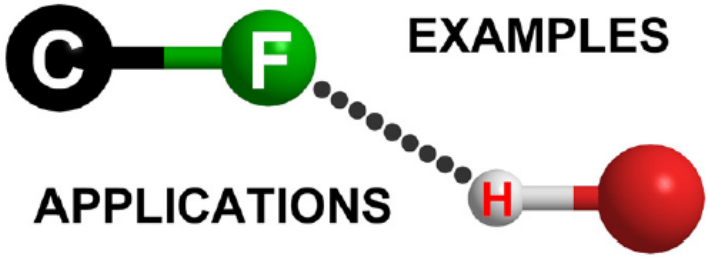
Organic Fluorine as a Hydrogen-Bond Acceptor: Recent Examples and Applications



Reporter: Xinjin Li

Feb 2nd, 2015

Content

1. Introduction

Whether or not organic
fluorine can act as a hydrogen-bond acceptor?

C–F bonds can act as weak, yet energetically favorable proton acceptors.

1983 ,1994, Glusker
2002, Desiraju
2012, Schneider

Schneider, H.-J. *Chem. Sci.* **2012**, *3*, 1381.

Fluorine lone pairs are not good hydrogen-bond acceptors.

1996, O'Hagan
1997, Dunitz and Taylor
2008, O'Hagan

O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37,* 308.

Enough evidence has been published to support the idea that organic fluorine is indeed a hydrogen-bond acceptor.

Champagne, P. A.; Desroches, J.; Paquin, J.-F. *Synthesis* **2015**, *47*, 306-322.

2. Properties of Hydrogen Bonds

2011, IUPAC set the following criteria for a X–H···Y hydrogen bond.

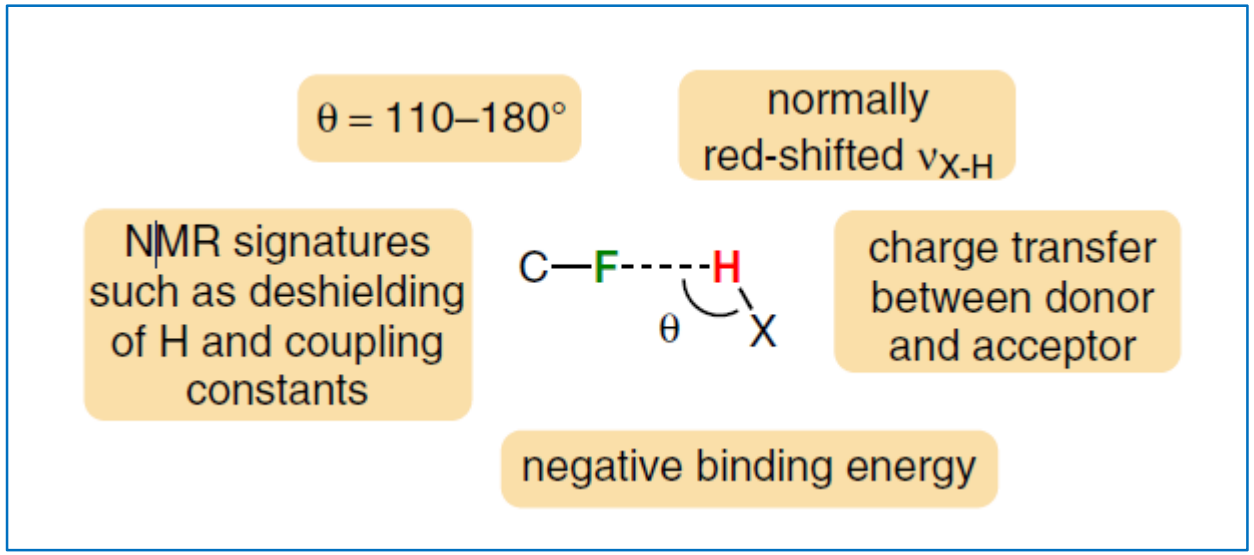


Figure 1 IUPAC requirements for hydrogen bonds

Pure Appl. Chem., **2011**, *83*, 1619–1636.
Pure Appl. Chem., **2011**, *83*, 1637–1641.

2. Properties of Hydrogen Bonds

Hydrogen bonds with organic fluorine are **quite different** from conventional hydrogen bonds and have specific properties.

(1) Organic fluorine is a weak hydrogen-bond acceptor.

(2) Energy calculations of weak C(sp^3/sp^2)-H···F-C(sp^3/sp^2) intermolecular interactions:

C(sp^2)–H is a better donor than C(sp^3)–H; C(sp^3)–F is a better acceptor than C(sp^2)–F .

(3) Shielded fluorine atoms are better acceptors and rank them as follows:

CH_3CH_2F (^{19}F δ = –212) > CH_3CHF_2 (^{19}F δ = –110) ≅ $CH_3CF_2CH_3$ (^{19}F δ = – 84.5) > CH_3CF_3 (^{19}F δ = –65).

