Fluoroarenes

DOI: 10.1002/anie.200902121

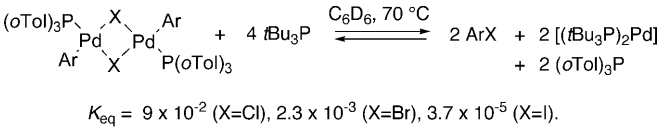
Transition-Metal-Mediated Reactions for C_{sp^2}–F Bond Construction: The State of Play**

John M. Brown and Véronique Gouverneur**

alkenes · arenes · homogeneous catalysis · fluorine · transition metals

Aryl fluoride synthesis has moved forward only sluggishly since the Balz–Schiemann reaction of diazonium salts was introduced in 1927. Renewed interest is driven by the recognition that fluoroaromatics are common targets in agrochemical synthesis and constitute an important class of pharmacophores.[1] Late fluorination of aromatics aids the preparation of short-lived ^{18}F-radiolabeled molecular probes for positron emission tomography (PET), imaging technology that has attracted global interest.[2] A central challenge is the short half-life of ^{18}F (ca. 109.7 min) combined with the need to produce radiotracers of high specific activity, criteria that favor nucleophilic fluorination methods, since the fluoride ion is directly available from cyclotron synthesis.[3] This Highlight discusses how the field of C_{sp^2}–F bond formation catalyzed or promoted by organometallic complexes has evolved since its conceptualization. Direct electrophilic fluorination of arylstannanes, arylgermanes, arylsilanes, and arylboronic acids was accomplished more than 20 years ago, but with relatively inaccessible and potent reagents such as $CsSO_4F$.[4] In addition, vinylstannanes are efficiently converted into vinyl fluorides by XeF_2, augmented by silver triflate or other silver salts. This method generally does not work as a route to aryl fluorides.[5]

Direct coupling is the simplest catalytic method available for the synthesis of C–X bonds, and palladium catalysis forms the mainstay. The common pathway involves a sequence of Pd^0 and Pd^{II} intermediates, with oxidative addition of an electrophile and reductive elimination of the coupled product as the key steps. Aryl fluoride synthesis thus requires C_{aryl}–F bond formation from the precursor $\{L_n(Ar–Pd–F)\}$. Careful work by Roy and Hartwig using higher halogen analogues demonstrated that the equilibrium disfavors reductive elimination.[6] By driving this equilibrium to the right through the use of excess tBu_3P, the aryl chloride or bromide is formed. (Scheme 1)



K_{eq} = 9 x 10^{-2} (X=Cl), 2.3 x 10^{-3} (X=Br), 3.7 x 10^{-5} (X=I).

Scheme 1. Halide reductive elimination (Roy and Hartwig). *o*Tol = *ortho*-tolyl, Ar = 2-Me-5-*t*BuC_6H_3. K_{eq} is referenced to a standard state of 1 M.

Aryl fluorides are presumably subject to a less unfavorable equilibrium than other halide precursors. The most stringent attempts to test this have come from the work of Grushin and Marshall. In their early publications,[7] reductive elimination from isolated [ArPdF] complexes failed, and the formation of P–F containing products derived from the phosphorus ligand was a significant side reaction. First, the diphosphine complex of Figure 1a (X = F) does not eliminate

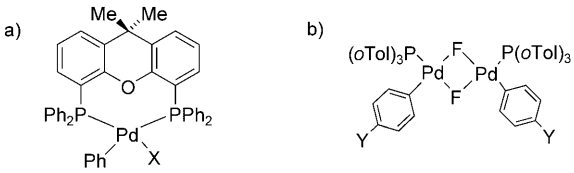


Figure 1. a) Comparative efficiency of elimination of Pd–F and Pd–CF_3; b) unsuccessful attempts at reductive elimination.

