Fluorination of Nonactivated Haloarenes via Arynes under Mild Conditions, Resulting from Further Studies toward Ar−F Reductive Elimination from Palladium(II)

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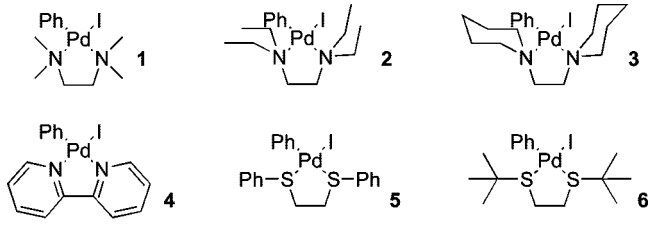
Summary: Attempted preparation of N,N- and S,S-chelate-stabilized arylpalladium fluorides has led to the finding of aryne-mediated fluorination of nonactivated haloarenes with Me_4NF in DMSO under mild conditions.

Fluoroaromatic compounds often exhibit biological activity and have been extensively used as building blocks and monomers in the synthesis of pharmaceuticals, agrochemicals, dyes, specialty polymers, and various advanced materials.[1,2] Despite the widely recognized usefulness of fluoroarenes, selective monofluorination of aromatic compounds still represents one of the most significant practical and intellectual challenges of modern synthetic methodology. The Balz−Schiemann reaction[3] dealing with costly, toxic, and often explosive diazonium compounds still remains the main method for the synthesis of monofluorinated aromatics.

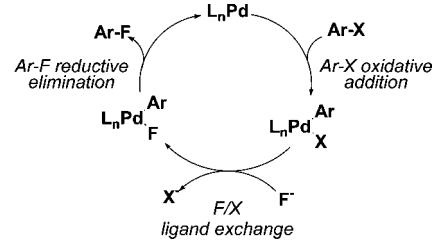
New routes to aromatic C−F bond formation have been highly sought. For a number of years, we have been working on one such route, the Pd-catalyzed fluorination of nonactivated haloarenes.[4] The problematic step for the proposed catalytic loop (Scheme 1) is Ar−F reductive elimination from Pd.[5] An overview of this problem has been recently reported,[5a] emphasizing the preference of tertiary phosphine stabilized arylpalladium(II) fluorides to take the undesired reaction path leading to P−F rather than Ar−F bond formation.[4a,5a,6,7] Such P−F bond forming reactions appear to be general and have also been observed for complexes of Ru,[8] Rh,[9] Ir,[10] and Pt.[11] This prompted us to seek Ar−F reductive elimination from Pd aryls that either were phosphine-free or were stabilized by phosphines that could be more reluctant to P−F bond formation. Herein we describe some of these attempts and how they have led to the finding of aromatic fluorination proceeding via aryne intermediates under mild conditions.

A series of iodo aryl Pd N,N-chelates, **1**−**4**,[12] and the two S,S-chelates **5**[13] and **6** were synthesized by reacting $Pd_2(dba)_3$ with PhI in the presence of the corresponding ligand.



The newly isolated **5** and **6** were fully characterized, including X-ray analysis (see the Supporting Information). Interestingly, working up the reaction with $PhSCH_2CH_2SPh$ without delay produced yellow **5**, whereas after the reaction solution had been left for several hours at room temperature prior to workup, a different, brown crystalline material **7** was isolated and identified as a product of dba insertion into the Pd−Ph bond of **5** (Scheme 2). This type of migratory insertion of dba into a Pd−Ar bond has been previously proposed on the basis of the observed formation of arylated dba products.[14] Apparently, **5** is remarkably capable of undergoing

Scheme 1



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(1) Clark, J. H.; Wails, D.; Bastock, T. W. *Aromatic Fluorination*; CRC Press: Boca Raton, FL, 1996.

(2) (a) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15.

(3) Balz, G.; Schiemann, G. *Chem. Ber.* **1927**, *60*, 1186.

