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The Organometallic Fluorine Chemistry of Palladium and Rhodium: Studies toward Aromatic Fluorination

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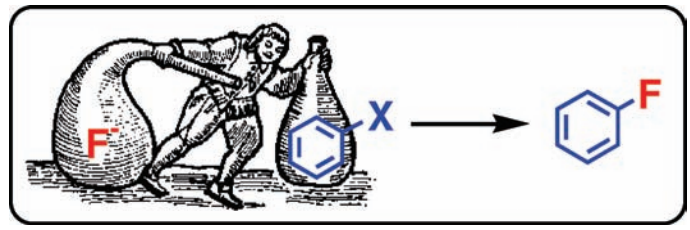
CONSPECTUS



Although springing from two established fields, organometallic chemistry and fluorine chemistry, organometallic fluorine chemistry is still in its early stages. However, developments in this area are expected to provide new tools for the synthesis of selectively fluorinated organic compounds that have been in high demand. Selectively fluorinated organic molecules currently account for up to 40% of all agrochemicals and 20% of all pharmaceuticals on the market. Our research efforts have been focused on the development of new organometallic and catalytic methods for the selective introduction of fluorine and the CF_3 group into the aromatic ring. Monofluorinated and trifluoromethylated aromatic compounds are still made by the old technologies that employ stoichiometric quantities of hazardous and costly materials. In this Account, we describe our studies toward the development of safe, catalytic alternatives to these methods.

We have synthesized, characterized, and studied the reactivity of the first aryl palladium(II) fluoride complexes. We have demonstrated for the first time that a Pd−F bond can be formed in a soluble and isolable molecular complex: this bond is more stable than previously thought. Toward the goal of fluoroarene formation via Ar−F reductive elimination, we have studied a number of σ-aryl Pd(II) fluorides stabilized by various P, N, and S ligands. It has been established that numerous conventional tertiary phosphine ligands, most popular in Pd catalysis, are unlikely to be useful for the desired C−F bond formation at the metal center because of the competing, kinetically preferred P−F bond-forming reaction. A metallophosphorane mechanism has been demonstrated for the P−F bond-forming processes at Rh(I) and Pd(II), which rules out the possibility of controlling these reactions by varying the amount of phosphine in the system, a most common and often highly efficient technique in homogeneous catalysis. The novel F/Ph rearrangement of the fluoro analogue of Wilkinson's catalyst $[(Ph_3P)_3RhF]$ and P−F bond-forming reactions at Pd(II) are insensitive to phosphine concentration and, because of the small size of fluorine, occur even with bulky phosphine ligands. These observations may guide further efforts toward metal-catalyzed nucleophilic fluorination of haloarenes.

We have also developed aryne-mediated and CuF_2/TMEDA-promoted aromatic fluorination reactions. The formation of fluoroarenes from the corresponding iodo- and bromoarenes in the presence of the CuF_2/TMEDA system is the first example of a transition metal-mediated fluorination of nonactivated aryl halides in the liquid phase.

Progress has also been made toward the development of aromatic trifluoromethylation. We have found unexpectedly facile and clean benzotrifluoride formation as a result of Ph−CF_3 reductive elimination from [(Xantphos)Pd(Ph)CF_3]. This observation demonstrates for the first time that the notoriously strong and inert metal−CF_3 bond can be easily cleaved (at 50−80 °C) as a result of reductive elimination to produce the desired aryl-trifluoromethyl bond, the only previously missing link of the catalytic loop. Our study of the novel complex $[(Ph_3P)_3RhCF_3]$ has led to a rationale for the long-puzzling strong trans influence (electron donation) of the CF_3 group which, in complete contrast, is known to be an electron acceptor in organic chemistry.

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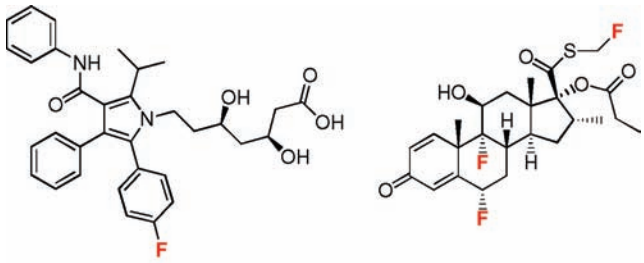
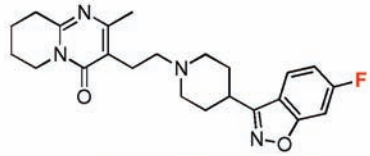
Introduction

Selectively fluorinated organic compounds possess a number of useful properties and find numerous applications, particularly in the synthesis of biologically active compounds.[1−4] "Approximately 40% of all agrochemicals and 20% of all pharmaceuticals on the current market are organic molecules containing at least one fluorine atom",[3] including three of the top 10 drugs (as of mid-2008):[5] Lipitor, Seretide, and Risperdal. Of all types of selectively fluorinated biologically active compounds, ones containing fluorine on aromatic rings are most frequently encountered. Obviously, availability of synthetic tools for selective aromatic fluorination is of considerable importance.



Lipitor (Atorvastatin); #1
(Hypercholesterolemia)
Pfizer; $13.8 billion

Seretide (Fluticasone); #4
(Asthma)
GlaxoSmithKline; $7.5 billion



Risperdal (Risperidone); #8
(Schizophrenia)
Johnson & Johnson; $5.0 billion

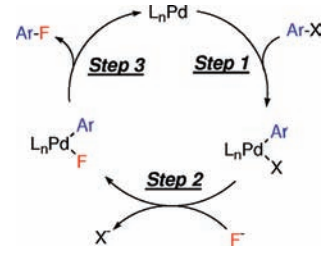
The aromatic C−F bond is exceptionally robust, being the strongest single bond to a heteroatom that carbon can form, e.g., D_{Ph-F} = 126 kcal/mol.[6] For nonactivated ("non-Meisenheimer") fluoroarenes this bond is also kinetically inert, which makes its activation and cleavage particularly difficult.[7] Though the reverse process (Ar−F bond formation) might seem like an easy task, in reality forming this bond, especially in a selective manner, represents one of the greatest challenges of modern synthetic methodology. There is still only one practical method for selective monofluorination of aromatic compounds, the Balz−Schiemann reaction that was first reported as early as 1927.[8] Despite dealing with potentially explosive, toxic, and corrosive arenediazonium compounds, the Balz−Schiemann reaction is performed on a large industrial scale because of the lack of alternatives to satisfy the increasingly high demand for fluoroarene intermediates. Other methods to selectively fluorinate aromatic compounds employ either highly toxic metal (Tl,[9] Pb[10]) compounds in stoichiometric quantities or costly chemicals such as diaryliodonium salts[11] and "positive fluorine" reagents.[12]

Direct nucleophilic displacement of the heavier halide of readily available and easily accessible chloro-, bromo-, and iodoarenes with fluoride (eq 1) would be the best way to selectively form the desired aromatic C−F bond. Reaction 1 is thermodynamically allowed and indeed does occur for aromatic substrates containing strong electron-withdrawing groups, e.g., NO_2 or CN. Such *activated* haloarenes undergo S_NAr fluorination via a Meisenheimer complex,[13] which, however, is too high in energy for the vast majority of ArX lacking strong electron-accepting substituents. As a result, these *nonactivated* substrates remain unreactive toward fluoride and other nucleophiles even under drastic conditions.