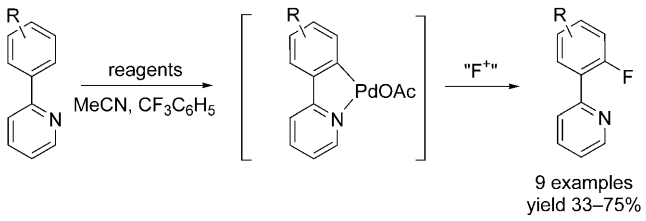
fluorobenzene under forcing conditions. The wide bite angle of the ligand facilitates reductive elimination however, indicated by the smooth synthesis of trifluorotoluene by mild thermolysis of the analogue (X = CF_3).[8a] In addition, complexes analogous to those in Scheme 1 but with bridging fluoride were reacted with a bulky phosphine (Buchwald's ligand) at 60 °C.[8b] Neither the phenyl nor *p*-anisyl complex gave any fluoroarene. A previous observation by Yandulov and Tran,[9] of the formation of approximately 10% of *p*-nitrofluorobenzene from the corresponding *p*-nitrophenyl–palladium complex was attributed to adventitious S_NAr-type reactions (Figure 1b). A critical point emerges; Pd^{II} in 16e configuration is not a promising intermediate for aryl fluoride synthesis. Reader, take note!

[*] Dr. J. M. Brown, Prof. V. Gouverneur
Chemistry Research Laboratory, University of Oxford
12 Mansfield Road, Oxford, OX1 3TA (UK)
Fax: (+44) 1865-275-644
E-mail: john.brown@chem.ox.ac.uk
veronique.gouverneur@chem.ox.ac.uk
Homepage: http://www.chem.ox.ac.uk/researchguide/vgouverneur.html

[**] We thank the Leverhulme Trust for a Fellowship (J.M.B.).

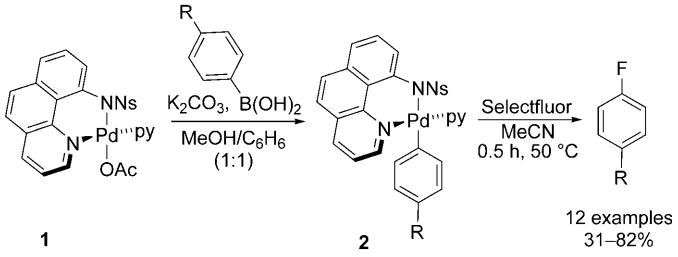
There is a current consensus that palladium(IV) intermediates do not normally participate in coupling reactions. A rare exception is the norbornene-induced coupling chemistry discovered by Catellani, which involves palladacycles in both Pd^{II} and Pd^{IV} states.[10] Indeed, early Pd^{IV} structural chemistry was dominated by species with chelating N,N-ligands and also C,N-palladacycles.[11] Sanford and co-workers had used a Pd^{II}–Pd^{IV} catalytic cycle to effect directed C_{aryl}–H oxidations which involve a Pd^{II}-palladacyclic intermediate. This palladacycle undergoes an oxidative addition step with the reagent, resulting in a Pd^{IV} intermediate prior to reductive elimination. In this way C–Cl and C–OAc functionality can be incorporated.[12] The principles developed led to the first successful catalytic C_{aryl}–F bond synthesis.

The most crucial conceptual advance was the recognition that Pd^{IV} intermediates reduce the barrier to C–X reductive elimination. Hence the logical next step—use an electrophilic fluorinating reagent as the oxidant.[13] 8-Methylquinoline (sp^3 CH) and pyridine-directed (sp^2 CH) fluorinations were performed in the presence of 7–10 mol% of $Pd(OAc)_2$ and 1.5–4.5 equivalents of either *N*-fluoropyridinium tetrafluoroborate or Selectfluor. (Scheme 2)



Scheme 2. Catalytic C_{aryl}–H bond fluorination; 100–110 °C, microwave.