(4) (a) Grushin, V. V. *Chem. Eur. J.* **2002**, *8*, 1006. (b) A reviewer's comment prompted us to reemphasize (see ref 5a) that Pd-mediated fluorination reactions reported by Sanford (aromatic),[4c] Sodeoka (aliphatic),[4d] and most recently Ritter (aromatic)[4e] all employ *electrophilic*, so-called "positive fluorine" reagents for the C−F bond formation. This electrophilic fluorination methodology[4c–e] cannot be used for the highly sought displacement of X in nonactivated ArX (X = I, Br, Cl, OTf, etc.) with fluoride and is therefore rather irrelevant to our approach to metal-catalyzed aromatic *nucleophilic* fluorination with the F^- (Scheme 1). Ritter's recent report[4e] describes the synthesis of fluoroarenes ArF by reacting Selectfluor with stoichiometric quantities of (σ-aryl)palladium reagents. The latter are prepared in five steps, with the overall yield of the ArF products for the entire reaction sequence being in the range of ca. 15−40% (usually around 30%), as calculated on the $Pd(OAc)_2$ starting material. In the step preceding the final fluorination with Selectfluor, the Pd center is arylated with arylboronic acids. It is noteworthy that in most instances $ArB(OH)_2$ reagents are made from ArMgX which may be fluorinated directly with the same Selectfluor reagent to produce the same product in one step and in higher yield (e.g., 61% for Ar = Ph).[4f] While Ritter[4e] anticipates his method to find applicaitons in ^{18}F-PET, practical routes to suffieciently active [F-18]-Selectfluor are nonexistent[4g] and may never be developed, as suggested by a number of fundamental scientific and engineering considerations.[4h] (c) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (d) Hamashima, Y.; Sodeoka, M. *Synlett* **2006**, 1467, and references cited therein. (e) Furuya, T.; Kaiser, M. H.; Ritter, T. *Angew. Chem., Int. Ed.*, **2008**, *47*, 5993. (f) Lal, G. S. *J. Org. Chem.* **1993**, *58*, 2791. (g) See, for example: Bolton, R. *J. Label Compd. Radiopharm.* **2002**, *45*, 485. Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2005**, *44*, 192. Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501. (h) In a recent highlight, the fluorination reaction[4e] is misinterpreted as catalytic in Pd, performed at room temperature, and important for ^{18}F-PET: *Nature* **2008,***454,*471.

(5) (a) Grushin, V. V.; Marshall, W. J. *Organometallics* **2007**, *26*, 4997. (b) While being of some academic interest, the most recently reported[5c] Ar–F reductive elemination from Pd(IV) cannot provide foundation for the highly sought catalytic reaction (Scheme 1) because unlike Pd(0), Pd(II) does not oxidatively add haloarenes. The most closely related Ar–Cl reductive eleimation from a similar Pd(IV) complex was earlier reported by Whitfield and Sanford.[5d](c) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060. (d) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142.

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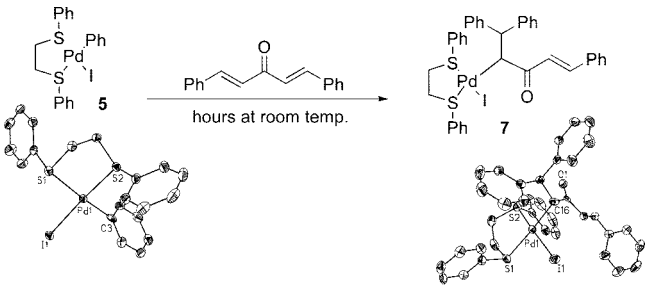
Scheme 2



migratory insertion with olefins, likely due to the labile Pd−S bonds. Upon Pd−S dissociation a vacant coordination site is created on Pd, which is occupied by dba prior to its insertion into the Pd−Ph bond. Note that **6**, bearing a more electron-donating t-Bu group on the sulfur, did not undergo dba insertion under similar conditions.

