ORGANOMETALLICS

Competitive Aryl–Fluorine and Aryl–Halogen (Halogen = Cl, Br) Bond Cleavage with Iridium Porphyrin Complexes

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Supporting Information

ABSTRACT: Base-promoted competitive Ar–F and Ar–X (X = Cl, Br) bond cleavage with iridium porphyrin complexes was investigated. Mechanistic studies suggested that Ir(ttp)⁻ (ttp = 5,10,15,20-tetra-*p*-tolylporphyrinato dianion) cleaves the Ar–F bond via nucleophilic aromatic substitution and Ir₂(ttp)₂ cleaves the Ar–X (X = Cl, Br) bond via metalloradical *ipso* substitution. Therefore, a stronger base, polar solvent, lower temperature, and iridium anion precursor favor Ar–F X = Cl, Br bond cleavage, while a weaker base, nonpolar solvent, higher temperature, and Ir₂(ttp)₂ precursor favor Ar–X (X = Cl, Br) bond cleavage.

n Ar-F bond is generally thermally, photochemically, electrooxidatively, and chemically stable due to its high bond dissociation energy (BDE), with that of the Ph-F bond being about 125 kcal/mol.¹⁻³ The activation of carbonfluorine bonds has gained increasing attention due to the challenge in defluorination,⁴ organic synthesis,^{3,5} and peptide sequencing.⁶ In the presence of Cl, Br, or I substituents, selective Ar-F bond cleavage is even more difficult.⁷⁻¹¹ This is a consequence of the much lower BDE of Ar-Cl. -Br. and -I (about 95, 80, and 65 kcal/mol, respectively) in comparison to that of Ar-F.¹ The Ar-F bond is inert toward most palladium,^{7,9} nickel,¹⁰ and cobalt¹¹ catalysts in cross-coupling,⁷ dehalogenation,⁸ and amination^{9,10} reactions in the presence of Cl or Br substituents. The Stille cross-coupling reaction of pfluorochlorobenzene with ArSnBu₂ catalyzed by $Pd(OAc)_2$ and XPhos (=2-dicyclohexylphosphino-2',4',6'-triisopropylbiphen-yl) gave 4-fluorobiaryl in 93% yield.^{7a} The Ar–Cl bond was cleaved rather than the Ar–F bond at the *para* or *meta* position with the catalyst $\{Pd(cinnamyl)Cl\}_2$.^{7b} Fluorobenzene was obtained in the hydrodehalogenation reaction of p-fluorochlorobenzene over a supported palladium catalyst.8 The Ar-Cl bond was aminated in the presence of an Ar-F bond with a nickel(0) catalyst and NHC ligand.¹⁰

Selective cleavage of the stronger Ar–F bond in the presence of other Ar–X bonds (X = Cl, Br, I) is very difficult, with only a few examples being reported in the last century. The first observation of C–F bond cleavage in the presence of a C–Cl bond was reported by Frank et al. on saturated chlorofluorocarbons with phosphorus in 1965. However, a chlorophilic process and elimination of fluoride anion rather than direct C– F bond cleavage account for the observed product.¹²

In the past 20 years, several approaches have been applied to achieve selective Ar–F bond cleavage in the presence of other halogen substituents. In the first approach, a fluorophilic phosphorus reagent was first used in 1993 to cleave the C–F bond. The reaction between diisopropyl sodiophosphite and



dibromofluoromethane gave C–F and C–Br bond cleavage products in a 1.7:1 ratio.¹³ The second approach employed carbon or oxygen nucleophiles by taking advantage of the better leaving ability of fluoride.¹⁴ The treatment of 1-bromo-3chloro-5-fluorobenzene with 2-(trimethylsilyl)ethanol and potassium bis(trimethylsilyl)amide gave the Ar–F bond cleavage product.^{14a} In the third approach, selective Ar–F bond cleavage has been accomplished by chelation control using an ortho directing group.¹⁵ The coordination of phenol to Mg facilitated oxidative addition of Ni to the adjacent C–F bond.^{15a} Recently, it was reported that the Ar–F bond ortho to an imine directing group was cleaved by a platinum complex even in the presence of a chlorine group ortho to the imine group. However, a directing imine group is a must and the mechanism of this selectivity was not reported.¹⁶

For simple fluorohalobenzenes without an ortho directing group, to our knowledge, few example of selective Ar–F bond cleavage with transition-metal complexes exist. In our continuing studies of Ar–X (X = Cl, Br, I) cleavage by metalloporphyrins,¹⁷ we have discovered competitive Ar–F and Ar–X (X = Cl, Br) bond cleavage with iridium porphyrin complexes and now report our findings.