(1) Panini, P.; Chopra, D. *CrystEngComm* **2013,** *15,* 3711.
(2) Dalvit, C.; Vulpetti, A. *ChemMedChem* **2011,** *6*, 104.

3. C(sp^2)–F as a Hydrogen-Bond Acceptor

3.1 O–H as Donor

(1) O–H is one of the strongest hydrogen-bond donors.

(2) Intramolecular hydrogen bonds are more likely to occur than intermolecular hydrogen bonds.

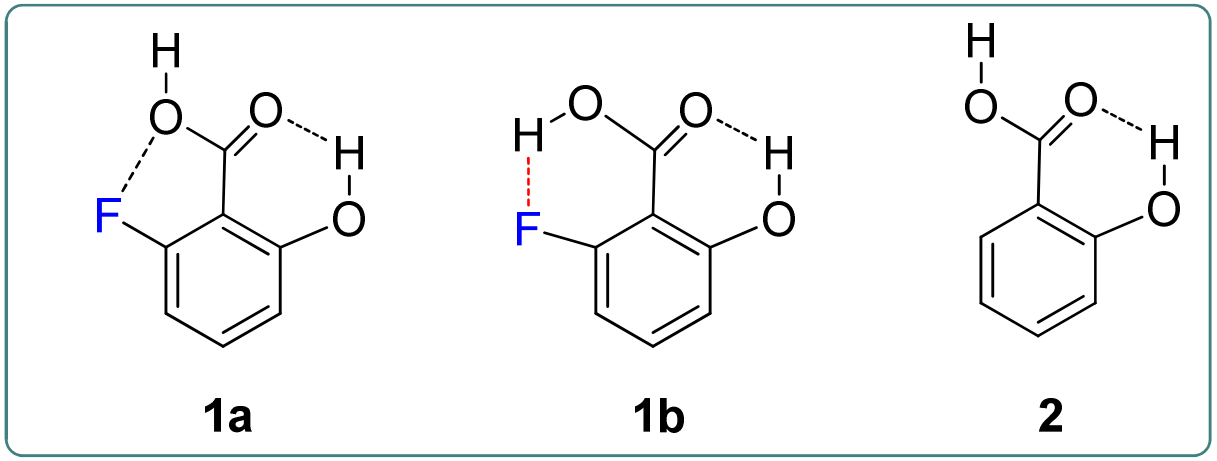


Figure 2 Most stable conformers of 6-fluorosalicylic acid (**1**) and salicylic acid (**2**)

Silla, J. M.; Duarte, C. J.; Rittner, R.; Freitas, M. P. *RSC Adv.* **2013,** *3, 25765.*

3.1 O–H as Donor

(1) One kind of hydrogen atom contact with the fluorine atom ($d_{H,F}$ = 2.11 Å).

(2) The O–H···F angle in the second conformer is 131.6°.

(3) The signal of the hydrogen atom of the hydroxyl group appears as a doublet [$^{1h}J_{(H,F)}$ = 6.0 Hz] in low polar solvents with an upfield shift (Δδ = 0.25–0.5 ppm)

