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Unprecedented Directing Group Ability of Cyclophanes in Arene Fluorinations with Diaryliodonium Salts

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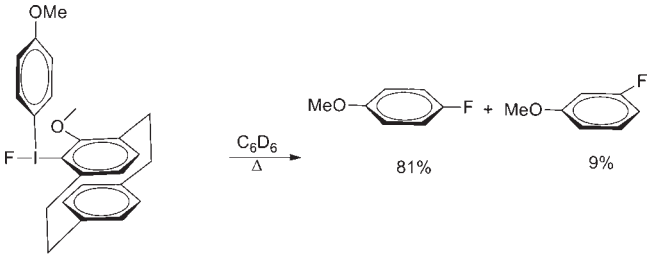
ABSTRACT



For the first time it is shown that exceptionally electron-rich arene rings can be fluorinated exclusively during the reductive elimination reactions of diaryliodonium fluorides. The 5-methoxy[2.2]paracyclophan-4-yl directing group simultaneously reduces unproductive aryne chemistry and eliminates ligand exchange reactions by a combination of steric and electronic effects. Use of the cyclophane directing group permits an unprecedented degree of control in fluorination reactions of diaryliodonium salts.

Rapid late-stage introduction of fluorine into biologically active compounds is essential for the synthesis of ^{18}F-labeled radiotracers for positron emission tomography.[1−3] Although significant advances in electrophilic radiofluorination have been made recently,[4] nucleophilic, fluoride-based approaches to radiotracers are preferred in imaging applications where radiochemical purity is essential.[5] For aromatic compounds bearing electron-withdrawing groups, nucleophilic aromatic substitution (S_NAr) of halide, nitro, or trimethylamine leaving groups by fluoride is a highly efficient process.[6−10] However, functionalization of electron-rich arenes with fluoride requires mediation by transition metal[11] or hypervalent main group atoms.

The reductive elimination of aryl fluorides from diaryliodonium salts was pioneered by Pike for arene radiofluorination.[12−14] Aided by our access to anhydrous fluoride reagents,[15] we were able to demonstrate that removal of inorganic salts from the reaction medium and the use of relatively nonpolar solvents dramatically increase the yields of fluorinated arenes from diaryliodonium fluorides.[16] Here we address some of the remaining roadblocks to efficient fluorination using I(III) compounds.

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The reductive elimination regiochemistry of diaryliodonium fluorides is generally controlled by electronic substituent effects; the most electron-poor ring is fluorinated selectively, and the electron-rich aryl iodide is eliminated. However, the extent to which electronic control can be utilized is limited, since highly electron-rich rings promote nonproductive decomposition reactions of diaryliodonium salts, presumably by inner-sphere redox processes. As an example, diaryliodonium salts featuring 4-(dialkylamino)phenyl groups have not been isolated, despite attempts to do so.[17] A second consideration is the surprisingly labile nature of aryl rings on I(III) fluorides; we demonstrated recently that rapid aryl group exchange among diaryliodonium fluorides occurs at room temperature in acetonitrile.[18] Here we show that appropriately substituted cyclophane ligands on iodine solve simultaneously the ligand exchange and regiospecificity problems by means of the same stereoelectronic effect.

Paracyclophane substituents have been shown to be superior directing groups for reductive elimination reactions of diaryliodonium salts;[19] regiospecificity is obtained even when electron-rich aryl rings, such as 4-methoxyphenyl, are functionalized. Significant out of plane steric bulk provided by the "capping" aryl ring results in a highly congested, strongly destabilized (by >4 kcal/mol) transition state for cyclophane functionalization. A rise in the free energy of activation for cyclophane functionalization steers the nucleophile toward the second aryl substituent. Regiospecific arene functionalization was demonstrated with the weakly basic azide, acetate, phenoxide, thiocyanate, and thiophenoxide nucleophiles. However, regiocontrol was lost when the more strongly basic trifluoroethoxide nucleophile was used; this basic group appeared to promote a mode of decomposition that involved formation of aryne intermediates.[19] The similar basicities of fluoride and trifluoroethoxide in polar aprotic solvents (CF_3CH_2OH, pK_a = 23.5; HF, pK_a = 15 in DMSO)[20] implied that aryne chemistry could also be a significant side reaction in cyclophane directed fluorinations of diaryliodonium salts.