Initially, Ir(ttp)(CO)Cl (1a; ttp = 5,10,15,20-tetra-*p*-tolylporphyrinato dianion) reacted with *p*-fluorochlorobenzene in the presence of K_2CO_3 in benzene at 150 °C to give a 60% yield of the Ar–Cl cleavage product, Ir(ttp)(4-fluorophenyl) (**3b**) (Table 1, entry 1). Unexpectedly, when the stronger base KOH was used, competitive Ar–F and Ar–Cl bond cleavage reactions occurred to give Ir(ttp)(4-chlorophenyl) (**3a**) and Ir(ttp)(4-fluorophenyl) (**3b**) in a 1:1 ratio (Table 1, entry 2). When THF was used as the solvent, the product ratio further increased to 3:1 (Table 1, entry 3). When the reaction

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Table 1. Competitive Ar-F and Ar-Cl Bond Cleavage with Iridium Porphyrin Complexes



temperature was lowered to 120 °C, the reaction became slower, and the ratio of **3a** to **3b** increased further (Table 1, entry 4). To our delight, when $Ir(ttp)SiEt_3$, a known precursor for $Ir(ttp)^{-18}$ was used as the starting material, exclusive Ar–F bond cleavage occurred to give **3a** in 90% yield (Table 1, entry 5).

To find out whether competitive Ar-F and Ar-Br occur, we then examined the reaction with *p*-fluorobromobenzene. When Ir(ttp)(CO)Cl was reacted with *p*-fluorobromobenzene and KOH in benzene, only Ar-Br cleavage product **3b** was obtained (Table 2, entry 1). However, in THF solvent, the

Table 2. Competitive Ar-F and Ar-Br Bond Cleavage with Iridium Porphyrin Complexes



reaction gave a trace amount of Ar–F bond cleavage product (Table 2, entry 2). The same temperature effect was observed, that the Ar–F bond cleavage product became significant when the temperature was lowered to 120 °C (Table 2, entry 3). With Ir(ttp)SiEt₃ (**1b**)/KOH used as the starting materials, the ratio of **3c** to **3b** further increased to 4:3 (Table 2, entry 4).

To investigate whether the Ar–F bond cleavage product is the kinetic product or the thermodynamic product formed from the Ar–Cl cleavage product, the reactivities of 3a and 3bwere studied. Both 3a and 3b were stable under the reaction conditions, and the recovery yields were quantitative (eqs 1 and 2). Thus, the reaction products are not interconvertible and the product ratios are kinetic.



To gain a mechanistic understanding of the competitive Ar-F and Ar-X (X = Cl, Br) bond cleavages, various iridium porphyrins were tested as the intermediates of these bond cleavages. Since we have earlier identified that ipso substitution addition-elimination of Ir^{II}(ttp) is responsible for Ar-Cl and Ar-Br bond cleavage,¹⁷ Ir^{II}(ttp) was tested for Ar-F bond cleavage. However, $Ir_2(ttp)_2$ (1e) reacted with fluorobenzene to give a complex mixture without any Ar-F bond cleavage product. As it is known that $Ir_2(ttp)_2$ equilibrates with Ir(ttp)H(1d) and Ir(ttp)⁻ (1c) under basic conditions,^{17,19} Ir(ttp)H (1d) and $Ir(ttp)^{-}$ (1c) were also tested for the Ar-F bond cleavage. Without base, Ir(ttp)H (1d) reacted with fluorobenzene to give a complex mixture as well. However, $Ir(ttp)^{-}(1c)$, generated from the Na/Hg reduction of Ir(ttp)(CO)Cl, reacted with fluorobenzene at 120 °C to give Ir(ttp)Ph (3d) in 40% yield (eq 3). Therefore, $Ir(ttp)^{-}$ (1c) is the most probable intermediate for Ar-F bond cleavage.

$$Ir(ttp)(CO)Cl \xrightarrow{N_2, 60 \circ C, 10 \text{ min}}_{THF, Na/Hg} Ir(ttp)^-Na^+$$

$$Ic (quantitative)$$

$$\xrightarrow{N_2, 60 \circ C, 2 \text{ days}}_{C_6H_5F} Ir(ttp)C_6H_5$$

$$3d (40\%) (3)$$

Scheme 1 shows the proposed mechanism for competitive cleavage of Ar–F and Ar–X bonds (X = Cl, Br). Initially, Ir(ttp)(CO)Cl (1a) undergoes ligand dissociation and ligand