Complexes **1**−**6** were treated with AgF in benzene under sonication, using our original method[15] for the synthesis of R_3P-stabilized arylpalladium fluorides.[4,6c–e,7] While the virtually insoluble **1** remained intact, all other iodopalladium phenyls readily reacted. The reactions produced either dark precipitates (**2** and **3**) or microcrystalline off-white solids which were not amenable to study due to insolubility (**4**−**6**). In all cases, neither were isolable palladium fluorides produced nor was C−F bond formation observed (^{19}F NMR).

The outcome of the reactions of **2**−**6** with AgF indicated that N and S ligands are not as capable of stabilizing the Pd−F bond as tertiary phosphines.[16] Hence, we turned our attention back to R_3P ligands, in search of ones that would be resistant to the undesired P−F bond formation. The latter likely occurs via intramolecular attack of the fluoride on the phosphorus to produce a metallophosphorane intermediate,[17] a process that requires significant geometry changes around the P atom. This mechanistic consideration pointed to 1,3,5-triaza-7-phosphaadamantane (PTA)[18] as a viable candidate, a cage phosphine which, upon coordination to a metal, was expected to be less prone to metallophosphorane formation due to its rigidity.

The complexes $[(PTA)_2Pd(Ph)X]$, where X = I (**8**), Br (**9**), were prepared in >90% yield by reacting $[(Ph_3P)_2Pd(Ph)X]$ with PTA and found to be trans in solution and in the solid state (Figure 1).

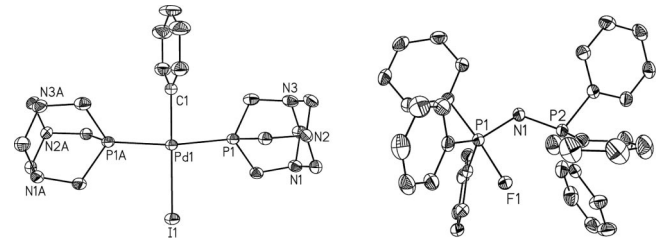
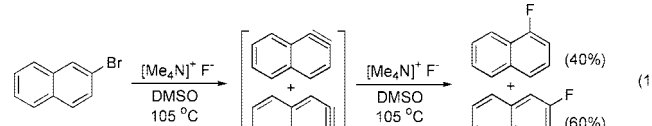


Figure 1. ORTEP drawings of **8** (left) and PPNF (right) with thermal ellipsoids drawn to the 50% probability level and all H atoms omitted for clarity.

Attempted preparation of $[(PTA)_2Pd(Ph)F]$ from **8** and AgF under sonication[15] failed, due to the insufficient solubility of **8** in benzene and toluene. The ultrasound-free reaction of **8** with AgF in CH_2Cl_2 produced a complex reaction mixture of decomposition products.[19] Hence, we explored the fluorination of bromobenzene with **8** or **9** as catalysts. With anhydrous CsF or KF in the presence or in the absence of 18-crown-6 in MeCN, glyme, diglyme, dioxane, or DMSO at 80−130 °C, no PhF formation was observed. To promote the in situ Pd−F bond formation, we then considered sources of most active fluoride,[20–22] often referred to as "naked" fluoride, including anhydrous $[Me_4N]F$[20] and $[Ph_3P{=}N{=}PPh_3]F$ (PPNF).[22,23] Although the latter did form on treatment of [PPN]CN with C_6F_6[24] (Figure 1),[25] its isolation in pure, colorless form in bulk appeared problematic. Therefore, $[Me_4N]F$ was chosen.