(1)

Being of purely kinetic character, the problem of nucleophilic fluorination of non-Meisenheimer haloarenes (eq 1) could be, in principle, solved by catalysis.[14] While palladium catalysis is now successfully used for aromatic C−N and C−O bond formation,[15] the mechanistically similar catalytic loop to form the C−F bond (Scheme 1) has never been reported to function. With Scheme 1 in mind, in the late 1980s to early 1990s, we carried out numerous experiments toward catalytic fluorination, using different metals (mostly Pd but also Ni, Pt, Ru, Rh, and Ir) with various tertiary phosphine ligands and fluoride sources. None of those experiments produced the desired aryl fluoride, suggesting that at least one of the three key steps in Scheme 1 was flawed. Involved in all Pd-catalyzed reactions of haloarenes, Ar−X oxidative addition to Pd(0), step 1, could not fail, whereas steps 2 and 3 were certainly in question since aryl palladium fluoride complexes were unknown. We therefore set the goal to synthesize the first fluoro Pd(II) aryls as model species to be formed in step 2 and study their reactivity, including Ar−F reductive elimination (step 3).

SCHEME 1. Pd-Catalyzed Aromatic Fluorination



Considerations of the Pd−F bonding and analysis of the literature did not provide much optimism for the synthesis of then unknown aryl palladium fluorides. Nonetheless, in 1997, we reported[16] the first isolated and fully characterized Pd(II) fluoride complexes, and five years later published a Concept Article[17] summarizing our early accomplishments in the new area. Since then, our work has focused on reactivity of new Pd(II) and also Rh(I) fluorides and resulted in important new developments. The goal of this Account is to present, analyze, and discuss these recent accomplishments in the context of both organometallic chemistry and catalysis. To draw the full picture, we will include herein some of the already reviewed[17] earlier data, albeit very concisely. A brief overview of our recent studies toward aromatic trifluoromethylation will also be presented in this Account.

Synthesis and Characterization of Pd(II) and Rh(I) Fluoro Complexes

We have developed two general methods for the synthesis of late transition metal fluoride complexes. One employs ultrasound-promoted I/F exchange between an iodo complex and AgF in solvents of low polarity. The other method is based on "neutralization" of M−OH species with $Et_3N \cdot (HF)_3$ ("TREAT HF"), an inexpensive and safe fluorinating agent. Use of TREAT HF in excess commonly leads to the formation of the corresponding bifluorides. All reported fluoro complexes synthesized by these methods in our laboratories are listed in Table 1.

The bonding, structural features, and solution behavior of the originally synthesized Pd(II) fluorides have been analyzed in our earlier research publications and 2002 Concept Article.[17] Herein we present only a succinct summary of that analysis complemented with more recent results. The fluorine atom bonded to tertiary phosphine-stabilized Pd(II) retains considerable basicity. This is manifested by short C−H···F contacts that have been found in every structurally characterized Pd−F complex. Electrophilic in nature, these H-bond-like C−H···F interactions alleviate Pd−F bond-destabilizing d_π−p_π filled/filled repulsion between the lone electron pairs on F with the filled d-orbitals on Pd. Because the empty $d_{x^2-y^2}$ orbital on square-planar, 16-e Pd(II) has zero overlap with the lone electron pairs on the fluoro ligand, additional stabilization of the Pd−F bond may occur via push−pull interactions of p_π on F with a π-acidic ligand trans to it, through filled d orbitals on the metal.[17,19,31] Nonetheless, fluoride on Pd(II) remains basic and can form intermolecular hydrogen bonds even when bridging two palladium atoms. A remarkable example is the stable adduct of $[(Cy_3P)_2Pd_2(Ph)_2(\mu\text{-}F)_2]$ with three molecules of dichloromethane, one of which bridges the two fluorines and the other two being terminal (Figure 1).[20]

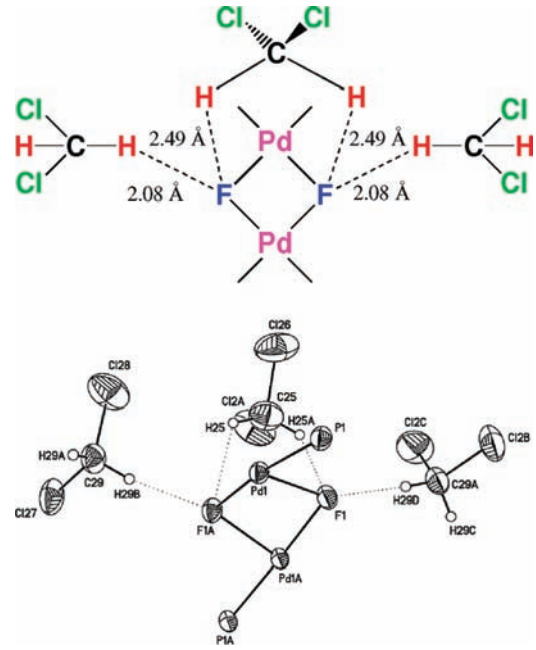


FIGURE 1. The $[Pd_2F_2]$ core of $[(Cy_3P)_2Pd_2(Ph)_2(\mu\text{-}F)_2]$ with three molecules of CH_2Cl_2 H-bonded to the fluoride ligands.[20]

An important observation was made most recently,[23] showing that *trans*-$[(PY)_2PdF_2]$ (PY = pyridine, 4-*t*-butylpyridine) appeared to be not only unexpectedly stable, but displayed by far the shortest Pd−F bonds (1.947(4)−1.958(4) Å). These bonds were anticipated to be strongly destabilized by filled/filled repulsion that could not be sufficiently alleviated because of the lack of a reasonably strong π-acidic ligand on the metal. Probably the field effects of the two *trans*-fluoro ligands strengthen the Pd−F bonds by increasing their ionicity, thereby enhancing the electrostatic component (charge control) of the bonding. This stabilization apparently overwhelms the destabilizing filled/filled d_π−p_π repulsion effects.[23]

Reactivity of Fluoro Pd(II) Aryls toward Ar−F Reductive Elimination

Our primary interest in the area has been Ar−F reductive elimination from Pd(II), the final step of the catalytic loop in Scheme 1. The original study[32] of the thermal decomposition of $[(Ph_3P)_2Pd(Ph)F]$ indicated that the desired Ph−F reductive elimination did not occur. A P−F bond was formed instead, giving rise to Ph_3PF_2 among other products (eq 2).