Scheme 1. Proposed Mechanism for Competitive Ar-F and Ar-X (X = Cl, Br) Bond Cleavage



substitution with OH⁻ to give Ir(ttp)OH, which undergoes reductive elimination and subsequent dimerization to give Ir₂(ttp)₂ (1e) and H₂O₂.^{20,21} Ir₂(ttp)₂ (1e) or, more accurately, Ir^{II}(ttp) monomer then cleaves the Ar–X (X = Cl, Br) bond to afford Ir(ttp)(4-fluorophenyl) (3b). Ir₂(ttp)₂ (1e) also reacts with hydroxide to form Ir(ttp)⁻ (1c),^{17,20,21} which undergoes *ipso* nucleophilic aromatic substitution (S_NAr) (addition– elimination) to give Ir(ttp)Ar.²² On the other hand, when Ir(ttp)SiEt₃ (1b) and KOH are used as the starting materials, they give Ir(ttp)⁻ (1c) first selectively. The independent reaction of Ir(ttp)SiEt₃ (1b) with KOH gave Ir(ttp)⁻ (1c), KOSiEt₃, and (Et₃Si)₂O, which formed from condensation of Et₃SiOH,²³ thus providing an experimental support (eqs 4 and S).²⁴

$$Ir(ttp)SiEt_{3} + KOH$$

$$\stackrel{11\%}{\xrightarrow{}} IOH_{10 \text{ equiv}}$$

$$\stackrel{200 \circ C}{\xrightarrow{}} Ir(ttp)^{-}K^{+} + KOSiEt_{3} + (Et_{3}Si)_{2}O$$

$$\stackrel{t=5 \text{ days}}{\xrightarrow{}} G\%$$
(4)

$$2\text{Et}_{3}\text{SiOH} \xrightarrow{\text{KOH}} (\text{Et}_{3}\text{Si})_{2}\text{O} + \text{H}_{2}\text{O}$$
(5)

Aryl halides can in principle undergo nucleophilic aromatic substitution with $Ir(ttp)^-$ to form a benzyne intermediate, which can then be attacked by $Ir(ttp)^-$ followed by protonation to give $Ir(ttp)Ar.^{25}$ Had the benzyne mechanism indeed operated, a 1:1 ratio of Ir(ttp)(4-FG-phenyl) and Ir(ttp)(3-FG-phenyl) would have formed (Scheme 2). However, this mechanism was excluded, since the regiochemistry of the starting material was retained.

The competitive cleavage of Ar–X (X = Cl, Br) and Ar–F bonds in an equilibrated $Ir(ttp)^-$ and $Ir_2(ttp)_2$ mixture under basic conditions is highly temperature and solvent depend-

Scheme 2. Ar–X (X = F, Cl, Br) Cleavage via the Benzyne Mechanism



ent.^{17,20,21} At higher temperature, a nonpolar solvent favors the radical process, while a polar solvent and lower temperature favor the ionic process. Therefore, Ar–X bonds (X = Cl, Br) were cleaved at high temperatures in benzene and Ar–F cleavage was more favored at lower temperatures in THF. As an Ar–Br bond is much weaker than an Ar–Cl bond, Ar–Br bond cleavage also occurred competitively at lower temperatures in THF.

In summary, selective Ar–F bond cleavage of *p*-fluorochlorobenzene was achieved. The competitive Ar–F and Ar–X (X = Cl, Br) bond cleavage was investigated. A stronger base, polar solvent, lower temperature, and iridium anion precursor favor Ar–F bond cleavage. On the other hand, a weaker base, nonpolar solvent, higher temperature, and $Ir_2(ttp)_2$ precursor favor Ar–X (X = Cl, Br) bond cleavage. $Ir_2(ttp)_2$ is responsible for the Ar–X (X = Cl, Br) bond cleavage, and $Ir(ttp)^-$ is the intermediate for Ar–F bond cleavage.

ASSOCIATED CONTENT

S Supporting Information

Text, figures, and tables giving a detailed mechanistic study for Ar–F bond cleavage and ¹H, ¹³C, and ¹⁹F NMR spectra. This material is available free of charge via the Internet at http:// pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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