We were excited to observe the formation of fluorobenzene (^{19}F NMR) from PhBr upon treatment with $[Me_4N]F$ in DMSO in the presence of 5−10% of **8** or **9** at 80−120 °C. The yield of Ph−F was modest, corresponding to only 3−5 equiv per Pd complex used. Attempted optimization was not successful but led to a critical observation: when 2-bromonaphthalene was used as the substrate in the presence of **9** at 105 °C, a ca. *3:2 mixture of 2-fluoronaphthalene and 1-fluoronaphthalene was obtained, immediately suggesting aryne intermediacy.*The same result was obtained when the experiment was repeated *in the absence of* **9** or any other source of palladium (eq 1). Furthermore, the yield of PhF from PhBr was higher when the Pd complex was omitted from the reaction. It became clear that the fluorination occurred via arynes and was *not* catalyzed by the Pd species.



(1)

While the century-old chemistry of arynes is widely used for aryl−carbon and aryl−heteroatom bond formation,[26] information on aryne-mediated fluorination is scarce and lacking in detail. We believe that carbon−fluorine bond formation via arynes was previously observed by Schwesinger's group. However, in their otherwise meticulous and highly detailed recent account of "naked" fluoride basicity and nucleophilicity, Schwesinger et al.[21b] mention this type of fluorination only in one brief sentence in the Conclusion, without providing any specifics or references to conventionally accessible literature sources,[27] except for one patent.[28]

(6) (a) Grushin, V. V. *Organometallics* **2000**, *19*, 1888. (b) Roe, D. C.; Marshall, W. J.; Davidson, F.; Soper, P. D.; Grushin, V. V. *Organometallics* **2000**, *19*, 4575. (c) Grushin, V. V.; Marshall, W. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4476. (d) Marshall, W. J.; Grushin, V. V. *Organometallics* **2003**, *22*, 555. (e) Grushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2006**, *128*, 12644.

(7) Yandulov, D. V.; Tran, N. T. *J. Am. Chem. Soc.* **2007**, *129*, 1342.

(8) (a) den Reijer, C. J.; Woerle, M.; Pregosin, P. S. *Organometallics* **2000**, *19*, 309. (b) den Reijer, C. J.; Dotta, P.; Pregosin, P. S.; Albinati, A. *Can. J. Chem.* **2001**, *79*, 693. (c) Geldbach, T. J.; Pregosin, P. S. *Eur. J. Inorg. Chem.* **2002**, 1907.

(9) (a) Grushin, V. V.; Marshall, V. J. *J. Am. Chem. Soc.* **2004**, *126*, 3068. (b) Macgregor, S. A.; Roe, D. C.; Marshall, W. J.; Bloch, K. M.; Bakhmutov, V. I.; Grushin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 15304. (c) Macgregor, S. A.; Wondimagegn, T. *Organometallics* **2007**, *26*, 1143.

(10) Blum, O.; Frolow, F.; Milstein, D. *J. Chem. Soc., Chem. Commun.* **1991**, 258.

(11) Jasim, N. A.; Perutz, R. N.; Whitwood, A. C.; Braun, T.; Izundu, J.; Neumann, B.; Rothfeld, S.; Stammler, H.-G. *Organometallics* **2004**, *23*, 6140.

(12) (a) Markies, B. A.; Canty, A. J.; de Graaf, W.; Boersma, J.; Janssen, M. D.; Hogerheide, M. P.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *J. Organomet. Chem.* **1994**, *482*, 191. (b) Marshall, W. J.; Grushin, V. V. *Can. J. Chem.* **2005**, *83*, 640.

(13) Complex **5** has been previously detected but not isolated: Paladino, G.; Madec, D.; Prestat, G.; Maitro, G.; Poli, G.; Jutand, A. *Organometallics* **2007**, *26*, 455.

(14) Stambuli, J. P.; Incarvito, C. D.; Bühl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 1184.

(15) (a) Fraser, S. L.; Antipin, M. Y.; Khroustalyov, V. N.; Grushin, V. V. *J. Am. Chem. Soc.* **1997**, *119*, 4769. (b) Pilon, M. C.; Grushin, V. V. *Organometallics* **1998**, *17*, 1774.

