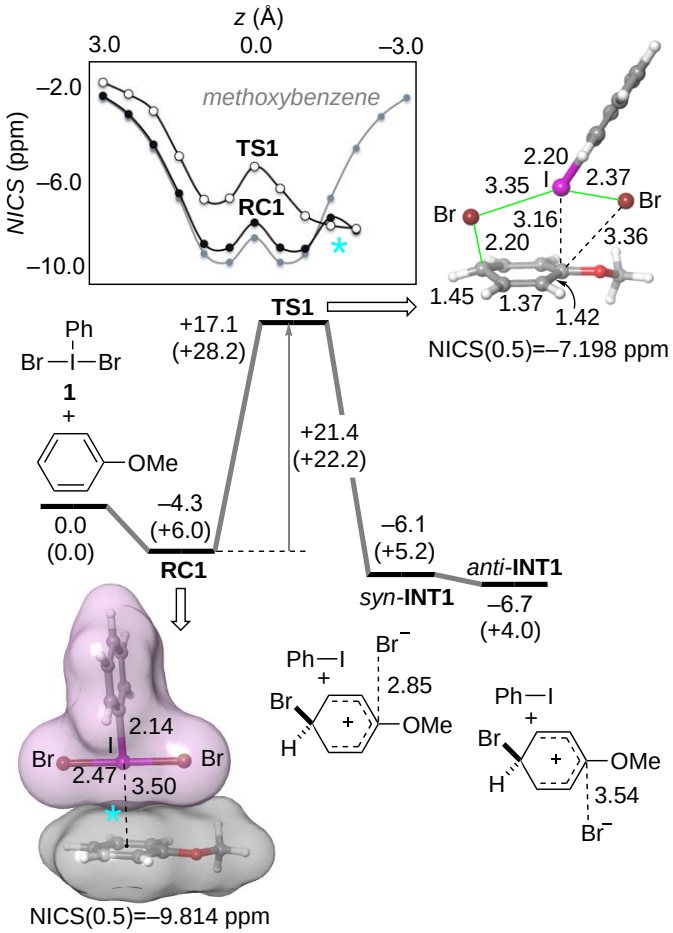



**Figure 1.** DFT results (B3LYP-D3(PCM=$CH_2Cl_2$)/6-31+G*&LANL2DZ level of theory) of the *para*-bromination of methoxybenzene. Nucleus Independent Chemical Shifts (NICS, in ppm) along the z-axis perpendicular to reactants, reactive complex (**RC1**) and transition structure (**TS1**) are shown. The NICS 0.5 Å below the molecular plane of methoxybenzene, denoted as NICS (0.5) are also given for **RC1** and **TS1**. The asterisk highlighted in blue indicates the local diamagnetic interaction between both reactants. Relative energies, in kcal/mol, are indicated for each stationary point. Numbers in parentheses correspond to the respective Gibbs energies, computed at 298 K. Bond distances are given in Å.

reactants the bromination step progresses to reach saddle point **TS1** (Figure 1). The new Br-C bond is quite advanced in **TS1** and the interaction between the remaining PhI and Br units with the carbon *ipso* to the methoxy group ensures the *para*-regioselectivity of the bromination with respect to the directing electron-releasing group. The reaction has an activation energy of ca. 21-22 kcal/mol, which parallels the partial loss of aromaticity associated with the addition process, as it is shown in the corresponding NICS profile (Figure 1). Formation of the C-Br bond constitutes the rate-limiting step of the complete reaction. Assuming a second order kinetics for this step, for normalized 1 M reactants and 298 K (the standard state in solution included in our calculations) the half-life $t_{1/2}$ of the reaction can be approximated as

$$t_{1/2} = \frac{1}{k[A]_0} \approx \frac{1}{[A]_0}\left[\frac{k_B \cdot 298}{h} exp\left(\frac{-\Delta G^a_{298}}{R \cdot 298}\right)\right]^{-1} = 3{,}146\ s$$

which corresponds to ca. 0.83 h and is in acceptable agreement with the experimentally observed reaction time of 4 h for complete conversion.

The next stationary point along the reaction coordinate is complex *syn*-**INT1**, in which there is a weak MeO(Ar)C···Br⁻ interaction. This intermediate evolves through a barrierless process towards the slightly more stable intermediate *anti*-**INT1**. These intermediates are stabilized by the presence of the phenyl iodide product resulting from the bromination step and by the methoxy group.