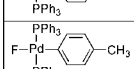
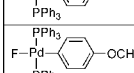
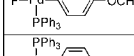
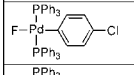
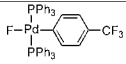
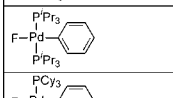
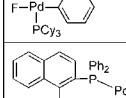
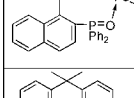
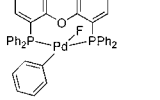
$$[(Ph_3P)_2Pd(Ph)F] \xrightarrow[110-120°C]{\text{toluene, } N_2} [(Ph_3P)_3Pd] + Pd + Ph_2 + Ph_3PF_2 + Ph_2PPPh_2 \quad (2)$$

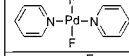
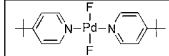
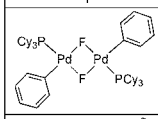
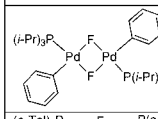
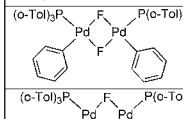
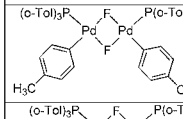
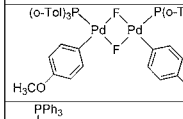
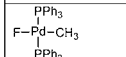
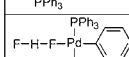
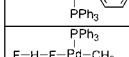
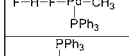
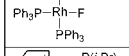
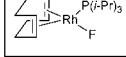
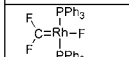
Two strategies could be considered for suppression of the kinetically favored P−F bond formation in order to promote the desired C−F reductive elimination: (i) modification of stabilizing ligands on Pd and (ii) use of another catalytic metal. At that point, P−F bond formation at a metal center was reported only for Ir.[33] Since then, however, P−F bond-forming reactions have been found for virtually every platinum group metal, including Pd,[32] Rh,[26,27] Ru,[34] and Pt.[35] Unknown and puzzling, the mechanism of these reactions was critical to understand in the hope of gaining control over the undesired P−F bond-forming process. This mechanistic information has been obtained from our studies of the fluoride analogue of Wilkinson's catalyst.[26,27]

The Fluoro Analogue of Wilkinson's Catalyst

We have developed a simple and efficient way to synthesize $[(Ph_3P)_3RhF]$ in >90% yield and for the first time fully characterized this complex, including X-ray diffraction (Scheme 2).[26] The reaction of $[(Ph_3P)_4Rh_2(\mu\text{-}OH)_2]$ with TREAT HF cleanly produced $[(Ph_3P)_4Rh_2(\mu\text{-}F)_2]$, the first, long-sought example of a sin-

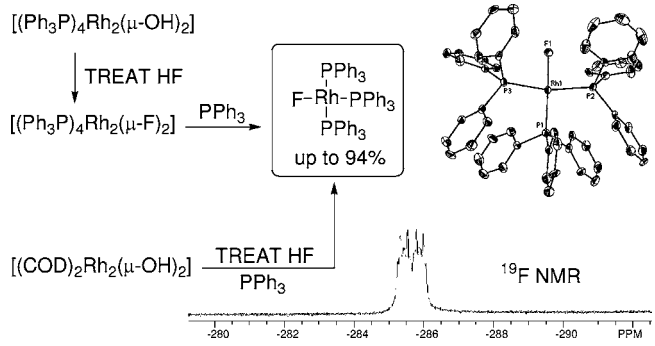
TABLE 1. Fluoro Complexes of Pd(II) and Rh(I), Synthesized by the AgF/Sonication (A) and TREAT HF (B) Methods

Fluoride Complex	Starting Material(s) (Method of Synthesis)	Yield, %	Characterization (EA = elemental analysis)	Ref
	$[(Ph_3P)_2Pd(Ph)I]$ (A)	96	X-ray, NMR, EA	16, 18
	$[(Ph_3P)_2Pd_2(Ph)_2(\mu\text{-}OH)_2]$ + PPh_3 (B)	98	X-ray, NMR, EA	16, 18
	$[(Ph_3P)_2Pd(C_6H_4CH_3)I]$ (A)	71-92	NMR, EA	18
	$[(Ph_3P)_2Pd(C_6H_4OCH_3)I]$ (A)	80-96	NMR, EA	18
	$[(Ph_3P)_2Pd(C_6H_4Cl)I]$ (A)	71-87	NMR, EA	18
	$[(Ph_3P)_2Pd(C_6H_4CF_3)I]$ (A)	80-86	NMR, EA	18
	$[(Ph_3P)_2Pd(C_6H_4NO_2)I]$ (A)	86-97	X-ray, NMR, EA	18, 19
	$[(Ph_3P)_2Pd(C_{10}H_7)I]$ (A)	92-98	NMR, EA	18
	$[(Me_3P)_2Pd(Ph)I]$ (A)	96	X-ray, NMR, EA	20
	$[(i\text{-}Pr_3P)_2Pd_2(Ph)_2(\mu\text{-}OH)_2]$ + $i\text{-}Pr_3P$ (B)	64	X-ray, NMR, EA	20
	$[(Cy_3P)_2Pd_2(Ph)_2(\mu\text{-}OH)_2]$ + Cy_3P (B)	64-96	NMR, EA	20
	$[(BINAP(O))Pd(Ph)I]$ (A)	72	NMR, EA	21
	$[(Xantphos)Pd(Ph)I]$ (A)	92	X-ray, NMR, EA	22
	$[Py_2Pd(Ph)I]$ (A)	75	X-ray, NMR, EA	23
	$[t\text{-}BuPy_2Pd(Ph)I]$ (A)	82	X-ray, NMR, EA	23

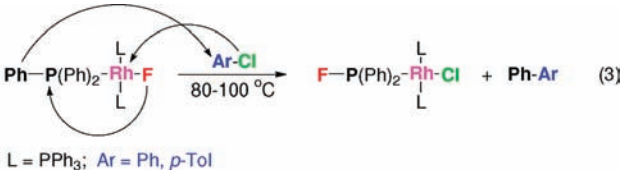
Fluoride Complex	Starting Material(s) (Method of Synthesis)	Yield, %	Characterization (EA = elemental analysis)	Ref
	$[Py_2PdI_2]$ (A)	90	X-ray, NMR, EA	23
	$[t\text{-}BuPy_2PdI_2]$ (A)	91	X-ray, NMR, EA	23
	$[(Cy_3P)_2Pd_2(Ph)_2(\mu\text{-}I)_2]$ (A)	80	X-ray, NMR, EA	20
	$[(i\text{-}Pr_3P)_2Pd_2(Ph)_2(\mu\text{-}I)_2]$ (A)	82	X-ray, NMR, EA	20
	$[(o\text{-}Tol_3P)_2Pd_2(Ph)_2(\mu\text{-}I)_2]$ (A)	79	X-ray, NMR, EA	24
	$[(o\text{-}Tol_3P)_2Pd_2(C_6H_4CH_3)_2(\mu\text{-}I)_2]$ (A)	88	X-ray, NMR, EA	24
	$[(o\text{-}Tol_3P)_2Pd_2(C_6H_4OCH_3)_2(\mu\text{-}I)_2]$ (A)	62	X-ray, NMR, EA	24
	$[(Ph_3P)_2Pd_2(Me)_2(\mu\text{-}OH)_2]$ + PPh_3 (B)	60-85	NMR, EA	18
	$[(Ph_3P)_2Pd_2(Ph)_2(\mu\text{-}OH)_2]$ + PPh_3 (B)	95-99	X-ray, NMR, EA	18, 25
	$[(Ph_3P)_2Pd_2(Me)_2(\mu\text{-}OH)_2]$ + PPh_3 (B)	85-90	NMR, EA	18
	$[(COD)_2Rh_2(\mu\text{-}OH)_2]$ + Ph_3P (B)	94	X-ray, NMR, EA	26, 27
	$[(COD)_2Rh_2(\mu\text{-}OH)_2]$ + $i\text{-}Pr_3P$ (B)	80	NMR, EA	28
	$[(COD)_2Rh_2(\mu\text{-}OH)_2]$ + Ph_3P, then CF_3SiMe_3 (B)	85	X-ray, NMR, EA	29
	$[(Ph_3P)_4Rh_2(\mu\text{-}OH)_2]$ (B)	88	X-ray, NMR, EA	26, 30

