JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

Deoxyfluorination of Phenols

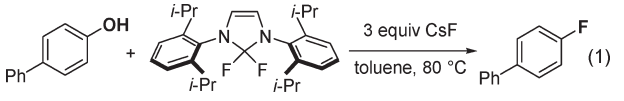
Pingping Tang, Weike Wang, and Tobias Ritter*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138, United States

Supporting Information

ABSTRACT: An operationally simple ipso fluorination of phenols with a new deoxyfluorination reagent is presented.

While several arene fluorination reactions have been reported within the past five years,[1,2] efficient fluorination of fine and bulk chemicals is still an unsolved problem.[3] Simple aryl fluorides can be accessed by conventional fluorination reactions such as the Balz−Schiemann reaction,[4] but currently, only two fluorination reactions are available to make functionalized fluoroarenes with a large variety of substitution patterns: Buchwald's palladium-catalyzed nucleophilic fluorination of aryl triflates[1j] and a silver-catalyzed electrophilic fluorination of aryl stannanes reported by our group.[11] Both reactions currently lack practicality: the palladium-catalyzed reaction requires anhydrous conditions and can give mixtures of constitutional isomers, and the silver-catalyzed reaction requires the stepwise synthesis of toxic aryl stannanes. Our goal was to develop a reliable and operationally simple fluorination reaction that provides more straightforward access to a wide variety of aryl fluorides. Here we present a fluorinating reagent that delivers aryl fluorides from phenols by a one-step ipso substitution (eq 1):



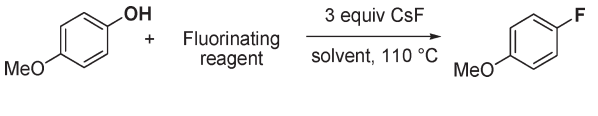
(1)

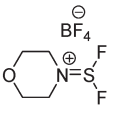
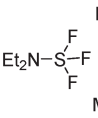
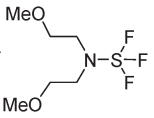
1 90%

The new deoxyfluorination reagent **1** was prepared by treatment of *N*,*N*-diaryl-2-chloroimidazolium chloride,[5] which is readily available in >100 g quantities (see the Supporting Information), with CsF. Reagent **1** can be handled in air as a solid but hydrolyzes upon prolonged storage in a wet atmosphere. It can be stored in a dry toluene solution for at least two months without detectable decomposition. The reactions of **1**, 4-methoxyphenol, and CsF in toluene and dioxane afforded 4-fluoroanisole in 82 and 88% yield, respectively (Table 1). The commercially available deoxyfluorination reagents[6] shown in Table 1 did not afford any detectable fluoroanisole under identical reaction conditions. Reactions performed in polar (MeCN) or protic solvents afforded no detectable aryl fluoride with any of the evaluated commercial fluorinating reagents and less than 10% yield with fluorinating reagent **1**.

A variety of phenols were evaluated for fluorination (Table 2). Phenols with electron-withdrawing groups reacted more rapidly than phenols substituted with electron-releasing functional groups and typically afforded >90% yields of fluorinated arene after heating at 80 °C for 3 h. In this study, we focused on electron-rich arenes because electron-poor arenes can typically be prepared by nucleophilic aromatic substitution.[7] Electron-rich phenols can be fluorinated by **1** upon heating at 110 °C for 20 h. It is noteworthy that even 4-fluoroaniline (**15**) can be prepared by the presented method.

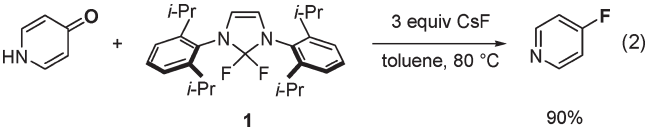
Table 1. Evaluation of Different Fluorination Reagents[a]



Fluorinating reagent:	MeCN	dioxane	toluene
 1	<1%	88%	82%
 Xtalfluor-E	<1%[b]	<1%[b]	<1%[b]
 Xtalfluor-M	<1%[b]	<1%[b]	<1%[b]
 DAST	<1%[b]	<1%[b]	<1%[b]
 DEOXYFLUOR	<1%[b]	<1%[b]	<1%[b]

[a] Yields were determined by ^{19}F NMR analysis with 1-fluoro-3-nitrobenzene as an internal standard. [b] The commercially available deoxyfluorination reagents afforded no detectable 4-fluoroanisole in MeCN, 1,4-dioxane, or toluene.