(4-Methoxyphenyl)([2.2]paracyclophan-4-yl)iodonium hexafluorophosphate **1(PF$_6$)** and (4-methoxyphenyl)-((7-methoxy[2.2]paracyclophan-4-yl)iodonium hexafluorophosphate **2(PF$_6$)** (Figure 1) were prepared as described previously[19] and converted to the fluoride salts by ion exchange with anhydrous tetramethylammonium fluoride[21] (TMAF) in acetonitrile. The residual $TMAPF_6$ was removed by evaporation of the solvent, suspension of the remaining solid in benzene, and passage of this solution through a 0.2 μm PTFE filter. NMR (^{1}H and ^{19}F) and ES-MS spectra of **1(F)** and **2(F)** were consistent with a single species in solution, indicating that fluoride-promoted aryl group exchange in diaryliodonium fluorides is suppressed by the cyclophane substituent. Thermal decomposition

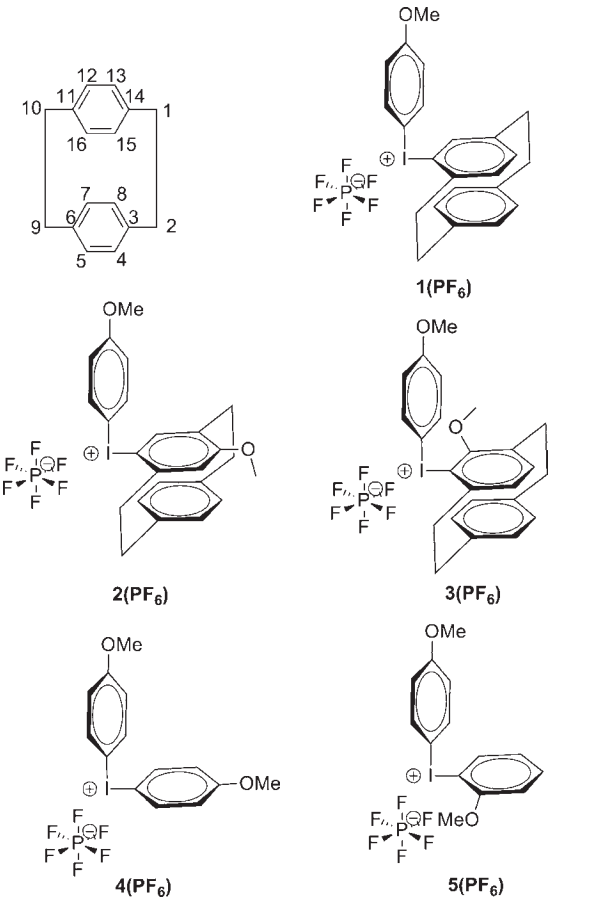

Figure 1. Numbering of the [2.2]paracyclophane ring system and the structures of the diaryliodonium hexafluorophosphate salts discussed in this work.

reactions of **1(F)** and **2(F)** (140 °C, d_6-benzene, 15 min) gave a mixture of fluorinated products (Figure 2). The relatively poor selectivity observed for arene fluorination contrasts strongly with the excellent selectivity observed previously for weakly basic nucleophiles (Table 1). Tellingly, roughly equal amounts of 4-fluoro-7-methoxy[2.2]paracyclophane and 4-fluoro-8-methoxy[2.2]paracyclophane were formed during the thermal decomposition reaction of **2(F)**, implicating arynes as likely reactive intermediates. Although the greater susceptibility of the relatively electron-rich cyclophane ligand to deprotonation is not well understood currently, we pursued a simple blocking strategy to suppress aryne formation and to restore regiocontrol.

(4-Methoxyphenyl)(5-methoxy[2.2]paracyclophan-4-yl)-iodonium hexafluorophosphate, **3(PF$_6$)**, in which both sites ortho to the I(III) center are substituted, was synthesized from 4-bromo[2.2]paracyclophane,[22] as is shown in Figure 3. Metal−halogen exchange yielded the organolithium reagent, which was quenched with trimethylborate and oxidized with hydrogen peroxide.[23] To introduce a halogen atom at the