gle compound of the type $[L_4M_2(\mu\text{-}X)_2]$ that can exist in *both* planar and bent forms (X-ray).[30] The treatment of $[(Ph_3P)_4Rh_2(\mu\text{-}F)_2]$ with PPh_3 afforded $[(Ph_3P)_3RhF]$ which can be made more conveniently in one step from $[(COD)_2Rh_2(\mu\text{-}OH)_2]$, Ph_3P, and TREAT HF (Scheme 2).[26]

SCHEME 2. Synthesis of the Fluoro Analogue of Wilkinson's Catalyst



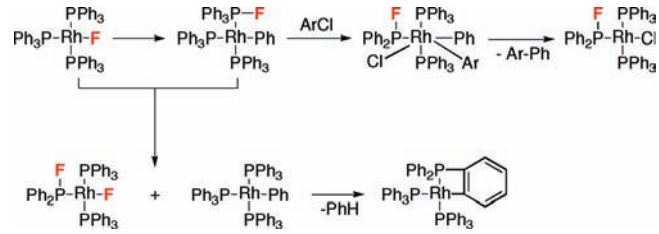
Late transition metal fluorides often display structural properties, solution behavior, and reactivity patterns that differ considerably from those of their well studied heavier halide analogues.[17,36] It was surprising to learn from the initial studies that regarding the crystal structure, degree of phosphine dissociation, and ability to decarbonylate DMF, $[(Ph_3P)_3RhF]$ appeared very similar to Wilkinson's catalyst $[(Ph_3P)_3RhCl]$.[26] Further studies, however, revealed unparalleled reactivity of the fluoride. In one experiment, $[(Ph_3P)_3RhF]$ was treated with haloarenes in the hope that Ph−X oxidative addition would occur, followed by Ph−F reductive elimination. That did not happen however. The reaction with PhCl or *p*-TolCl cleanly produced biaryl and a novel Rh(I) complex, *trans*-$[(Ph_3P)_2Rh(Ph_2PF)(Cl)]$ (X-ray), as a result of an unexpected, highly selective process involving C−Cl, Rh−F, and P−C bond cleavage and C−C, Rh−Cl, and P−F bond formation (eq 3).[26]



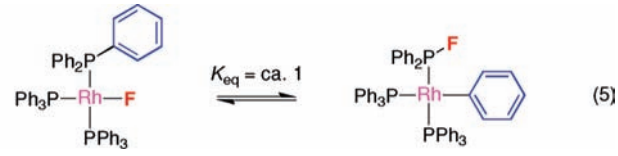
The outcome of the thermal decomposition of $[(Ph_3P)_3RhF]$ in benzene was as striking. In contrast to Wilkinson's catalyst, which dimerizes upon loss of one phosphine when heated in a neutral solvent, $[(Ph_3P)_3RhF]$ did not produce stable $[(Ph_3P)_4Rh_2(\mu\text{-}F)_2]$. A totally different, highly selective reaction occurred instead to give benzene, a well-known cyclometalated Rh complex, and new *trans*-$[(Ph_3P)_2Rh(Ph_2PF)(F)]$ in a 1:1:1 molar ratio (eq 4).[26]

To rationalize these peculiar results (eqs 3 and 4) a rearrangement was proposed,[26] in which the fluorine on Rh and one of the phenyls on the PPh_3 ligands interchange their positions. Odd and unprecedented in itself, this proposed Rh−F/P−Ph exchange nonetheless accounted for the experimental observations (Scheme 3). The rearranged complex, a σ-Ph−Rh(I) species, is electron-enriched and hence should be capable of oxidatively adding haloarenes. The resultant diaryl Rh(III) intermediate would then undergo C−C reductive elimination to furnish the observed final products (eq 3). In the absence of an electrophile such as ArCl, the rearranged Rh−Ph complex and the as yet unreacted $[(Ph_3P)_3RhF]$ would exchange their phosphine ligands, so that the Rh−F bond is stabilized to a greater extent by the less donating and more π-acidic $P(F)Ph_2$ ligand. The second complex emerging from this exchange, $[(Ph_3P)_3Rh(Ph)]$, was known to undergo cyclometalation leading to the other two observed final products (eq 4).[26]

SCHEME 3. Proposed Mechanisms of Reactions 3 and 4



Our detailed further study[27] of reaction 4 by ^{19}F NMR indeed revealed involvement of an intermediate (Figure 2), which was subsequently isolated and confirmed to be *cis*-$[(Ph_3P)_2Rh(Ph_2PF)(Ph)]$ by X-ray diffraction, exactly as previously proposed (Scheme 3). The exchange (eq 5) was found to be reversible with $K_{eq} \approx 1$ in benzene at 30−70 °C. A kinetic study of the rearrangement allowed for the determination of activation parameters $E_a = 22.7 \pm 1.2$ kcal mol^{-1}, $\Delta H^{\ddagger} = 22.0 \pm 1.2$ kcal mol^{-1}, and $\Delta S^{\ddagger} = -10.0 \pm 3.7$ eu and pointed to a *unimolecular process not influenced by extra* PPh_3.



Of the two possible mechanisms for the Rh−F/P−Ph exchange (Scheme 4), pathway 1 involves oxidative addition (Ph transfer to Rh), followed by P−F reductive elimination, a sequence that was poorly consistent with some experimen-