(16) Marshall, W. J.; Grushin, V. V. *Organometallics* **2004**, *23*, 3343.

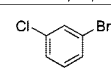
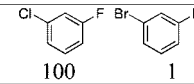
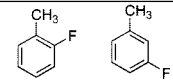
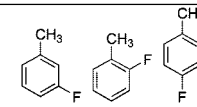
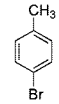
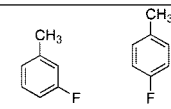
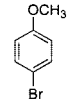
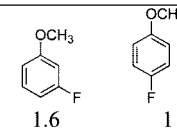
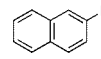
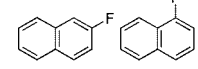
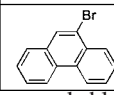
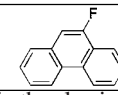
(17) Macgregor, S. A. *Chem. Soc. Rev.* **2007**, *36*, 67.

(18) (a) Daigle, D. J. *Inorg. Synth.* **1998**, *32*, 40. (b) Phillips, A. D.; Gonsalvi, L.; Romerosa, A.; Vizza, F.; Peruzzini, M. *Coord. Chem. Rev.* **2004**, *248*, 955, and references cited therein.

While an aryne mechanism might intuitively be most plausible for the patented fluorinations,[28] it does not seem to be consistent with some of the results claimed, such as the exclusive formation of 1-chloro-2-fluorobenzene from 1,2-dichlorobenzene[28] (see below).

Our results are summarized in Table 1. All reactions were run in glass vessels with agitation. The reaction mixtures were analyzed by GC-MS and ^{19}F NMR with an internal standard, and the isomeric structures of the fluoroarene products were unambiguously assigned on the basis of their distinct and characteristic ^{19}F NMR chemical shifts.[29]Bromoarenes gave rise to the fluorinated products in higher yields than analogous chloroarenes. In full accord with this, the reaction of 1-chloro-3-bromobenzene led to the formation of 1-chloro-3-fluorobenzene and 1-bromo-3-fluorobenzene in a ca. 100:1 ratio (Table 1, entry 2), along with traces of the ortho isomers. This indicated that, after deprotonation of the most acidic C−H bond between the Cl and Br atoms, the next step involves preferential elimination of the Br^-, a better leaving group than chloride in anhydrous DMSO. Similarly, the reaction of 1-bromo-3-iodobenzene with $[Me_4N]F$ produced 1-bromo-3-fluorobenzene as the main fluoroarene product. The isomer distribution patterns for the bromotoluene and bromoanisole series (Table 1, entries 3−8) are remarkably similar to those reported in the classical papers by Roberts and co-workers[30] for haloarene aminations via arynes.

Table 1. Aromatic Fluorination of Nonactivated Haloarenes (3 Equiv) with $[Me_4N]F$ (1 Equiv) in DMSO at Initial $[F^-] \approx 10\%$

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	

Absolute yields of the ArF products (Table 1) can be calculated only if the stoichiometry of the reaction is known. Mechanistic considerations suggest that *3 equiv* of Me_4NF might be needed for the introduction of *one* fluorine atom into the aromatic ring via the aryne mechanism (Scheme 3). In the first step of the reaction, a CH bond ortho to the halogen is deprotonated by the *first* equivalent of fluoride that is highly basic,[20–22] despite its high solvation energy in DMSO.[31] As a result, HF is formed that instantly consumes the *second* equivalent of F^- to form stable bifluoride, FHF^-. Indeed, large quantities of bifluoride are always produced in the reaction (^{19}F NMR). The *third* equivalent of fluoride is needed for nucleophilic addition to the aryne in the C−F bond forming step.[32] Thus, the fluoride likely plays a triple role in the reaction, namely C−H deprotonation, neutralization of the HF produced, and nucleophilic addition across the formally triple bond of the aryne electrophile. One might argue that the reaction is stoichiometric in the fluoride as the nucleophile but only catalytic in the F^- as the base. If the FHF^- produced in the first step (Scheme 3) added to the aryne and/or if the fluoroaryl anion deprotonated the bifluoride, then the F^- that originally acted as the base would be regenerated. It is unlikely, however, that bifluoride can successfully compete with much more nucleophilic fluoride for addition to the aryne electrophile. Furthermore, as has been observed in this work and reported by others,[33] anhydrous