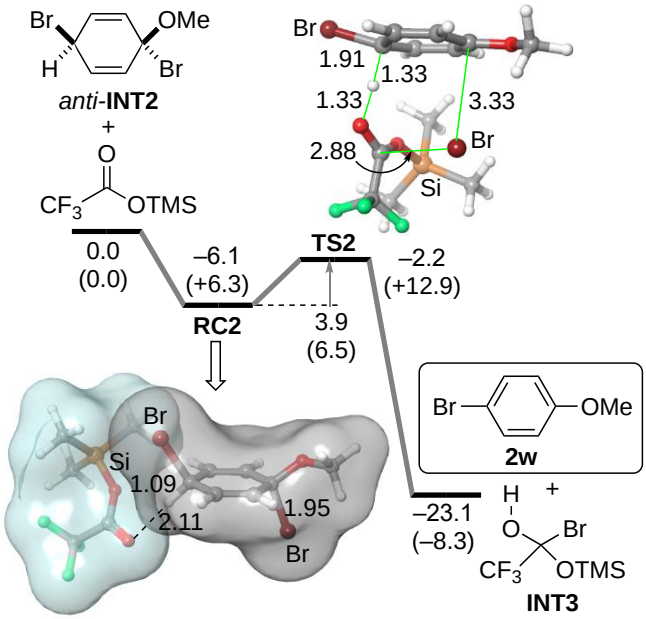



**Figure 2.** DFT results of the formation of 4-bromomethoxybenzene **2w** in the presence of trimetylsilyl trifluoroacetate. See Figure 1 caption for further details.

Intermediate *anti*-**INT1** can interact with one equivalent of TMSOTFA to yield cyclohexa-1,4-dienyl dibromide *anti*-**INT2**, in which the formation of the second C-Br bond has been completed (Figure 2). A fleeting van der Waals reactive complex **RC2** was located on the potential energy surface, from which concerted but asynchronous transition structure **TS2** is reached with an activation energy of only 4-6 kcal/mol. This cyclic saddle point corresponds to a type II dyotropic reaction[33] involving the concerted transfer of the H and Br atoms from *anti*-**INT2** to TMSOTFA. In this step, the aromaticity of the substrate is partially recovered in **TS2**, thus resulting in a lower activation energy. Finally, 1-bromo-4-methoxybenzene **2w** is formed together with tetrahedral intermediate **INT3** through an exothermic and exergonic step that

evolves to the formation of HBr and the recovery of one equivalent of TMSOTFA. This stepwise mechanism provided by the DFT calculations is compatible with the main features of the experimental results, namely the role of the electron releasing group and the *para*-orientation of the bromination with respect to this director substituent. Of course, when *para* positions are not available the *ortho* position with respect to the directing group would be the preferred one (Scheme 1).

We also investigated the direct bromination of anisole with two equivalents of $Br_2$ to yield 2,4-dibromoanisole **2g** (Scheme 4). The computed reaction profile at 298 K in dichloromethane solution is gathered in Figure 3. These calculations show a quite complex stepwise mechanism consisting in two consecutive addition-elimination processes on *para* and *ortho* positions of anisole. From reactive complex **RC3** addition of one bromine atom to the *para* position results in the formation of zwitterionic intermediate **INT4**. All our attempts to locate the corresponding transition structure met with no success. This can be related with the very advanced saddle points found by Smith[34a] and Liljenberg et al.[34b] in their studies on the bromination of benzene and anisole with $Br_2$ to yield bromobenzene and 4-bromoanisole **2w**, respectively. These authors found that the transition structures associated with the formation of the addition step showed C···Br distances of 2.04-2.13 Å, which correspond to an almost completely formed C-Br bond. Intermediate **INT4** can evolve towards an slightly more stable analogue **INT5**, whose elimination of the C4-H bond via **TS3** yields para-intermediate **2w** together with one equivalent of hydrobromic acid. This elimination step occurs with a calculated activation free energy of 9.9 kcal/mol. Intermediate **INT6** produces the formation of the second C2-Br bond via loose saddle point **TS4**. Addition intermediate **INT7** recovers its aromaticity via a second elimination step mediated by transition structure **TS5** to yield dibrominated product **2g** together with a second equivalent of hydrobromic acid. In summary, this mechanistic profile shows a multistep process involving many weakly bound ionic pairs that can evolve in other reaction pathways that can result in lower yields. In addition, our results show that the second bromination step in the presence of these intermediates is less kinetically demanding and therefore, the transformation of **2w** into **2g** is difficult to control.