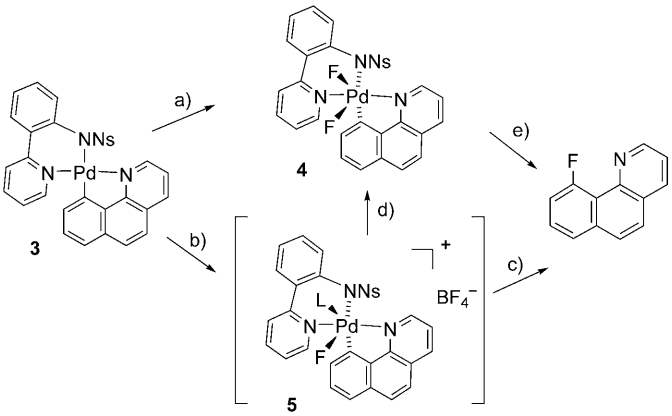
Evidence for a Pd^{IV} intermediate has appeared in three recent papers. Complementing the work of Sanford and co-workers, Ritter and co-workers studied the palladium-mediated fluorination of arylboronic acids with Selectfluor.[14] The arylpalladium complexes **2** were prepared by transmetalation of the acetatopalladium complex **1** with various arylboronic acids. Notably, the ensuing X-ray crystal structure, with a chelating diamine ligand, is well equipped to stabilize the Pd^{IV} state. (Scheme 3) Oxidative fluorination of the phenyl complex with Selectfluor at 50 °C in MeCN produced fluorobenzene in 81% yield. Related sequences produced fluoroaromatics decorated with either electron-rich or electron-poor



Scheme 3. Intermediates in a stepwise aryl fluoride synthesis. Both complexes **1** and **2** were characterized by X-ray crystallographic analysis. py = pyridine.

substituents, in 46–82% yield for the final step (*p*-HOC_6H_4F: 31%).

The palladacycle **3** looks like an effective Pd^{IV} precursor, and adduct **4** was successfully prepared on its treatment with xenon difluoride and analyzed by ^{19}F NMR methods, showing two distinct coupled resonances (Scheme 4).[15] X-ray crystal-

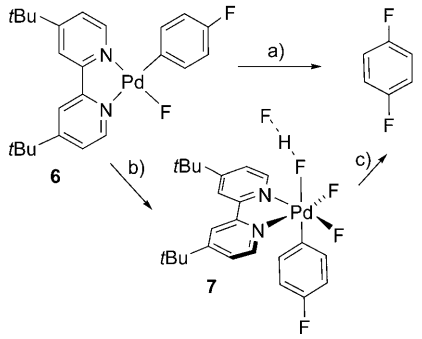


Scheme 4. Aryl fluoride synthesis via isolated intermediates; a) XeF_2, MeCN, 58%; b–c) Selectfluor, MeCN, RT, then 50 °C, 94%; d) $Me_4NF{\cdot}4H_2O$, 88%; e) DMSO, 150 °C, 97%. Ns = *o*-nitrobenzenesulfonyl.

lographic analysis of **4** not only confirmed its structure unambiguously but also indicated adequate positioning of the aryl group and the *cis* fluorine for reductive elimination. Upon heating to 150 °C, complex **4** underwent reductive elimination to give C_{aryl}–F in 97% yield. The second covalent Pd–F inhibits elimination. Thus the cationic complex **5** formed in situ in MeCN without added Me_4NF reacts to form the product directly at 50 °C; this intermediate **5** can be detected by NMR, and has a half-life of approximately 70 minutes at 23 °C. In the presence of Me_4NF, complex **5** is converted into the difluoride **4**.

In a related study carried out by Ball and Sanford, it was first demonstrated that the complexes **6**, stabilized by the rigid bidentate ligand L = *t*Bu-bpy (bpy = bipyridine; prepared from [LPd(Ar)I] and AgF), reacted with 3 equivalents of XeF_2 at 90 °C in nitrobenzene to give the corresponding aryl fluorides, as well as a small amount of the biaryl (Scheme 5).[16] The Pd^{IV} complex **7** was formed upon treatment of the Pd^{II} species **6** with XeF_2 and its structure confirmed by X-ray crystallographic analysis. Complex **7**, featuring the unusual bifluoride ligand, does not undergo reductive elimination to give C_{aryl}–F upon heating but rather intercomplex C_{aryl}–C_{aryl} coupling, contrasting with the pathway for **4** or **5**. In the presence of an excess of XeF_2 however, **6** produced *para*-difluorobenzene in high yields. It was speculated that XeF_2 might serve to sequester the FHF ligand, thereby promoting the reductive elimination step to give C_{aryl}–F.