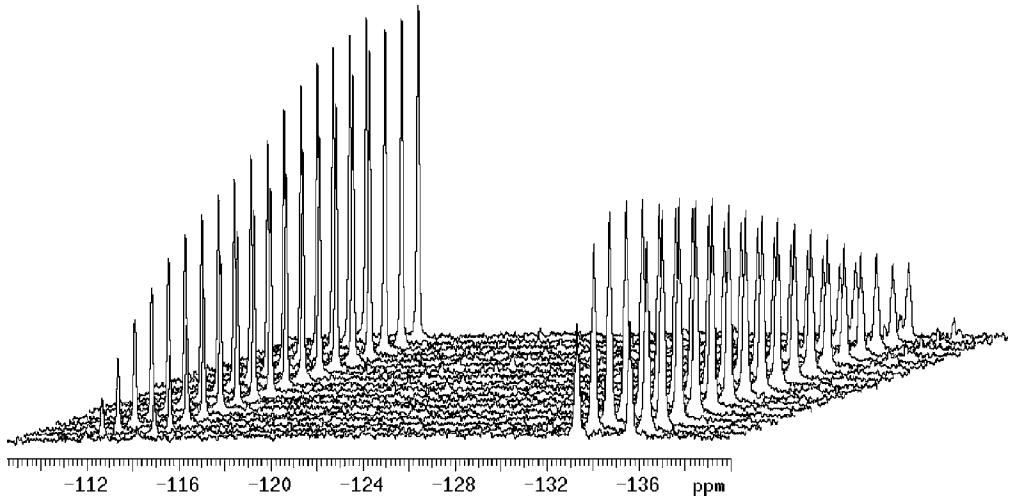
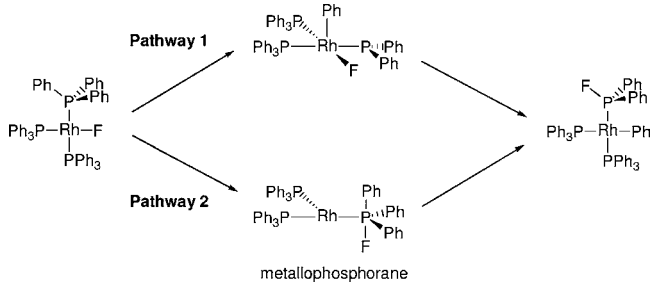


FIGURE 2. Evolution in the P−F region of the ^{19}F NMR spectra acquired over the course of the thermal decomposition of $[(Ph_3P)_3RhF]$ in benzene at 75 °C. The downfield and upfield resonances are from the final product *trans*-$[(Ph_3P)_2Rh(Ph_2PF)(F)]$ and the intermediate *cis*-$[(Ph_3P)_2Rh(Ph_2PF)(Ph)]$, respectively (Scheme 3).

tal data,[27] including the lack of rate dependence on the amount of extra phosphine in the system. Pathway 2 starts with intramolecular nucleophilic attack of the coordinated fluoride on a cis phosphine, leading to a metallophosphorane intermediate, followed by phenyl transfer. This Macgregor's metallophosphorane mechanism involving change in the oxidation state on P but not on Rh was favored in the original publication[27] and subsequently established[37] in a high-level computational study on the full system.

SCHEME 4. Two Possible Pathways for the F/Ph Exchange in $[(Ph_3P)_3RhF]$

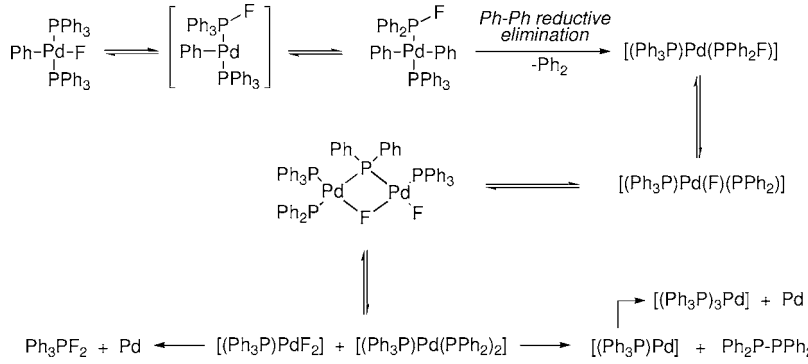


Attempted Ar−F Reductive Elimination from Pd(II) in the Presence of Various Tertiary Phosphines

Well before the extra-phosphine-insensitive metallophosphorane mechanism was established for the F/Ph rearrangement of $[(Ph_3P)_3RhF]$,[27,37] it was noticed[32] that the thermal decomposition of $[(Ph_3P)_2Pd(Ph)F]$ (eq 2) leading to P−F bond formation was not affected by added PPh_3. (Interestingly, extra phosphine strongly inhibited the competing Ar−Pd/Ar−P exchange that apparently proceeds via a mechanistically distinct P−C reductive elimination/P−C oxidative addition pathway.) The metallophosphorane intermediacy in the production of Ph_3PF_2 from $[(Ph_3P)_2Pd(Ph)F]$ (Scheme 5)[24] prompts the disappointing yet most important conclusion: unlike many elementary steps in catalysis, such as oxidative addition and reductive elimination, *the undesired P−F bond formation at Pd does not require a vacant coordination site on the metal and hence cannot be controlled by varying the amount of extra phosphine in the system*.

All fluoro palladium aryls bearing assorted tertiary phosphine ligands (Table 1) have been thermally decomposed, alone or in the presence of various phosphines or other additives, to always produce P−F bonds and never C−F bonds. Although the formation of small quantities of 4-$NO_2C_6H_4F$ from a 4-$NO_2C_6H_4$−Pd−F complex has been reported,[38] this C−F bond might have emerged from an S_NAr-type process rather than Ar−F reductive elimination.[24] A BINAP(O) aryl fluoride complex has been especially designed to keep the F and Ph ligands cis and the only P center bound to Pd trans to F to promote Ph−F and suppress P−F bond formation.[21] This however, did not lead to the desired result, and once more only P−F bond formation took place, likely due to facile dissociation of the labile[39] Pd−O bond. Encouraged by the remarkably facile Ar−CF_3 reductive elimination from a Pd center stabilized by Xantphos (see below),[22] we attempted decomposition of the analogous fluoride, but again without success. Apparently because of the small size of fluorine, P−F bond formation occurred even for such bulky ligands as *t*-Bu_3P, *o*-Tol_3P, the

SCHEME 5. Metallophosphorane-Mediated P−F Bond Formation at Pd (eq 2)



t-Bu analogue of Xantphos, and some of Buchwald's biphenyl-based phosphines.

Phosphorus-Free Ligands

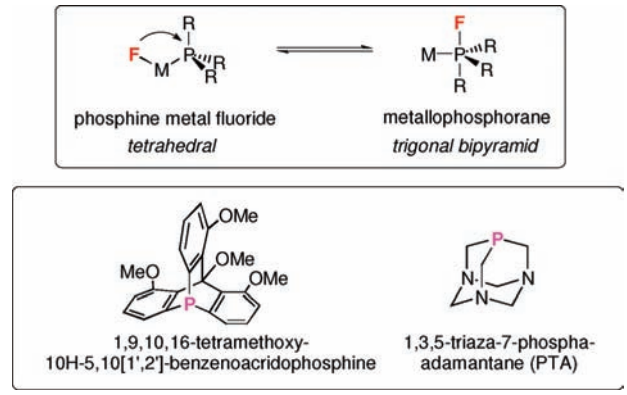
Eliminating tertiary phosphines altogether would be the best way to avoid the undesired P−F bond formation. Our attempts to use N-heterocyclic carbenes (NHCs) indicated that Ar−NHC reductive elimination from Pd(II) can be very facile,[40] and hence in complexes of the type $[(NHC)_nPd(Ar)F]$, the fluoride is unlikely to compete successfully with the NHC for binding to the σ-aryl.