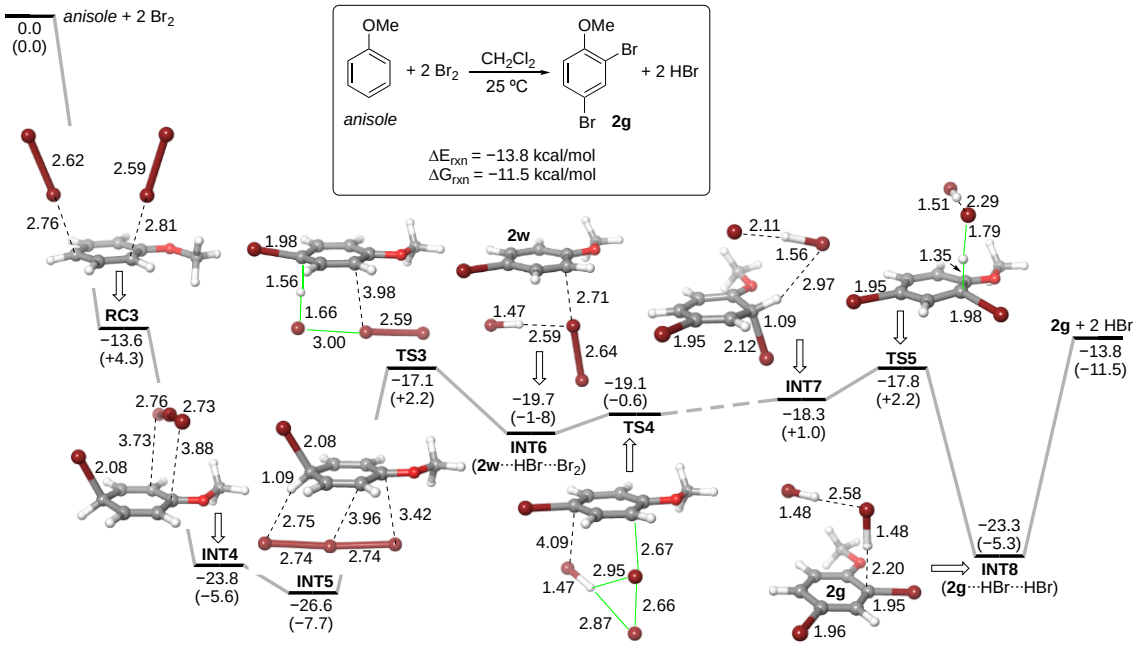
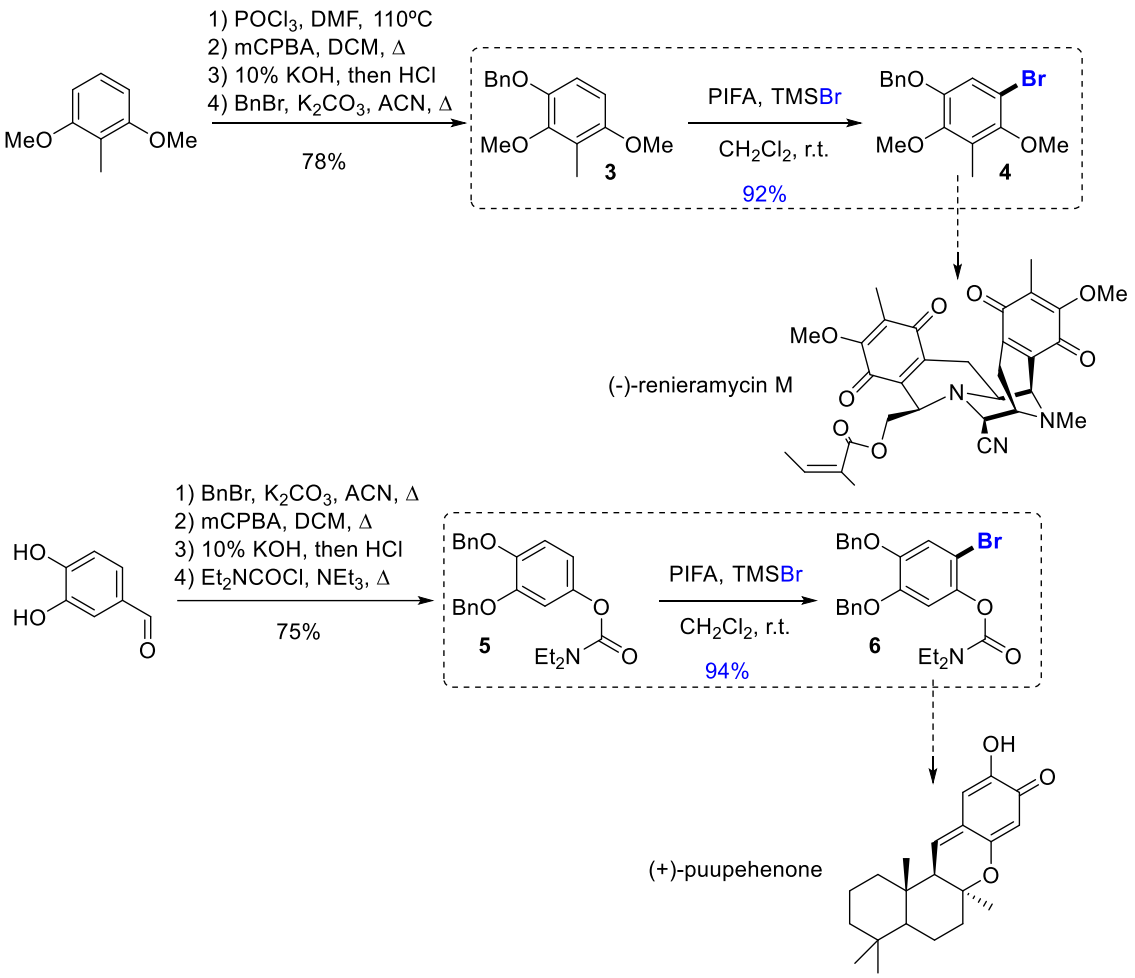