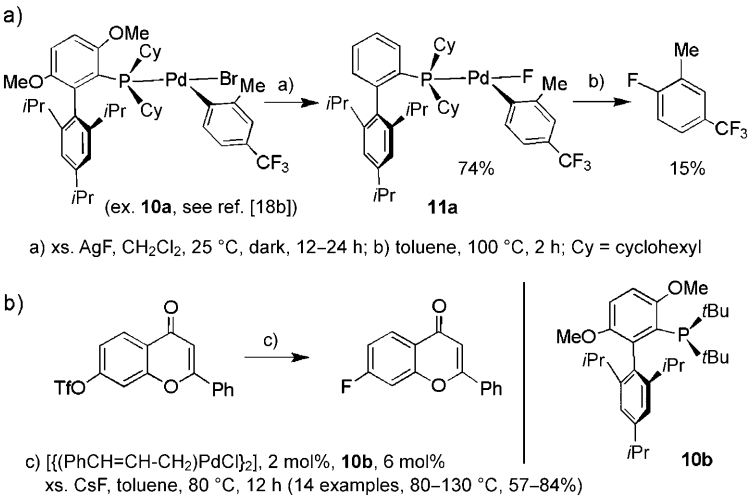
In more recent developments, an alternative mechanistic pathway for oxidative coupling reactions involving dimeric palladium(III) complexes has been proposed by both the Ritter and Sanford research groups. The proposals are supported by elegant structural and mechanistic work, with



Scheme 5. Induced aryl fluoride elimination; a) XeF_2 (3 equiv), 90 °C, ≤60%; b) XeF_2, 70 °C, 2.5 min, 38%; c) XeF_2, 80 °C, 92%.(solvent= nitrobenzene)

key intermediates for both C–H chlorination by $PhICl_2$,[17a] and C–H arylation by iodonium salts,[17b] shown in Figure 2. In the former case, the product-forming reductive elimination step occurs readily at ambient temperature. It is not clear whether the bimetallic pathway can be exploited for aryl fluoride synthesis. Tentative evidence for a bimetallic dipalladium difluoride was provided by the reaction of the precursor to complex **8a** with XeF_2. The putative difluoride product was stable at room temperature, as it reacted with Me_3SiOAc and gave the corresponding diacetate **8b** and Me_3SiF cleanly. Formation of the aryl fluoride was not reported, but this work opens up the possibility of a Pd^{III}-mediated route.

To summarize thus far: Pd^{IV} intermediates formed from electrophilic sources of fluorine as "F^+" hold promise as precursors to aryl fluorides, but efforts to utilize Pd^{II} and nucleophilic F^- had been thwarted. Earlier comments in this Highlight (see Scheme 2) had noted the failure of 16e arylpalladium fluorides to liberate the aryl fluoride moiety on heating. The first real and substantial advance comes in a new paper from Buchwald and co-workers.[18a] With a sufficiently bulky phosphine ligand, the 14e tricoordinated complex remains stable, and is reactive towards reductive elimination. Preliminary work included characterization by X-ray crystallographic analysis of the T-shaped intermediate **11a**, which is derived from ligand **10a** and shown in Scheme 6a, and successful demonstration of its thermolysis to the desired aryl fluoride. Further optimization experiments led to a robust and general catalytic method for aryl fluoride synthesis, starting from the corresponding triflates and using CsF as the fluoride source. For effective catalysis, the more bulky ligand **10b** was required. The chemistry works for both electron-poor and electron-rich aryl triflates, but in the latter case a regioisomer formed by fluorination at the *ortho* rather than the *ipso* to palladium is formed to a minor extent, this side reaction is alleviated by changing the solvent to cyclohexane. This route possesses high functional group tolerance, which is an appealing characteristic for drug discovery but requires forcing conditions, thus indicating that further optimization is necessary for ^{18}F-PET applications (Scheme 6).