(19) (a) Since this modification of our original method[15] was proposed,[19b] it has reportedly failed in the synthesis of other Pd(II) fluorides[6e,7] but appeared useful for the preparation of certain Ir(III) fluoro complexes.[19c](b) Yahav, A.; Goldberg, I.; Vigalok, A. *J. Am. Chem. Soc.* **2003**, *125*, 13634. (c) Bourgeois, C. J.; Garratt, S. A.; Hughes, R. P.; Larichev, R. B.; Smith, J. M.; Ward, A. J.; Willemsen, S.; Zhang, D.; DiPasquale, A. G.; Zakharov, L. N.; Rheingold, A. L. *Organometallics* **2006**, *25*, 3474.

(20) (a) Christe, K. O.; Wilson, W. W. *J. Fluorine Chem.* **1990**, *47*, 117. (b) Christe, K. O.; Wilson, W. W.; Wilson, R. D.; Bau, R.; Feng, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 7619.

(21) (a) Schwesinger, R.; Link, R.; Thiele, G.; Rotter, H.; Honert, D.; Limbach, H. H.; Maennle, F. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1372. (b) Schwesinger, R.; Link, R.; Wenzl, P.; Kossek, S. *Chem. Eur. J.* **2006**, *12*, 438.

(22) Grushin, V. V. *Angew. Chem., Int. Ed.* **1998**, *37*, 994.

(23) (a) There have been a few reports describing the synthesis of PPNF in methanol,[23b] water,[23c] and aqueous acetonitrile.[23d] The preparation methods for these forms of PPNF, along with their reported characterization and reactivity, suggest that none of them is a source of highly active fluoride such as the PPNF generated in situ under rigorously anhydrous conditions.[22] (b) Douglas, W.; Ruff, J. K. *J. Organomet. Chem.* **1974**, *65*, 65. (c) Martinsen, A.; Songstad, J. *Acta Chem. Scand., Ser. A* **1977**, *31*, 645. (d) Berkessel, A.; Brandenburg, M. *Org. Lett.* **2006**, *8*, 4401.

(24) As described for the synthesis of anhydrous $[Bu_4N]F$: Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050.

(25) The covalent form of PPNF (Figure 1) was obtained by reacting [PPN]CN with C_6F_6 in MeCN, followed by treatment with THF and precipitation with ether. When the reaction was repeated in MeCN or EtCN at a high concentration, treatment with THF produced other crystalline forms of PPNF, in which no covalent P−F bond was present (X-ray). Numerous attempts to obtain an accurate enough structure of those ionic forms failed. The P−F bond in the covalent form of PPNF (Figure 1) is uncommonly long in the crystalline state (1.8196(9) Å) and is ionized in solution (MeCN, DMSO), as judged by the lack of P−F coupling in the ^{19}F and ^{31}P NMR spectra.

(26) (a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. (b) Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier: London, 1968. (c) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992. (d) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701, 2575. (e) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem. Int. Ed.* **2003**, *42*, 502. (f) Winkler, M.; Wenk, H. H.; Sander, W. In *Reactive Intermediate Chemistry*; Moss, R. A., Platz, M. S., Jones, M., Jr., Eds.; Wiley: Hoboken, NJ, 2004; pp 741−794. (g) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579.