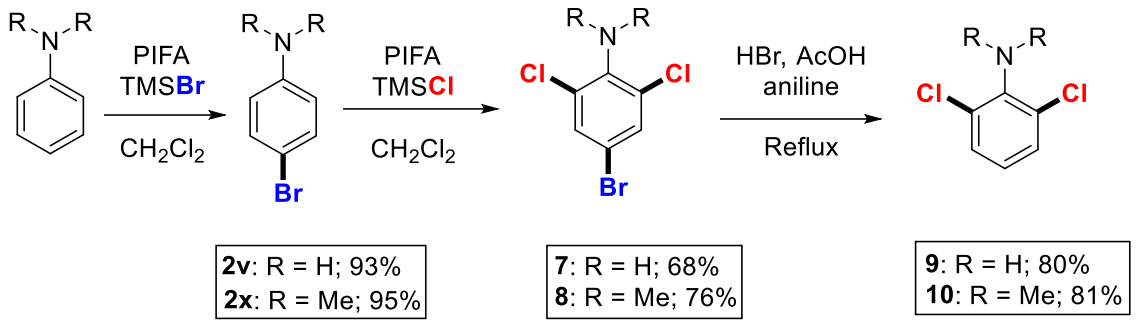

**Figure 3**. Computed reaction profile of the dibromination of anisole to yield 2,4-dibromoanisole **2g**. See Figure 1 caption for additional details.

In order to demonstrate the general applicability of this methodology, we have used our conditions in the monobromination of two densely substituted intermediates (**3** and **5,** which were prepared as previously described[35,36]) of the synthesis of high added valuable anticancer molecules (Scheme 5). By one hand, the bromination of **3**[35,36] gave **4** in a nicely 92% yield, a key intermediate of the synthesis of (-)-renieramycin M. This reaction is competitive with the previously described procedure[33] (NBS, 0ºC, 8h), which implied a column chromatography. Secondly, the bromination of **5**[36] afforded exclusively compound **6** (94%), which can be transformed to (+)-puupehenone.[37]




**Scheme 5.** Bromination key steps in the synthesis of valuable anticancer compounds.

As a synthetic application of PIFA combined with both TMSBr and TMSCl[19] we performed the synthesis shown in Scheme 6. 2,6-Dichloroaniline (**9**) is used in the preparation of the well-known anti-inflammatory drug Diclofenac.[38] Our proposal is based on the use of bromine as a useful protective group.[39] First, the PIFA-TMSBr system afforded **2w** and **2x** in 5 minutes (*para* isomers were exclusively achieved). Next, 4 equiv. of TMSCl in combination with PIFA (2 equiv.) were used for the dichlorination. Finally, debromination was performed in acid conditions obtaining **9** and **10**[40] in three steps in 51 and 59% overall yields respectively.