Strong hydrogen-bond donors such as alcohols are not tolerated unless the hydrogen atom of the alcohol OH group is engaged in intramolecular hydrogen bonding, such as in **28**. Amides derived from ammonia and primary amines, which are potential hydrogen-bond donors, are challenging substrates for the fluorination reaction. For example, 4-fluorobenzamide was isolated in only 20% yield. Phenols featuring amides derived from secondary amines such as **17** can be fluorinated, as can 2- and 4-pyridones (eq 2; also see structures **23** and **25** in Table 2). Both compound classes afford products that lack N−H hydrogen-bond donors. Importantly, deoxyprotonated products and constitutional isomers were not observed throughout our study; all substitutions were ipso substitutions with fluoride. The palladium-catalyzed fluorination of aryl triflates[1j] can give constitutional isomers; for example, fluorination of the triflate derived from 4-methoxyphenol afforded 3-fluoroanisole as the major product (58%) and only 25% **12**.



(2)

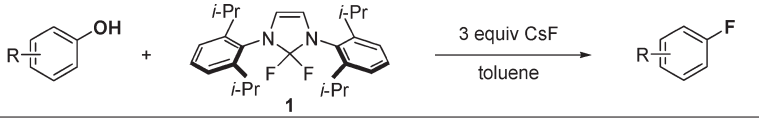
1 90%

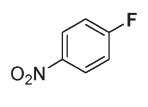
We propose that the mechanism for fluorination proceeds via a 2-phenoxyimidazolium bifluoride salt such as **30** that is formed

Received: May 25, 2011
Published: July 07, 2011

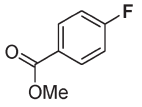
dx.doi.org/10.1021/ja2048072 | *J. Am. Chem. Soc.* 2011, 133, 11482–11484

Table 2. Deoxyfluorination of Phenols with Reagent 1[a]

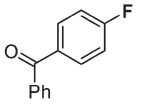




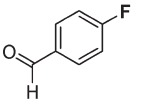
2, 93%
(80 °C, 3 h)



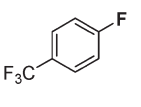
3, 98%[b]
(80 °C, 3 h)



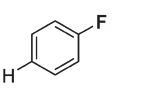
4, 95%
(80 °C, 3 h)



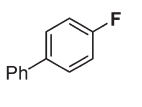
5, 95%[b]
(80 °C, 3 h)



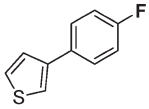
6, 92%[b]
(80 °C, 3 h)



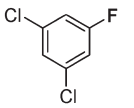
7, 82%[b]
(80 °C, 18 h)



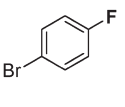
8, 90%
(80 °C, 18 h)



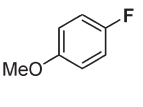
9, 91%
(80 °C, 18 h)



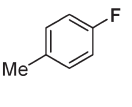
10, 88%[b]
(80 °C, 18 h)



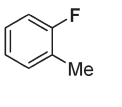
11, 88%[b]
(80 °C, 18 h)



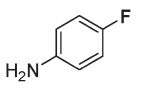
12, 82%[b]
(110 °C, 20 h)



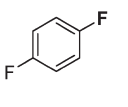
13, 81%[b]
(110 °C, 20 h)



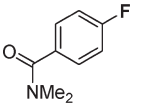
14, 87%[b,c,d]
(110 °C, 20 h)



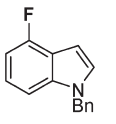
15, 75%[b,c]
(110 °C, 20 h)



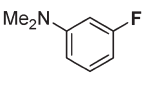
16, 74%[b]
(110 °C, 20 h)



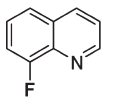
17, 91%
(110 °C, 20 h)



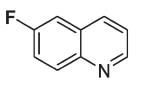
18, 86%
(110 °C, 20 h)



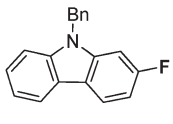
19, 88%[c]
(110 °C, 20 h)



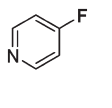
20, 90%
(110 °C, 20 h)



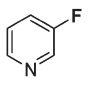
21, 92%
(110 °C, 20 h)



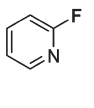
22, 95%
(110 °C, 20 h)