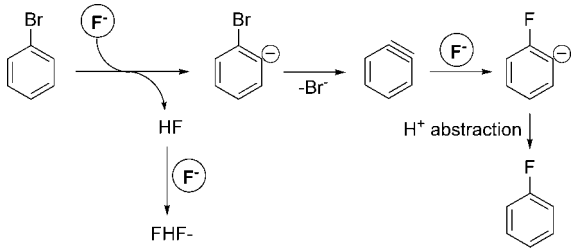
(27) Two Ph.D. theses, one by R. Link and the other by P. Wenzl, as cited in refs 58 and 60 of the account.[21b] We have not been able to find either thesis and/or its abstract in the STN International Dissertation Database, Scopus, and Scifinder.

(28) Nobori, T.; Fujiyoshi, S.; Hara, I.; Hayashi, T.; Shibahara, A.; Funaki, K.; Mizutani, K.; Kiyono, S. U.S. Patent 6,469,224, 2002.

(29) (a) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. (b) Sterk, H.; Fabian, W. *Org. Magn. Reson.* **1975**, *7*, 274. (c) Arunima; Kurur, N. D. *Magn. Reson. Chem.* **2005**, *43*, 132.

(30) (a) Roberts, J. D.; Semenow, D. A.; Simmons, H. E., Jr.; Carlsmith, L. A. *J. Am. Chem. Soc.* **1956**, *78*, 601. (b) Roberts, J. D.; Vaughan, C. W., Jr.; Carlsmith, L. A.; Semenow, D. A. *J. Am. Chem. Soc.* **1956**, *78*, 611.

Scheme 3



[Me_4N]F does deprotonate DMSO to produce bifluoride in the temperature range used for the fluorination reactions (Table 1). For instance, we found that, at 90 °C, a 10% solution of [Me_4N]F in anhydrous DMSO produced bifluoride in ca. 5% and 10% yield (^{19}F NMR) after 1 and 2.2 h, respectively (for more data, see below). Furthermore, a phosphazenium fluoride has been demonstrated to deprotonate such weak acids as dibenzocycloheptane (pK_a in DMSO 32.8) and 4-methylbiphenyl (extrapolated pK_a in DMSO 37.6).[21b] For comparison, pK_a values of DMSO have been reported at 31.3[34] and 35.1.[35]

On the basis of the *carefully proposed* stoichiometry (Scheme 3), the total fluorination yields in the reactions employing ArX substrates in excess (Table 1) were in the range of 10−65%, as calculated on the amount of Me_4NF used. The NMR yield of PhF from PhBr after 12 h at 110 °C was calculated at 60%. All bromoanisoles and bromotoluenes, being less reactive, gave rise to the corresponding fluoroarenes in only 10−30% yield. The two isomeric fluoronaphthalenes (Table 1, entry 9) were produced in 65% total yield. The yield of 9-fluorophenanthrene (entry 10) was 55%.

The remarkably high reactivity of "naked" fluoride,[20–22] both as a base and as a nucleophile, is the key for the aryne-mediated aromatic fluorination, yet is also a yield-lowering factor in this reaction. As a strong base, Me_4NF can deprotonate even very weakly CH-acidic DMSO in the temperature range required for the aryne generation. As a strong nucleophile, the F^- in Me_4NF is known to react with its own counterion to give MeF and Me_3N.[20] After a 5% solution of Me_4NF in DMSO-d_6 was kept at 90 °C for 24 h, ^{1}H and ^{19}F NMR analysis indicated that approximately 25% of the salt had decomposed to produce FDF^- (−142.5 ppm, t, J_{D-F} = 18 Hz) and FHF^- (−142.0 ppm, d, J_{H-F} = 120 Hz) in a 3.7:1 molar ratio, and all four isotopomers of MeF (Figure 2), pointing to efficient H/D exchange between the solvent and the Me_4N^+ cation. In the ^{1}H NMR spectrum, the exchange was manifested by multiplet resonances from the H,D isotopomers of Me_3N, Me_4N^+, and MeF at 2.1, 3.2, and 4.2 ppm, respectively. Clearly, both DMSO and Me_4N^+ undergo deprotonation by the strongly basic fluoride under these conditions. Note that to deprotonate DMSO and Me_4N^+ [36] strong bases are employed, such as NaH and PhLi, respectively. When the PhBr fluorination with Me_4NF (Table 1) was repeated in DMSO-d_6, a significant incorporation of deuterium into the fluorobenzene product was observed (^{19}F NMR and GC-MS). This is conceivably due to H/D exchange at the first deprotonation step that is probably reversible, as well as to the DMSO solvent being the primary proton (deuteron) donor in the final step of the fluoroarene formation.