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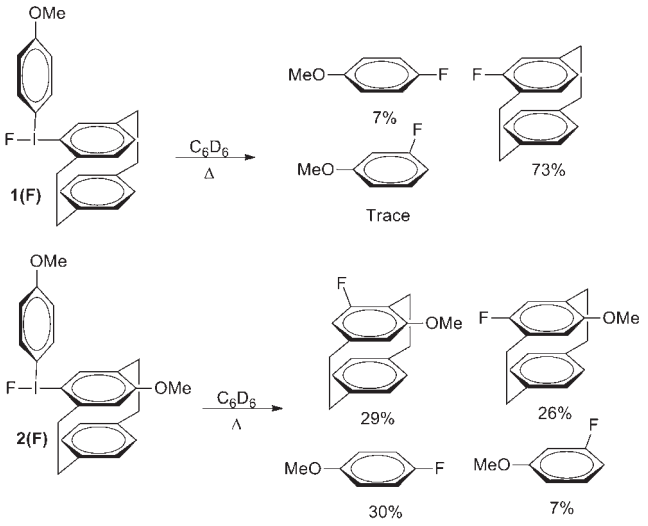

Figure 2. Thermal decomposition of [2.2]paracyclophane-substituted diaryliodonium fluorides **1(F)** and **2(F)**.

Table 1. Yields[a] of Reductive Elimination Products from **1(X)** and **2(X)** with Various Nucleophiles

	1(X)		2(X)	
X	MeOPh-X[a]	Cyc-X[a]	MeOPh-X	Cyc-X
N_3	86	14	96	0
SCN	81	18	92	0
OPh	51	40	84	0
SPh	43	52	82	0
OAc	68	31	51	0
OCH_2CF_3	19	39	42[b] (22+ 20)	37[b] (18 + 19)
F	7	73	37[b] (30 + 7)	55[b] (29 + 26)

[a] All yields were determined by ^{1}H NMR spectroscopy and confirmed by GC-MS. The products are functionalized anisoles (MeOPh-X) and functionalized paracyclophanes (Cyc-X). [b] Total amount of two different regioisomers. Numbers in parentheses refer to the total amount of expected and rearranged functionalized product, respectively

5-position, ortho-lithiation required installation of the diethylcarbamoyl directing group, as was reported previously.[24,25] (Direct lithiation of 4-methoxy-[2.2]paracyclophane was not successful in our hands; modeling indicated that steric congestion forces the methyl group above the cyclophane ring, thereby aligning the oxygen lone pairs in an inappropriate geometry to coordinate an incoming organolithium reagent.) Transmetalation with zinc chloride was essential for successful introduction of the 4-methoxyphenyliodonium diacetate moiety; the corresponding cyclophanyltributylstannane could not be coaxed to "transmetalate" with 4-methoxyphenyliodonium diacetate under any standard conditions.[26]

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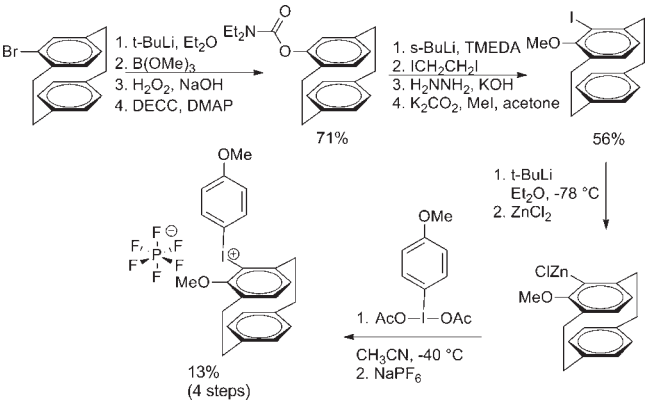

Figure 3. Synthesis of **3(PF$_6$)**.

3(PF$_6$) was converted to **3(F)** by ion exchange with anhydrous TMAF in acetonitrile and desalted according to the procedure described previously for **2(F)**. ^{1}H NMR spectra of **3(F)** in both acetonitrile and benzene showed no evidence of aryl group exchange.

Thermal decomposition of **3(F)** at 140 °C (15 min) gave a mixture of 4-fluoro- (72%) and 3-fluoroanisole (15%). Small amounts of inorganic silicon fluorides were also formed, presumably from the reaction of free fluoride or bifluoride with the borosilicate glass NMR tube. No fluorinated cyclophane was detected in the reaction mixture, supporting the hypothesis that aryne formation was largely responsible for the fluorocyclophanes observed during the thermal decomposition of **2(F)**, and confirming Chun and co-workers' observations that the methoxy group is not an effective ortho-director.[27]

In an attempt to gauge the temperature-dependence of the fluorination selectivity, thermolysis reactions of **3(F)** were also conducted at 80 °C in benzene (6 h). Reactions run at this temperature were a bit more selective, but production of 3-fluoroanisole could not be suppressed completely (Figure 4).