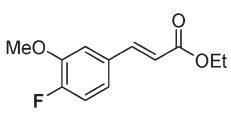
23, 90%[b]
(80 °C, 18 h)



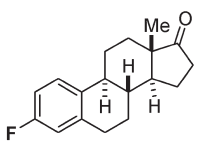
24, 84%[b]
(110 °C, 20 h)



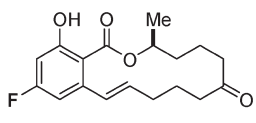
25, 50%[b,c,e]
(110 °C, 20 h)



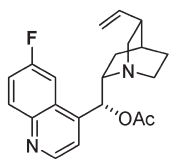
26, 88%
(110 °C, 20 h)



27, 90%
(110 °C, 20 h)



28, 75%
(110 °C, 20 h)



29, 95%
(110 °C, 20 h)

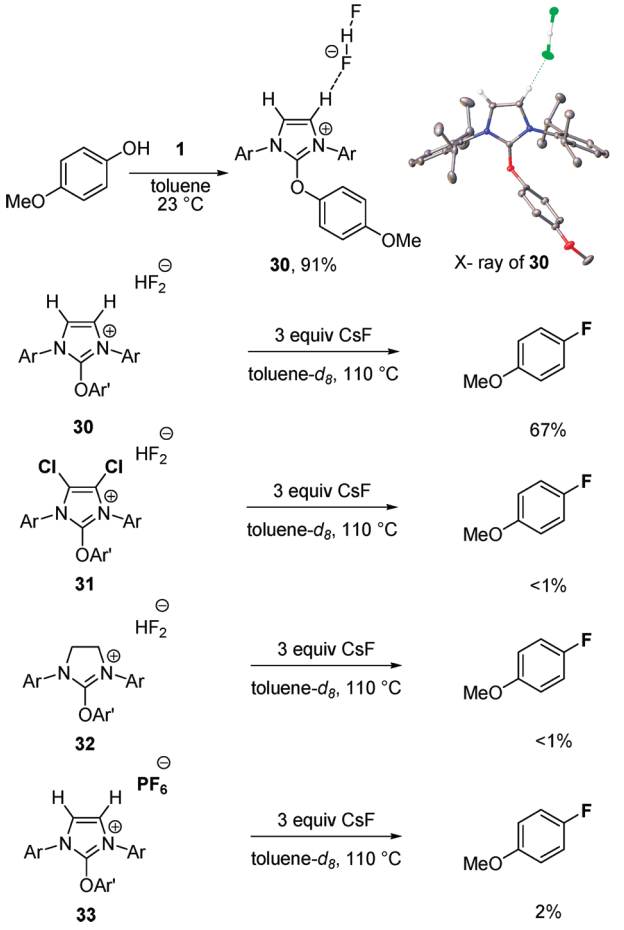
[a] Reaction conditions: 1.2 equiv of **1**, concentration = 0.1 M. Toluene was used as standard solvent because its boiling point (111 °C) is higher than that of 1,4-dioxane (101 °C). [b] Yields were determined by ^{19}F NMR analysis with 1-fluoro-3-nitrobenzene as a standard. [c] 1,4-Dioxane was used as the solvent. [d] 20 mol % $ZnPh_2$ was added;[8] the yield was 55% in the absence of $ZnPh_2$. [e] 20 mol % $ZnPh_2$ was added;[8] the yield was 25% in the absence of $ZnPh_2$.