A number of complexes of the type [(N−N)Pd(Ph)I] and [(S−S)Pd(Ph)I] with bidentate N−N and S−S ligands have been prepared and treated with AgF.[41a,42] Neither PhF nor isolable Pd−F species were produced in our work,[42] in some cases likely due to solubility problems. Most recently, Ball and Sanford[41a] reported more easily soluble [(4,4′-di-*t*-butyl-2,2′-bipyridyl)Pd(Ar)F], which they isolated and fully characterized. Although these complexes produced ArF upon treatment with oxidizing "positive" fluorine reagents such as XeF_2 via a Pd(IV) intermediate,[41a] their thermal decomposition gave rise to Ar_2 and no fluoroarenes.[41b] This is in line with the results of our study[23] of phenyl Pd(II) fluorides stabilized by monodentate pyridine ligands, *trans*-$[(PY)_2Pd(Ph)F]$ (PY = pyridine, 4-*t*-butylpyridine), which produced biphenyl on heating. In continuation of these studies, we have recently found that treating *trans*-$[(2,4,6\text{-collidine})_2Pd(Ph)I]$ or *trans*-$[(2,6\text{-lutidine})_2Pd(Ph)I]$ with excess AgF and PhI at 50−100 °C in 2,4,6-collidine or 2,6-lutidine, respectively, gave rise to small quantities of PhF. The latter was probably produced via oxidation to Pd(IV) by Ag(I), because the reaction was not catalytic in Pd, no PhF was formed when AgF was replaced with CsF, and the thermal decomposition of preisolated $[(2,4,6\text{-collidine})_2Pd(Ph)F]$ gave only biphenyl and no fluorobenzene. As we have already emphasized,[24,42] Ar−F bond formation using "positive" fluorine reagents[12,41a,43] or at Pd(IV)[41a,43] is beyond our interests since Pd(II)/Pd(IV) catalysis does not involve Pd(0) and hence cannot utilize haloarenes, the most attractive aromatic substrates.

Cage Phosphines and Aromatic Fluorination via Arynes

Metallophosphorane-mediated P−F bond formation requires geometry change at phosphorus from tetrahedral to trigonal bipyramid (Scheme 6). It was therefore reasoned[42] that some rigid "cage" phosphines might be more resistant to the undesired P−F bond formation.

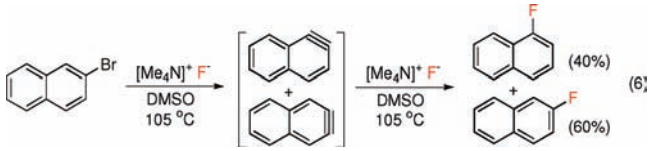
SCHEME 6. Geometry Change at P upon Metallophosphorane Formation and Examples of Cage Phosphines



Two cage phosphines have been tested, 1,3,5-triaza-7-phosphaadamantane (PTA)[42] and a phosphatripticene (1,9,10,16-tetramethoxy-10*H*-5,10[1′,2′]-benzenoacridophosphine).[44] The phosphatripticene appeared to be insufficiently stabilizing for Pd which quickly precipitated out as palladium black in a series of catalytic fluorination experiments. Complexes of the type *trans*-$[(PTA)_2Pd(Ph)X]$ (X = I, Br) were successfully prepared but the synthesis of the corresponding fluoride (X = F) failed because of solubility problems.[42] Hence $[(PTA)_2Pd(Ph)Br]$ was used as added catalyst for reactions of PhBr with CsF or KF, albeit without success. To promote Pd−F

bond formation in situ, a more reactive source of fluoride, $[Me_4N]F$, was employed.

We were delighted to observe the formation of fluorobenzene from bromobenzene upon treatment with $[Me_4N]F$ in DMSO in the presence of 5−10% of $[(PTA)_2Pd(Ph)Br]$ at 80−120 °C. However, when 2-bromonaphthalene was used under the same conditions, a 3:2 mixture of 2-fluoronaphthalene and 1-fluoronaphthalene was formed, immediately suggesting aryne intermediacy. Indeed, omitting the Pd complex in a repeat of that experiment produced the same result, indicating that the fluorination was aryne-mediated and not catalyzed by Pd (eq 6).

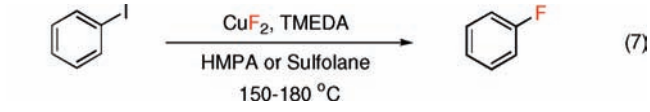


(6)

The exceptional basicity of active, often so-called "naked" fluoride[45] is apparently sufficient to deprotonate haloarenes, giving rise to arynes, which subsequently undergo nucleophilic addition of fluoride. A series of haloarenes have been fluorinated this way (Table 2).[42] The observed isomer distribution patterns were in full accord with an aryne mechanism. Interestingly, for the introduction of one fluorine atom into the aromatic ring, 3 equiv of Me_4NF might be required. After the haloarene is deprotonated by the first equivalent of the fluoride, the HF produced instantly consumes another equivalent of the F^- to form stable bifluoride FHF^-. The third equivalent of fluoride is needed for the C−F bond formation via nucleophilic addition to the aryne. The highest yields were observed for fluorobenzene (60%), fluoronaphthalenes (65%), and 9-fluorophenanthrene (55%).[42]

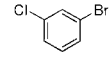
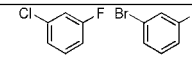
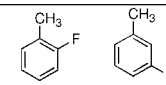
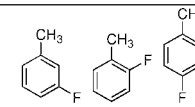
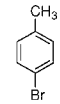
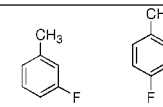
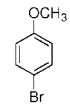
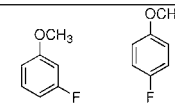
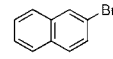
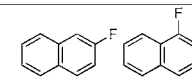
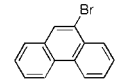
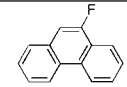
Aromatic Fluorination with CuF_2/TMEDA

Although our studies have been focused mostly on Pd, other metals have also been explored. It has been found that anhydrous CuF_2 in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) fluorinates iodo- and bromoarenes, e.g., eq 7.[46] The reaction occurs in HMPA or sulfolane at 150−180 °C and is low-yielding but not mediated by arynes, because the fluorinations of 2-iodo- and 2-bromonaphthalenes produced exclusively 2-fluoronaphthalene.