Scheme 6. a) Preliminary experiments demonstrating the feasibility of aryl fluoride synthesis by the 14 electron route; b) optimized conditions for catalytic synthesis.

Other metals, notably silver and gold, have been employed in the quest for catalytic routes to aryl fluorides. A new mode of electrophilic activation featuring silver salts has been applied to the fluorination of arylstannanes.[19] In the absence of an additive or electron-donating groups, the direct reaction of arylstannanes with electrophilic fluorinating agents is slow. Ritter and co-workers revisited this chemistry and discovered that in the presence of 2 equivalents of AgOTf, the fluorination of arylstannanes with Selectfluor, or better its PF_6 analogue (F-TEDA-PF_6), occurred efficiently at room temperature within 20 minutes. A competing pathway resulted in the formation of up to 20% of hydrodestannylated products. Mechanistic work suggests that an isolable arylsilver species is formed by transmetalation, and can undergo fluorination with F-TEDA-PF_6. Higher yields can be obtained upon addition of 0.6 equivalents of AgOTf to this intermediate, indicating that a second bimetallic species was the reactive entity. Catalytic turnover was achieved, albeit in lower yield, by employing 10 mol% AgOTf and 2 equivalents of NaOTf. These experiments support the reaction pathway shown in Scheme 7. A similar, but experimentally more

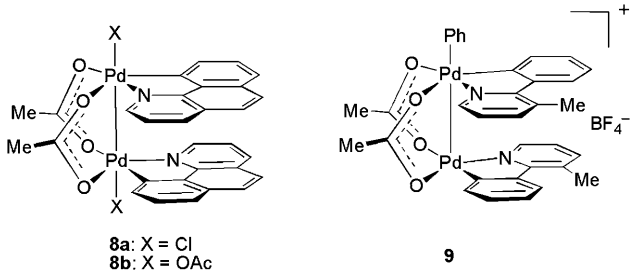
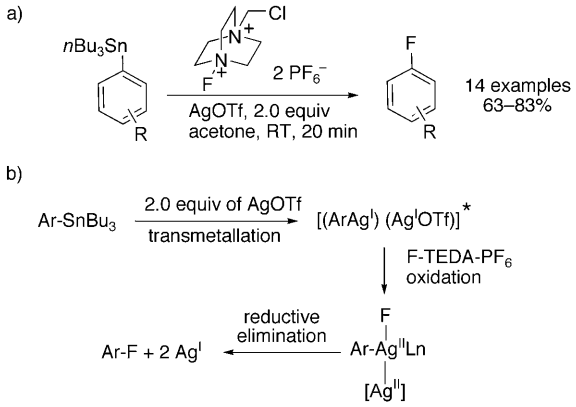


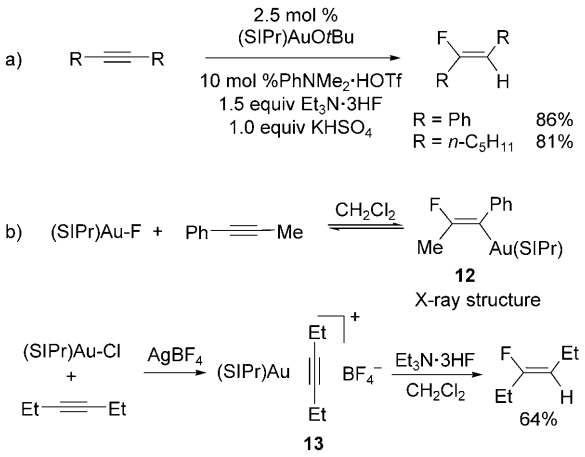
Figure 2. Pd^{III} intermediates in chlorination (complex **8a**, characterized by X-ray crystallographic analysis) and in arylation (complex **9** inferred from kinetic analysis). In Ref. [17b] an alternative open Pd^{IV}–Pd^{II} dimer structure was also suggested.