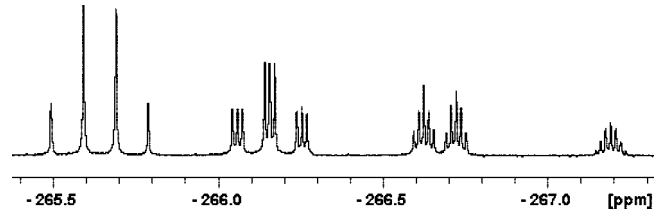


Figure 2. ^{19}F NMR signals from CH_3F, CH_2DF, CHD_2F, and CD_3F (J_{H-F} = 46 Hz; J_{D-F} = 7 Hz) formed upon heating of Me_4NF in DMSO-d_6 at 90 °C for 24 h.

As follows from the above, it would be desirable to identify an aprotic solvent which, while providing good solubility and stability to Me_4NF, was even less reactive to the active fluoride than DMSO in the required temperature range. This appears to be nontrivial, as DMF, NMP, MeCN, and ethereal solvents are considerably less stable toward strong bases, Me_4NF included. When the 9-bromophenanthrene reaction (Table 1, entry 10) was repeated in HMPA, less than 10% conversion was observed and only trace amounts of 9-fluorophenanthrene were formed, along with comparable small quantities of phenanthrene. DMSO seems to be especially suitable as a medium for the reaction. We carefully propose that the CH acidity of DMSO is in the right range for the fluorination reaction, being low enough for the active fluoride to survive yet sufficient for serving as a proton donor to the carbanion emerging upon F^- addition to the aryne electrophile. It is also noteworthy that Me_4NF was found to be insoluble in pivalonitrile even at its boiling point of around 107 °C.

In conclusion, N,N- and S,S-chelate-stabilized palladium iodo aryls neither form isolable Pd−F species nor produce fluoroarenes upon treatment with AgF under sonication. These studies, however, have led to the finding of aryne-mediated fluorination of nonactivated haloarenes with Me_4NF in DMSO under mild conditions (80−110 °C).

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Supporting Information Available: Text giving experimental details and CIF files giving X-ray analysis data for **5**−**8** and PPNF. This material is available free of charge via the Internet at http://pubs.acs.org.

OM800520E

(31) Dillow, G. W.; Kebarle, P. *J. Am. Chem. Soc.* **1988**, *110*, 4877.

(32) A side reaction of fluoride addition to an independently generated aryne has been documented: Kolomeitsev, A. A.; Vorobyev, M.; Gillandt, H. *Tetrahedron Lett.* **2008**, *49*, 449.

(33) Bastos, M. M.; Barbosa, J. P.; Pinto, A. C.; Kover, W. B.; Takeuchi, Y.; Boechat, N. *J. Braz. Chem. Soc.* **2001**, *12*, 417.

(34) Steiner, E. C.; Gilbert, J. M. *J. Am. Chem. Soc.* **1965**, *87*, 382.

(35) Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295.

(36) (a) Wittig, G.; Wetterling, M.-H. *Liebigs Ann. Chem.* **1947**, *557*, 193. (b) Wittig, G.; Krauss, D. *Liebigs Ann. Chem.* **1964**, *679*, 34.