The generation of significant amounts of 3-fluoroanisole from the decomposition of **3(F)** contrasts with the trace amounts formed under identical conditions from the symmetrical compound bis(4-methoxyphenyl)iodonium fluoride, **4(F)**. However, the more closely related, unsymmetrically substituted iodonium salt, (2-methoxyphenyl)(4-methoxyphenyl)iodonium fluoride, **5(F)**, provides 2-fluoroanisole (59%), 3-fluoroanisole (15%), and 4-fluoroanisole (25%) at high temperature (benzene, 140 °C, 15 min), and 2-fluoroanisole (65%), 3-fluoroanisole (9%), and 4-fluoroanisole (23%) at 80 °C. These results suggest that a methoxy group ortho to the I(III) center promotes aryne formation. Modeling (B3LYP/DGDZVP, ZPE, and thermal corrections) of the ground state structures of the **4(F)** and **5(F)** along with the structures of the corresponding diaryliodonium cations (Figure 5) indicates that an ortho

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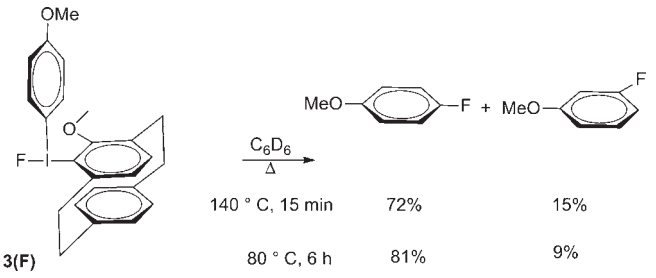

Figure 4. Thermal decomposition of **3(F)**.

methoxy substituent stabilizes an I(III) center to a greater extent than a para methoxy group and reduces the gas phase fluoride ion affinity of the I(III) by 1.52 kcal/mol. Weaker I−F interactions should lead to an increase in fluoride ion basicity, leading, in turn, to a more accessible aryne pathway.

In summary, here we have demonstrated that cyclophane-derived diaryliodonium salts bearing the electron-rich 4-methoxyphenyl substituent can yield fluorinated anisoles exclusively. Previously, the 4-methoxyphenyl group was considered to be the "gold-standard" directing group for radiochemical fluorinations of diaryliodonium salts, and 4-fluoroanisole could not be obtained except in low yield from the symmetrical iodonium salt.[12] The cyclophane ligand in **2(F)** was shown to be resistant to fluorination through a reductive elimination pathway, but the combination of cyclophane steric demand and electron donation of the *p*-methoxy substituent enables easy access to a competing aryne fluorination pathway. Blocking of the position ortho to the I(III) center in **3(F)** precludes cyclophane aryne formation and results in exclusive fluorination of the anisole ring. The use of cyclophane as a directing group for I(III)-mediated fluorinations is a promising approach, particularly if highly electron-rich

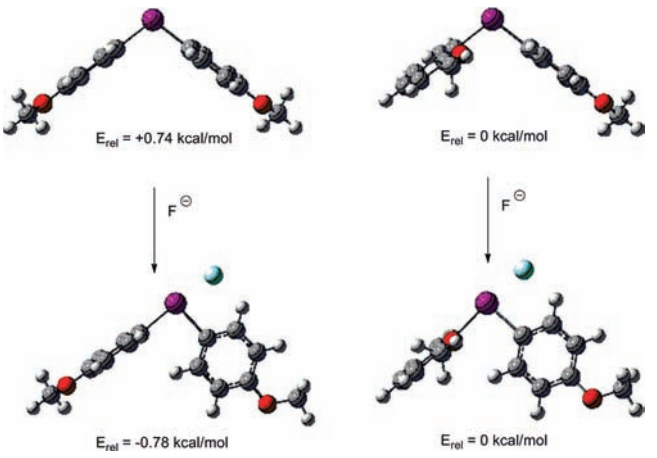

Figure 5. Calculated (B3LYP/DGDZVP) optimized structures and relative energies of the (2-methoxyphenyl)4-methoxyphenyliodonium cation (top right), the bis(4-methoxyphenyl) iodonium cation (top left), **4(F)** (bottom left), and **5(F)**, bottom right.

fluorinated aromatic compounds are the targets. Efforts are underway to streamline the synthesis of cyclophane-substituted diaryliodonium salts to make these compounds more accessible.

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Supporting Information Available. Experimental procedures and analytical data for all new compounds and synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.