**Scheme 6.** Synthesis of **9** and **10**.

In summary, we have developed a mild, metal-free procedure for the bromination of arenes based on the combination of PIFA and TMSBr. The protocol resulted to be *para*-selective upon using activated aromatic substrates. To the best of our knowledge, no examples of *para* selective brominations of activated aromatic compounds based on the use of PIFA and TMSBr are reported. DFT calculations on the *para*-bromination of methoxybenzene as a model system revealed a stepwise mechanism in which the limiting step is the formation of the C-Br bond in the *para* position with respect to the methoxy substituent, which acts as the directing group through an electrostatic stabilization with the second bromine atom. The *trans*-1,4-dibromo intermediate yields 1-bromo-4-methoxybenzene by means of a type II dyotropic reaction with concomitant recovery of aromaticity, which is the driving force of this second stage of the reaction. The method proved to be useful in the synthesis of key intermediates of the synthesis of densely substituted biologically valuable compounds.

**Experimental section**

General Information

The chemicals and solvents have been purchased from Sigma Aldrich or Fluorochem. Solvents have been previously dried conveniently. GLC chromatography was performed on a capillary column (5% biphenyl and 95% dimethylpolysiloxane) of 15 m × 0.25 mm with a stationary phase diameter of 0.25 µm. Column chromatography was performed on silica gel (230−400 mesh). $^{1}$H NMR spectra were recorded operating at 250, 360, and 400 MHz. $^{13}$C NMR spectra were registered at 63, 91, and 101 MHz.

General procedure for the bromination reaction using PIFA-TMSBr

In a multi-reaction tube 1.8 mmol of PIFA (720 mg, 1 equiv.) were dissolved in 12 mL of dry $CH_2Cl_2$ under argon atmosphere. Next, 3.30 mmol of TMSBr (2.0 equiv.) were added to the solution. The clear solution turned clear orange. Then, the corresponding arene was added in

one portion (1.7 mmol) allowing the reaction to proceed at room temperature. When the reaction was over, the solution was poured into water and extractions with $CH_2Cl_2$ were performed. The organics were evaporated, and the crude was well dried under high vacuum yielding the desired bromoarene.

2-bromo-1,3,5-triisopropylbenzene (**2a**):[41] Colourless oil. From the reported procedure, 280 mg (81% yield) were obtained from 250 mg (1.22 mmol) of **1a**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 1.28 (d, $^3J_{(H,H)}$ = 7.5 Hz, 18H), 2.94 (m, 1H), 3.52 (m, 2H), 7.02 (s, 2H).

2-bromo-1,3,5-trimethylbenzene (**2b**):[42] Colourless oil. From the reported procedure, 662 mg (80% yield) were obtained from 500 mg (4.16 mmol) of **1b**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 2.31 (s, 3H), 2.44 (s, 6H), 6.95 (s, 2H). GC-MS: m/z 197.9 $(M)^+$, 199.9 $(M+2)^+$ and 119 $(M-Br)^+$.

2-bromo-1,3,5-trimethoxylbenzene (**2c**):[43] Yellowish solid. mp. 98-100ºC. From the reported procedure, 2,58 g (88% yield) were obtained from 2,00 g (11.90 mmol) of **1c**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 3.83 (s, 3H), 3.90 (s, 6H), 6.20 (s, 2H).

2-bromo-1,4-dimethoxylbenzene (**2d**):[44] Oil. From the reported procedure, 668 mg (85% yield) were obtained from 500 mg (3.62 mmol) of **1d**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 3.77 (s, 3H), 3.84 (s, 3H), 6.83 (bs, 2H), 7.14 (s, 1H). GC-MS: m/z 215.9 $(M)^+$, 217.9 $(M+2)^+$.

3-bromo-4-(dimethylamino)benzaldehyde (**2e**):[45] Solid. m.p. 51-53ºC. From the reported procedure, 492 mg (92% yield) were obtained from 350 mg (2.35 mmol) of **1e**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 2.89 (s, 6H), 7.02 (d, $^3J_{(H,H)}$ = 8.9 Hz, 1H), 7.66 (dd, $^3J_{(H,H)}$ = 8.9 Hz, $^4J_{(H,H)}$ = 1.8 Hz, 1H), 7.96 (d, $^4J_{(H,H)}$ = 1.8 Hz, 1H), 9.74 (s, 1H).