Scheme 7. Silver(I)-mediated fluorination of arylstannanes; a) overall reaction, b) postulated pathway. *$[(ArAg^I)_5 (Ag^IOTf)_2]$ is isolable from Et_2O; with additional AgOTf the intermediate $[(ArAg^I) (Ag^IOTf)]$ can be observed in Me_2CO. Tf = trifluoromethanesulfonyl, F-TEDA-BF_4 = Selectfluor.

convenient approach, employs base-activated arylboronic acids in place of the stannanes.[20]

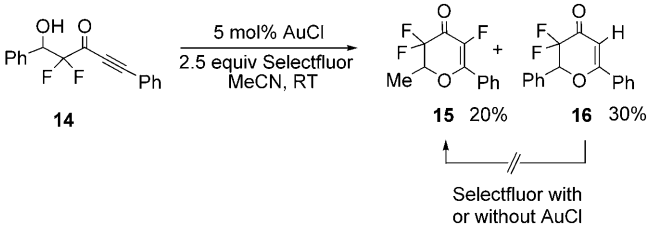
Gold-catalyzed reactions have been investigated for the construction of C_{sp^2}–F but not as an approach to fluoroaromatics. In 2007, Sadighi and co-workers reported that fluoroalkenes are accessible upon gold-catalyzed hydrofluorination of alkynes.[21a] The addition of (SIPr)AuF to a 1:1 mixture of 1-phenyl-1-propyne and CH_2Cl_2 generated a new organogold species **12**, which was characterized by X-ray crystallographic analysis. Mechanistic studies showed that the independently generated cationic complex **13** reacts with $Et_3N{\cdot}3\,HF$, a nucleophilic and mildly acidic fluoride source, to form (*Z*)-3-fluoro-3-hexene in 64% yield (relative to BF_4^- as determined by ^{19}F NMR methods). Also, exposure of the vinylgold intermediate (e.g. **12**) to trifluoroacetic acid released the fluoroalkene. Additional optimization studies led to the identification of the best reaction conditions to perform these hydrofluorinations (Scheme 8). In the catalytic cycle reported by Sadighi and co-workers, the hydrofluorination of



Scheme 8. Gold(I)-catalyzed hydrofluorination of alkynes; a) overall reaction; b) mechanistic studies. SIPr = 1,3-bis(2,6-diisopropylphenyl)-imidazolin-2-ylidene.

alkynes terminates with a protodeauration of the vinylgold intermediate. Based on the same principle, Miller and co-workers more recently demonstrated that gold-catalyzed-directed-hydrofluorination is possible allowing for regio- and stereocontrolled addition of HF across functionalized alkynes.[21b]

Fluorodeauration of a vinylgold offers a distinct approach, validated with the gold(I)-catalyzed 6-*endo-dig* cyclization of difluorinated ynones conducted in the presence of the electrophilic N–F reagent Selectfluor.[22] For the alkoxyfluorination of the ynone **14**, the oxidative fluorination of the transient vinyl gold species is the likely pathway to account for the formation of the trifluorinated dihydropyranone **15**. The protodeaurated product **16**, the major product of the reaction, did not undergo fluorination with Selectfluor in the presence or in the absence of gold catalyst (Scheme 9).



Scheme 9. Gold(I)-catalyzed alkoxyfluorination of ynones.

Further understanding of these and related reactions will accelerate the development of new reactions. To date, methods using both nucleophilic or electrophilic fluorinating reagents are available to access aryl (or alkenyl) fluorides, thus allowing for immediate applications in pharmaceutical research.[23] More work is necessary to facilitate the ^{18}F radiolabeling of unactivated aromatics (or alkenes). For ^{18}F-labeling, electrophilic fluorinations are less favorable as the labeled products are typically produced with lower specific activity.[3] A genuine paradigm shift in ^{18}F-radiochemistry will therefore occur if the chemistry of Buchwald can be further optimized to ^{18}F-aryl fluorides, or if high specific activity electrophilic N–F reagents are made available.

Received: April 20, 2009
Published online: October 13, 2009

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