(7)

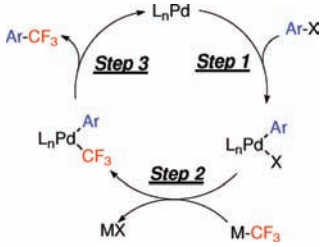
TABLE 2. Aromatic Fluorination of Nonactivated Haloarenes (3 equiv) with $[Me_4N]F$ (1 equiv) in DMSO[42]

Entry	Substrate	T (°C)	Time (h)	Products (molar ratio)
1	 X = Cl, Br, I	90-110	12-24	
2		90	24	 100 1
3		110	12	 1.3 1
4		110	12	 2.5 1.2 1
5		110	12	 1.7 1
6		110	12	
7		110	12	
8		110	12	 1.6 1
9		105	24	 1.5 1
10		110	3	

Trifluoromethyl Complexes of Pd and Rh

Cross-coupling of haloarenes with CF_3-transferring nucleophilic reagents to produce benzotrifluorides is yet another major challenge for catalysis. While considerable progress has been made in the demand-driven development of trifluoromethylation methods in organic chemistry in general,[47] the first example of metal-

SCHEME 7. Pd-Catalyzed Aromatic Trifluoromethylation

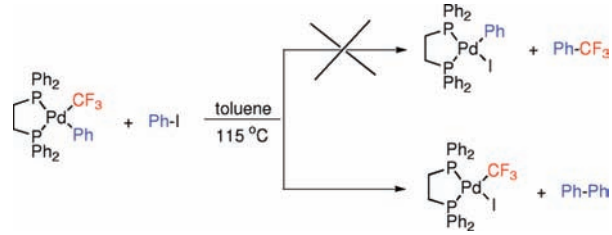


catalyzed nucleophilic trifluoromethylation of haloarenes was reported only recently.[48] Certainly a remarkable achievement, this Cu-catalyzed transformation, however, can be performed only on highly reactive iodoarenes containing electron-withdrawing groups on the ring and some iodoheterocycles. While Ni- and Pd-catalyzed cross-couplings of aromatic halides with metal alkyls are broadly used in synthesis,[49] the highly sought analogous Ar−CF_3 coupling reactions still remain unknown. The problem with the catalytic loop shown in Scheme 7 is the widely recognized[50] inertness and strength of the late transition metal−CF_3 bond. In sharp contrast with methyl Pd(II) aryls that can undergo Ar−CH_3 reductive elimination at room temperature and even below, their trifluoromethyl analogues remain intact for hours and even days at 130−135 °C.[51,52] We set the goal to design a Pd(II) complex that is capable of undergoing clean and facile Ar−CF_3 reductive elimination, step 3 in Scheme 7.

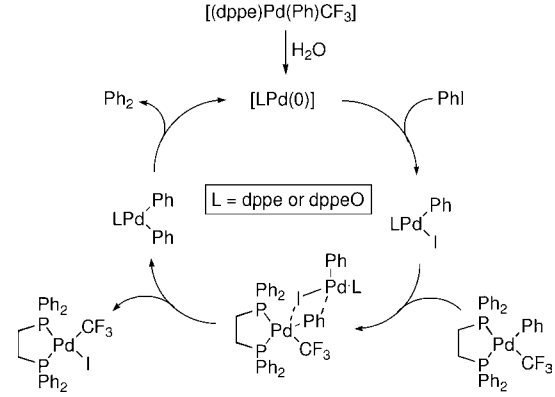
The new Pd(II) and Rh(I) trifluoromethyl complexes prepared in our laboratories are listed in Table 3. Ruppert's reagent, CF_3SiMe_3, was used to trifluoromethylate the metal−halogen bond in the starting complex. For the synthesis of the CF_3 metal derivatives bearing strongly chelating ligands such as tmeda, dppe, dppp, and dippp, conventional chloro, bromo, and iodo starting complexes could be used in the presence of CsF to activate the Si−CF_3 bond.[52] This method is not suitable, however, for complexes containing monodentate or weakly binding bidentate phosphines which easily undergo nonselective, irreversible displacement with CF_3 under such conditions. Nonetheless, [$(Ph_3P)_2$Pd(Ph)CF_3], [(Xantphos)Pd(Ph)CF_3], and [$(Ph_3P)_3$RhCF_3] were successfully synthesized in 82−88% yield from the corresponding fluorides and CF_3SiMe_3 in the absence of CsF.

To model the catalytic formation of $PhCF_3$ at Pd (Scheme 7), [(dppe)Pd(Ph)CF_3] was thermolyzed in the presence of PhX (X = I, Cl) to trap the Pd(0) byproduct, [(dppe)Pd].[52] Unexpectedly, however, the reaction took a different path leading to [(dppe)Pd(CF_3)X] and biphenyl (Scheme 8). A detailed study of this striking transformation revealed that it was induced by traces of adventitious water, which caused reduction of a small quantity of the initial Pd(II) complex to Pd(0), which catalyzed the reaction. As shown in Scheme 9, the zero-valent Pd catalyst generated in situ oxidatively adds PhX to give a σ-Ph−Pd(II) species that undergoes transmetalation with [(dppe)Pd(Ph)CF_3], followed by Ph−Ph reductive elimination to give the final products and regenerate Pd(0). Two pathways have been identified for the water-induced reduction of [(dppe)Pd(Ph)CF_3] to Pd(0): (i) α-F elimination, followed by hydrolysis of the difluorocarbene species to carbonyl, migratory insertion, and reductive elimination of PhC(X)O (X = F, OH, or OOCPh) and (ii) the Pd(II)/P(III) to Pd(0)/P(V) redox process[39] leading to dppeO, Pd(0), and CF_3H.[52]

SCHEME 8. Thermal Decomposition of [(dppe)Pd(Ph)CF_3] in the Presence of PhI



SCHEME 9. Mechanism of the Reaction Shown in Scheme 8



Under rigorously anhydrous conditions, both [(dppe)Pd(Ph)CF_3] and [(dppp)Pd(Ph)CF_3] appeared to remain intact even at 130−135 °C,[52] as expected.[50,51] Only after 6−64 h at 145 °C in xylenes did the complexes decompose to give 10−30% of $PhCF_3$ in a sluggish and poorly selective reaction.[52] In sharp contrast, *$PhCF_3$ was produced in quantitative yield from [(Xantphos)Pd(Ph)CF_3] at as low as 50−80 °C* (eq 8).[22] This reaction for the first time demonstrated feasibility of the key Ar−CF_3 reductive elimination step for the proposed Pd-catalyzed trifluoromethylation of aryl halides (Scheme 7).

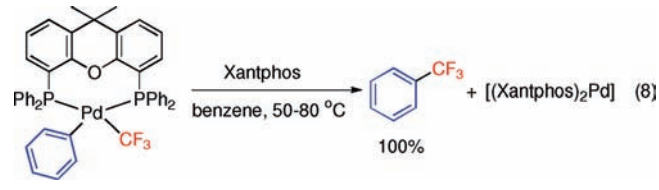
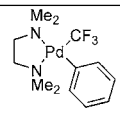
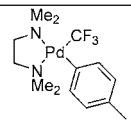
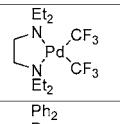
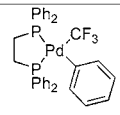
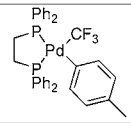
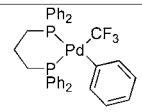
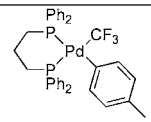
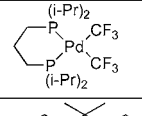
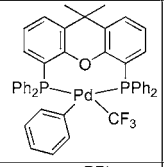
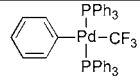
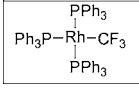


TABLE 3. New Trifluoromethyl Complexes of Pd(II) and Rh(I)