by condensation of a phenol with **1** (Scheme 1). Salt **30** was formed upon mixing 4-methoxyphenol and **1** and could be isolated in 91% yield. A hydrogen bond between one hydrogen atom of the imidazolium heterocycle and the bifluoride counteranion was identified in the crystal structure of **30** (C−F distance in **C**−H···**F**−H−F = 3.0 Å). We postulate that a similar hydrogen bond is also present in solution in apolar solvents: when hexafluorophosphate salt **33** was treated with bifluoride, a shift in the ^{1}H NMR resonance of the hydrogen atoms of the imidazolium heterocycle from 7.56 to 7.98 ppm was observed (see the Supporting Information). Bifluoride is a strong hydrogen-bond acceptor.[9] Hydrogen bonding could facilitate fluorination because it renders the uronium a better nucleofuge or because bifluoride salts such as **30** exist as soluble tight ion pairs in apolar solvents, with close proximity of fluoride to the ipso carbon. In agreement with both hypotheses, imidazolium salts **31** and **32**, which lack the opportunity for similar hydrogen bonding, did not afford detectable aryl fluoride upon heating. Likewise, exchange of the bifluoride for the less strongly hydrogen-bond-accepting counteranion PF_6 lowered the reaction yield to 2%. Moreover, the commercially available deoxyfluorinating reagents shown in Table 1 lack the ability to form intermediates suitable for C(sp^2)−H···F−H−F hydrogen bonding as found in **30**, which may explain the difference between the deoxyfluorinating reactivities of the known reagents and **1**. Quantitative rate measurements, such as a Hammett analysis with different substituents in the para position of the phenol, were not obtained because the reaction mixture was heterogeneous. The heterogeneous mixture may also explain the difference in the yield of fluorination when fluorination was performed with isolated **30** (67%, reaction incomplete) rather than with **30** formed in situ in the presence of excess CsF (82%).

In conclusion, we have developed a practical deoxyfluorination of phenols that can be used conveniently from milligram to multigram scale. Whereas hydrogen bonding is undesirable in conventional nucleophilic fluorination chemistry because it reduces the nucleophilicity of fluoride, hydrogen bonding appears to be crucial for the fluorination reaction presented here. A disadvantage of the transformation is the generation of a stoichiometric amount of waste, the urea byproduct. However, the deoxyfluorination proceeds in one step from phenols. Ultimately, a fluorination reaction that could combine the operational simplicity

dx.doi.org/10.1021/ja2048072 |J. Am. Chem. Soc. 2011, 133, 11482–11484

Scheme 1. Studies of Hydrogen Bonding[a]



[a] Ar = 2,6-diisopropylphenyl; Ar′ = 4-methoxylphenyl.

of the transformation presented here, the catalysis approach of the Buchwald fluorination, and the ability to fluorinate complex molecules late-stage as accomplished by the silver-catalyzed fluorination would significantly advance the field of fluorination.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectroscopic data for all new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
ritter@chemistry.harvard.edu

■ ACKNOWLEDGMENT

We thank Dr. Shao-Liang Zheng for his help with X-ray data collection and structure determination. This work was supported by NSF (CHE-0952753) and NIH-NIGMS (GM088237).

■ REFERENCES

(1) For transition-metal-mediated C−F bond formation, see: (a) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (b) Akana, J. A.; Bhattacharyya, K. X.; Müller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 7736. (c) Kaspi, A. W.; Yahav-Levi, A.; Goldberg, I.; Vigalok, A. *Inorg. Chem.* **2008**, *47*, 5. (d) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5993. (e) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060. (f) Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 1662. (g) Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 3796. (h) Wang, X.; Mei, T. S.; Yu, J. Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520. (i) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860. (j) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661. (k) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard, W. A., III; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793. (l) Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150. (m) Tang, P.; Ritter, T. *Tetrahedron* **2011**, *67*, 4449.

(2) For other recent arene fluorination reactions, see: (a) Sun, H.; DiMagno, S. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2720. (b) Yamada, S.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 2215. (c) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2219.

(3) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470.

(4) (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (b) Furuya, T.; Klein, J. E. M. N.; Ritter, T. *Synthesis* **2010**, 1804.

(5) Mendoza-Espinosa, D.; Donnadieu, B.; Bertrand, G. *J. Am. Chem. Soc.* **2010**, *132*, 7264.

(6) (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574. (b) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M. *Chem. Commun.* **1999**, 215. (c) Hayashi, H.; Sonoda, H.; Fukumura, K.; Nagata, T. *Chem. Commun.* **2002**, 1618. (d) Beaulieu, F.; Beauregard, L. P.; Courchesne, G.; Couturier, M.; LaFlamme, F.; L'Heureux, A. *Org. Lett.* **2009**, *11*, 5050.

(7) For selected nucleophilic aromatic fluorination reactions, see: (a) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273. (b) Adams, D. J.; Clark, J. H. *Chem. Soc. Rev.* **1999**, *28*, 225. (c) Kuduk, S. D.; DiPardo, R. M.; Bock, M. G. *Org. Lett.* **2005**, *7*, 577. (d) Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050.

(8) The role of $ZnPh_2$ has not yet been established.

(9) Kollman, P. A.; Allen, L. C. *J. Am. Chem. Soc.* **1970**, *92*, 6101.