Methyl 3-bromo-4-methoxybenzoate (**2f**):[46] Solid. m.p. 97-99ºC. From the reported procedure, 295 mg (67% yield) were obtained from 300 mg (1.80 mmol) of **1f**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 3.91 (s, 3H), 3.98 (s, 3H), 6.95 (d, $^3J_{(H,H)}$ = 8.6 Hz, 1H), 7.98 (d, $^3J_{(H,H)}$ = 8.6 Hz, $^3J_{(H,H)}$ = 2.0 Hz, 1H), 8.13 (d, $^3J_{(H,H)}$ = 2.0 Hz, 1H). GC-MS: m/z 243.9 $(M)^+$, 245.9 $(M+2)^+$.

2,4-dibromo-1-methoxybenzene (**2g**):[47] Solid. m.p. 58-60ºC. From the reported procedure, 103 mg (72% yield) were obtained from 100 mg (0.53 mmol) of **1g**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 3.90 (s, 3H), 6.79 (d, $^3J_{(H,H)}$ = 8.8 Hz, 1H), 7.40 (dd, $^3J_{(H,H)}$ = 8.8 Hz, $^4J_{(H,H)}$ = 2.4 Hz, 1H), 7.69 (d, $^4J_{(H,H)}$ = 2.4 Hz, 1H).

2,4-dibromo-*N,N*-dimethylaniline (**2h**):[48] Oil. From the reported procedure, 485 mg (87% yield) were obtained from 400 mg (2.00 mmol) of **1h**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ =

2.80 (s, 6H), 6.96 (d, $^{3}J_{(H,H)}$ = 8.8 Hz, 1H), 7.38 (dd, $^{3}J_{(H,H)}$ = 8.8 Hz, $^{4}J_{(H,H)}$ = 2.4 Hz, 1H), 7.71 (d, $^{4}J_{(H,H)}$ = 2.4 Hz, 1H).

2-bromo-4-(*tert*-butyl)phenol (**2i**):[49] Solid. m.p. 49-51ºC. From the reported procedure, 262 mg (86% yield) were obtained from 200 mg (1.33 mmol) of **1i**. $^{1}$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 1.32 (s, 9H), 5.45 (bs, 1H), 6.99 (d, $^{3}J_{(H,H)}$ = 8.7 Hz, 1H), 7.26 (dd, $^{3}J_{(H,H)}$ = 8.7 Hz, $^{4}J_{(H,H)}$ = 2.5 Hz, 1H), 7.49 (d, $^{4}J_{(H,H)}$ = 2.5 Hz, 1H).

2-bromo-*N,N*-dimethyl-4-(trifluoromethyl)aniline (**2j**):[50] Oil. From the reported procedure, 99 mg (35% yield) were obtained from 200 mg (1.06 mmol) of **1j**. $^{1}$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 2.89 (s, 6H), 7.11 (d, $^{3}J_{(H,H)}$ = 8.4 Hz, 1H), 7.54 (d, $^{3}J_{(H,H)}$ = 8.4, 1H), 7.81 (bs, 1H).

4-bromo-2-nitrophenol (**2k**):[51] Solid. m.p. 88-91ºC. From the reported procedure, 157 mg (20% yield) were obtained from 500 mg (3.59 mmol) of **1k**. $^{1}$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 7.09 (d, $^{3}J_{(H,H)}$ = 8.9 Hz, 1H), 7.68 (dd, $^{3}J_{(H,H)}$ = 8.9 Hz, $^{4}J_{(H,H)}$ = 2.4 Hz, 1H), 8.27 (d, $^{4}J_{(H,H)}$ = 2.4 Hz, 1H), 10.51 (s, 1H).

5-bromo-2-hydroxybenzaldehyde (**2l**):[52] Solid. m.p. 50-52ºC. From the reported procedure, 7.16 g (87% yield) were obtained from 5.00 g (40.94 mmol) of **1l**. $^{1}$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 6.93 (d, $^{3}J_{(H,H)}$ = 8.8 Hz, 1H), 7.62 (dd, $^{3}J_{(H,H)}$ = 8.8 Hz, $^{4}J_{(H,H)}$ = 2.4 Hz, 1H), 7.69 (d, $^{4}J_{(H,H)}$ = 2.4 Hz, 1H), 9.86 (s, 1H), 10.95 (s, 1H). GC-MS: m/z 199.9 $(M)^{+}$, 201.9 $(M+2)^{+}$.