Trifluoromethyl Complex	Method of preparation	Yield, %	Characterization (EA = elemental analysis)	Ref
	[(tmeda)Pd(Ph)I] + CF_3SiMe_3 + CsF	91	X-ray, NMR, EA	53
	[(tmeda)Pd(Tol)I] + CF_3SiMe_3 + CsF	90	NMR, EA	53
	[(teeda)$PdCl_2$] + CF_3SiMe_3 + CsF	59	X-ray, NMR, EA	53
	[(dppe)Pd(Ph)I] + CF_3SiMe_3 + CsF or [(tmeda)Pd(Ph)CF_3] + dppe + $KHSO_4$	69 85	X-ray, NMR, EA	53
	[(tmeda)Pd(Tol)CF_3] + dppe + $KHSO_4$	96	NMR, EA	53
	[(tmeda)Pd(Ph)I] + dppp + CF_3SiMe_3 + CsF	71	X-ray, NMR, EA	53
	[(tmeda)Pd(Tol)CF_3] + dppp + $KHSO_4$	87	NMR, EA	53
	[(dippp)$PdCl_2$] + CF_3SiMe_3 + CsF	85	X-ray, NMR, EA	53
	[(Xantphos)Pd(Ph)F] + CF_3SiMe_3	88	X-ray, NMR, EA	22
	[$(Ph_3P)_2$Pd(Ph)F] + CF_3SiMe_3	82	X-ray, NMR, EA	22
	[$(Ph_3P)_3$RhF] + CF_3SiMe_3 + excess PPh_3	84	X-ray, NMR, EA	29

Our studies have also shed some light on the long-standing puzzle of the M−CF_3 bonding. Widely recognized as an inductive electron acceptor in organic chemistry, the CF_3 group is nonetheless known[50] to exhibit strong trans influence, implying powerful electron donation to the metal. A clear manifestation of that is the virtually superimposable pair of molecules [(dppe)Pd(CF_3)Cl] and [(dppe)Pd(CH_3)Cl].[52] These two complexes exhibit essentially identical coordination geometry around the Pd centers, with the Pd−P bond distances trans to the CF_3 and CH_3 ligands being 2.345(1) and 2.339(1) Å, respectively, in contradiction to the vastly different values of σ_m (Hammett), F (Swain−Lupton, modified), and σ_F (Taft) for CH_3 vs CF_3 ($\sigma_m = -0.07$ vs 0.43, $F = 0.01$ vs 0.38, and $\sigma_F = 0.01$ vs 0.46). The recent finding[29] of extreme fluxionality of [$(Ph_3P)_3$-$RhCF_3$] (12.1 s^{-1} at −100 °C) prompted a computational study, which established that the transition state for intramolecular phosphine exchange is a trigonal bipyramid with one empty axial position and one occupied by CF_3. Because electron donation from the axial ligand is critical for stabilization of the transition state, natural charges were calculated for a series of [$(PH_3)_3$RhX], where X is an anionic ligand, including CF_3 and CH_3. In accord with the experimentally and computationally determined $\Delta H^{\ddagger}$ values, the computed negative charge on Rh in [$(PH_3)_3RhCF_3$] (−0.52) *exceeds* that in [$(PH_3)_3RhCH_3$] (−0.48), despite the opposite, strong charges on the carbons of the CF_3 (+0.79) and the CH_3 (−0.96) ligands. The positive charge on the carbon atom of the CF_3 ligand is probably stabilized by p_π back-donation from the fluorines. This study[29] provides the first rationale for the previously perplexing strong trans influence of the CF_3 group.

Conclusions and Outlook

The problem of metal-catalyzed nucleophilic fluorination of haloarenes is as difficult as it is important. While mechanistically similar to the feasible and widely used catalytic cross-coupling reactions of aryl halides and triflates to form Ar−C, Ar−N, Ar−O, and Ar−S bonds, an analogous practical, efficient Ar−F bond-forming process has not been developed as yet. Our long-standing effort toward this development has been based on both "catalysis by scouting" and "catalysis by design" approaches. The first approach was used in the early stages of the project, and had we ignored the second approach, we might have still been running numerous futile, failure-guaranteed experiments. However, our organometallic fluorine chemistry studies over the past decade have produced a considerable understanding of the requirements for the catalytic Ar−F (and also Ar−CF_3) bond formation. It has been established for the first time that Pd(II) bearing a σ-aryl ligand can form a stable bond to fluoride. A number of novel and diverse fluoro complexes of Pd(II) and Rh(I) have been prepared and studied in detail to reveal their unusual properties and intriguing, unparalleled reactivity. Among other remarkable findings, our work has shown that conventional tertiary phosphines, which are most widely used for Pd catalysis, are unlikely to be useful for the desired C−F bond

formation at the metal center. The kinetically preferred intramolecular nucleophilic attack of the fluoro ligand on the coordinated phosphorus, leading to P−F bond formation, does not require a vacant coordination site and may be difficult to prevent even by using bulky phosphines because of fluorine's small size. Our research has led to the development of aryne-mediated and Cu-promoted aromatic fluorination reactions of nonactivated aryl halides, the first example of clean and facile $Ar-CF_3$ bond formation at Pd, and clarification of the previously puzzling strong trans influence of the CF_3 group. We expect these findings to be useful for future research in the area, which will undoubtedly continue. Indeed, most recently, after this Account was submitted for publication, Buchwald's group reported[53] the first Pd-catalyzed fluorination of aryl triflates with CsF, using *t*BuBrettPhos and BrettPhos ligands. Although mixtures of ArF isomers are produced in certain cases (e.g., for Ar = p-$MeOC_6H_4$ and p-MeC_6H_4), in general the reaction works well for electron-deficient and ortho-substituted ArOTf. We are pleased that our work summarized in this Account is viewed by the authors as "instrumental" and "key" in their achieving success in the area.[53b]

This is DuPont CR&D Contribution No. 8934. I am grateful to all of my ex-students and collaborators on this project, whose names are on the papers cited in the References section. My special thanks go to Research Crystallographer William J. Marshall (DuPont) for numerous X-ray studies, Dr. D. Christopher Roe (DuPont) for kinetic and selected NMR experiments, and Professor Stuart A. Macgregor (Heriot-Watt University) for collaboration, computational studies, and many fruitful discussions. Dr. Christopher P. Junk is thankfully acknowledged for reading the manuscript and for valuable suggestions.

BIOGRAPHICAL INFORMATION

Vladimir Grushin, a native of Moscow, Russia, obtained his Ph.D. degree from Moscow State University. He then spent several years doing research at the Institute of Organo-Element Compounds of the Russian Academy of Sciences and at the University of Ottawa before joining the faculty at Wilfrid Laurier University, Ontario, Canada. In 1997, he took a research position at DuPont CR&D in Wilmington, Delaware. After 12 years with DuPont, he is now returning to academia as a faculty at The Institute of Chemical Research of Catalonia (Institut Català d'Investigació Química; ICIQ) in Tarragona, Spain. His research interests span organic and inorganic chemistry, including catalysis, organometallic fluorine chemistry, C−F bond formation, and aromatic nucleophilic substitution reactions of nonactivated haloarenes. He has over 150 publications, including 26 issued patents.

FOOTNOTES

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