5-bromo-2-hydroxybenzoic acid (**2m**):[53] Solid. m.p. 205-207ºC. From the reported procedure, 1.29 g (82% yield) were obtained from 1.00 g (7.24 mmol) of **1m**. $^{1}$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 6.95 (d, $^{3}J_{(H,H)}$ = 8.8 Hz, 1H), 7.62 (dd, $^{3}J_{(H,H)}$ = 8.8 Hz, $^{4}J_{(H,H)}$ = 2.4 Hz, 1H), 8.05 (d, $^{4}J_{(H,H)}$ = 2.4 Hz, 1H), 10.38 (s, 1H).

2,6-dibromo-4-methylphenol (**2n**):[54] Solid. m.p. 47-49ºC. From the reported procedure, 265 mg (74% yield) were obtained from 200 mg (1.07 mmol) of **1n**. $^{1}$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 2.28 (s, 3H), 5.73 (s, 2H).

5-bromo-2,4-dimethoxy-3-methylphenol (**2o**):[55] Oil. From the reported procedure, 134 mg (91% yield) were obtained from 100 mg (0.60 mmol) of **1o**. $^{1}$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 2.27 (s, 3H), 3.77 (s, 3H), 3.84 (s, 3H), 5.79 (s, 1H).

3-bromo-4-hydroxy-5-methoxybenzaldehyde (**2p**):[56] Solid. m.p. 213-214ºC. From the reported procedure, 267 mg (88% yield) were obtained from 200 mg (1.31 mmol) of **1p**. $^{1}$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 4.01 (s, 3H), 6.57 (bs, 1H), 7.37 (d, $^{4}J_{(H,H)}$ = 1.6 Hz, 1H), 7.66 (d, $^{4}J_{(H,H)}$ = 1.6 Hz, 1H), 9.81 (s, 1H). GC-MS: m/z 231.9 $(M)^{+}$, 233.9 $(M+2)^{+}$.

4-bromo-2-methylthiophene (**2q**):[57] Oil. From the reported procedure, 766 mg (86% yield) were obtained from 500 mg (5,00 mmol) of **1q**. $^1$H NMR (400 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 2.50 (s, 1H), 6.71 (m, 1H), 7.00 (d, $^4J_{(H,H)}$ = 3.6 Hz, 1H).

1-bromonaphthalene (**2r**):[44] Oil. From the reported procedure, 249 mg (77% yield) were obtained from 200 mg (1.56 mmol) of **1r**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 4.00 (s, 3H), 6.57 (bs, 1H), 7.38 (d, $^4J_{(H,H)}$ = 1.6 Hz, 1H), 7.66 (d, $^4J_{(H,H)}$ = 1.6 Hz, 1H), 9.81 (s, 1H).

9-bromoanthracene (**2s**):[58] Solid. m.p. 98-99.5ºC. From the reported procedure, 288 mg (100% yield) were obtained from 200 mg (7.24 mmol) of **1s**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 7.57 (m, 4H), 8.03 (m, 2H), 8.57 (m, 3H).

9,10-dibromoanthracene (**2t**):[59] Solid. m.p. 224-226ºC. From the reported procedure, 217 mg (83% yield) were obtained from 200 mg (0.78 mmol) of **1t**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 7.66 (m, 4H), 8.61 (m, 4H). GC-MS: m/z 335.8 $(M)^+$, 333.8 $(M-2)^+$, 337.8 $(M+2)^+$.

4-bromophenol (**2u**):[60] Solid. m.p. 60-61ºC. From the reported procedure, 352 mg (96% yield) were obtained from 200 mg (2.12 mmol) of **1u**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 5.76 (s, 1H), 6.75 (d, $^3J_{(H,H)}$ = 8.9 Hz, 2H), 7.35 (d, $^3J_{(H,H)}$ = 8.9 Hz, 2H).

4-bromoaniline (**2v**):[61] Solid. m.p. 58-60ºC. From the reported procedure, 343 mg (93% yield) were obtained from 200 mg (2.14 mmol) of **1v**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 3.67 (bs, 2H), 6.58 (d, $^3J_{(H,H)}$ = 9.0 Hz, 2H), 7.26 (d, $^3J_{(H,H)}$ = 9.0 Hz, 2H). GC-MS: m/z 170.9 $(M)^+$, 172.9 $(M+2)^+$ and 92 $(M-Br)^+$.

4-bromoanisole (**2w**):[62] Oil. From the reported procedure, 325 mg (94% yield) were obtained from 200 mg (1.85 mmol) of **1w**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 3.80 (s, 3H), 6.81 (d, $^3J_{(H,H)}$ = 9.0 Hz, 2H), 7.40 (d, $^3J_{(H,H)}$ = 9.0 Hz, 2H). GC-MS: m/z 185.9 $(M)^+$, 187.9 $(M+2)^+$.

4-bromo-(*N,N*)-dimethylaniline (**2x**):[63] Solid. m.p. 51-53ºC. From the reported procedure, 314 mg (95% yield) were obtained from 200 mg (1.65 mmol) of **1x**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 2.95 (s, 3H), 6.62 (d, $^3J_{(H,H)}$ = 8.9 Hz, 2H), 7.34 (d, $^3J_{(H,H)}$ = 8.9 Hz, 2H).

4-bromo-(*N*)-methylaniline (**2y**):[64] Oil. From the reported procedure, 228 mg (88% yield) were obtained from 150 mg (1.40 mmol) of **1y**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 2.84 (s, 3H), 3.69 (bs, H), 6.56 (d, $^3J_{(H,H)}$ = 9.0 Hz, 2H), 7.16 (d, $^3J_{(H,H)}$ = 9.0 Hz, 2H).

*N*-acetyl-4-bromoaniline (**2z**):[65] Solid. m.p. 166-169ºC. From the reported procedure, 328 mg (83% yield) were obtained from 250 mg (1.85 mmol) of **1z**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 2.19 (s, 3H), 7.30 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H), 7.47 (d, $^3J_{(H,H)}$ = 8.8 Hz, 2H).

1-(benzyloxy)-5-bromo-2,4-dimethoxy-3-methylbenzene (**4**):[35] Oil. Following the general procedure, 252 mg were obtained (92% yield) after column chromatography purification from 210 mg (0.81 mmol) of **3**. Oil. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 2.29 (s, 3H), 3.79 (s, 3H), 3.86 (s, 3H), 5.08 (s, 2H), 7.04 (s, 1H), 7.43 (m, 5H).

4,5-bis(benzyloxy)-2-bromophenyl diethylcarbamate (**6**):[37] Oil. Following the general procedure, 297 mg were obtained (94% yield) from 265 mg (0.65 mmol) of **5**. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 1.28 (m, 6H), 3.47 (m, 4H), 5.12 (s, 2H), 5.14 (s, 3H), 6.93 (s, 1H), 7.16 (s, 1H), 7.44 (m, 10H).

Synthetic procedure for the preparation of **7**, **8**, **9** and **10**:

4-bromo-2,6-dichloroaniline (**7**):[66] Synthesized following the method previously reported in our group,[20] 190 mg (68% yield) were obtained from 200 mg (1.16 mmol) of 4-bromoaniline (**2v**). Solid, m.p. 82-85ºC. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 4.48 (bs, 2H), 7.34 (s, 2H).

4-bromo-2,6-dichloro-*N*,*N*-dimethylaniline (**8**):[67] Synthesized following the method previously reported in our group,[19] 408 mg (76% yield) were obtained from 400 mg (2.00 mmol) of 4-bromo-*N*,*N*-dimethylaniline(**2x**). Oil. $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 3.04 (s, 6H), 7.38 (s, 2H).

2,6-dichloroaniline (**9**):[68] Prepared following the reported procedure.[38] 322 mg (80% yield) were obtained from 600 mg (2.49 mmol) of 4-bromo-2,6-dichloroaniline (**7**). Oil, $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 4.47 (bs, 2H), 6.64 (t, $^3J_{(H,H)}$ = 8.5 Hz, 1H) 7.19 (d, $^3J_{(H,H)}$ = 8.5 Hz, 2H).

2,6-dichloro-*N,N*-dimethylaniline (**10**):[69] Prepared following the reported procedure.[39] 287 mg (81% yield) were obtained from 500 mg (1.86 mmol) of 4-bromo-2,6-dichloro *N*,*N*-dimethylaniline (**8**). Oil, $^1$H NMR (250 MHz, [D]$CDCl_3$, 25ºC, TMS): δ = 2.92 (s, 6H), 6.98 (t, $^3J_{(H,H)}$ = 8.4 Hz, 1H) 7.29 (d, $^3J_{(H,H)}$ = 8.4 Hz, 2H).

**Associated content**

The Supporting Information includes the $^1$H NMR spectra, the CG-MS chromatograms and the details of the computational data.

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