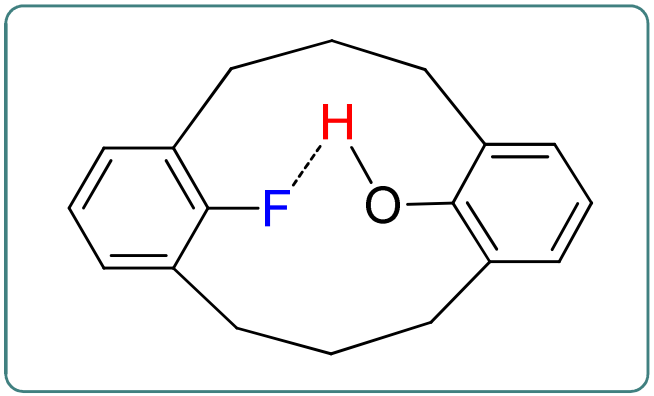


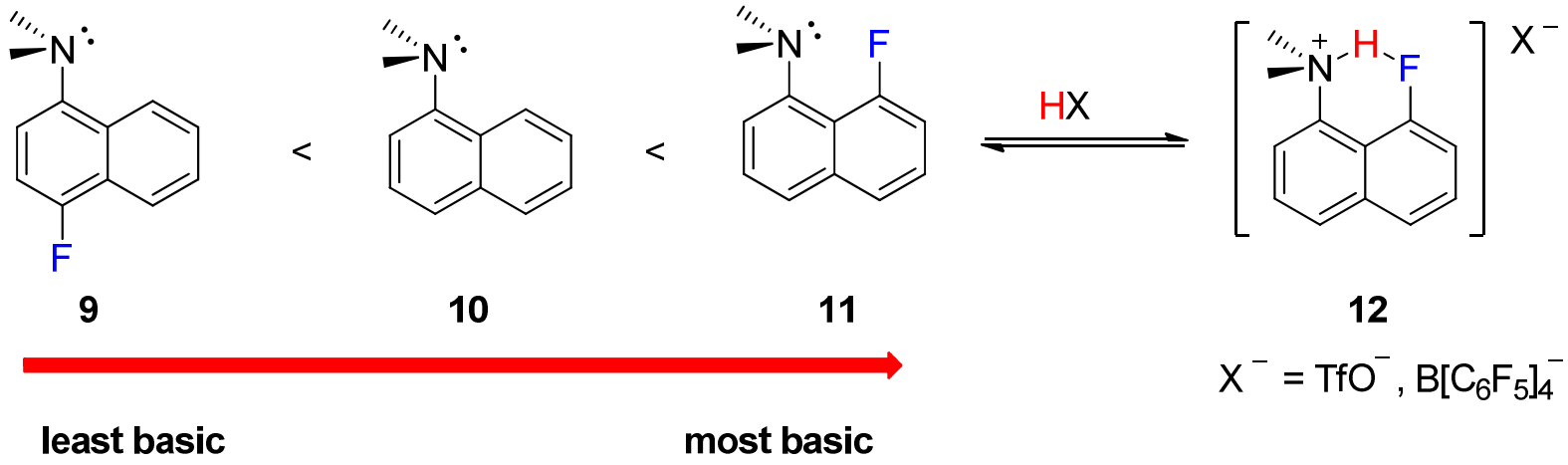
Figure 3 9-Fluoro-18-hydroxy-[3.3]metacyclophane contains a O–H···F–C hydrogen bond

Takemura, H.; Kotoku, M.; Yasutake, M.; Shinmyozu, T. *Eur. J. Org. Chem.* **2004**, 2019.

3.2 N–H as Donor

(1) Calculations predicted a 66 cm^{-1} IR red shift for the N–H stretch band of **12** relative to protonated **10.**

(2) Salt **12** (X– = TfO^-, $B[C_6F_5]_4^-$) was also characterized by X-ray crystallography (d_{HF} = 2.13 Å, ∠N–H–F = 120.7°), and ^{19}F NMR analysis [$^{1h}J_{(H,F)}$ = 43.7 Hz].

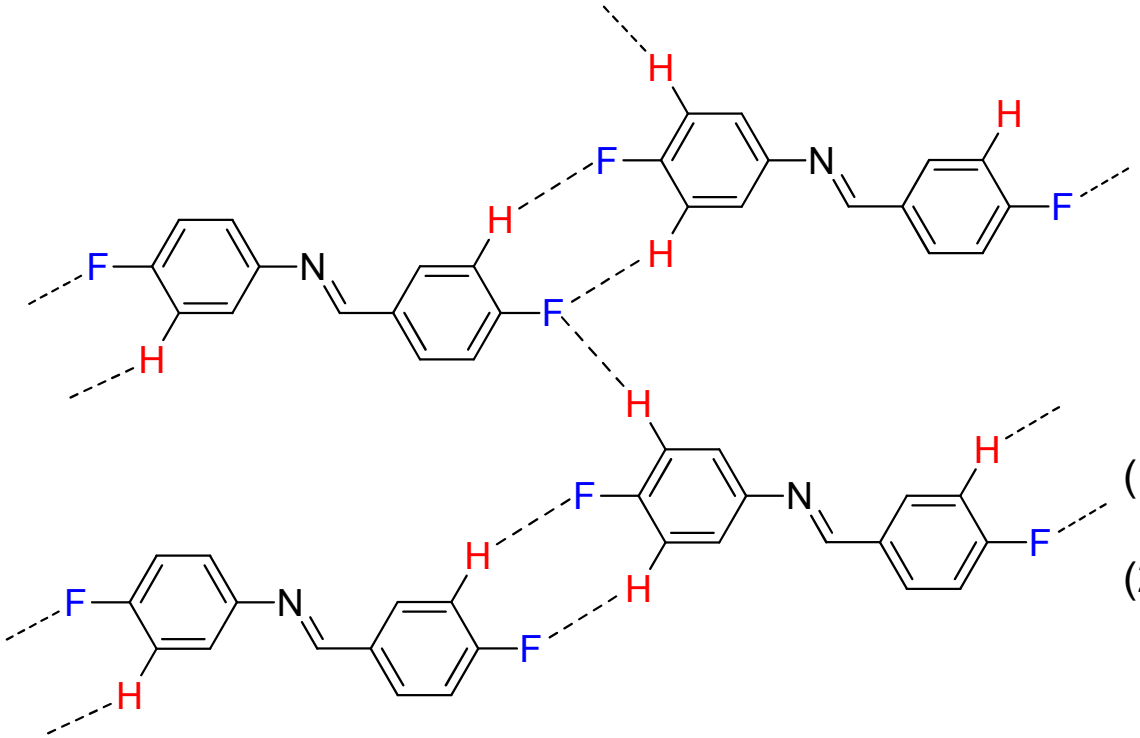


Scheme 1 Relative basicity and explanation for increased basicity of **11**

Scerba, M. T.; Johnson, M. A.; Lectka, T; and et al. *J. Org. Chem.* **2011**, *76*, 7975.

3.3 C(sp^2)–H as Donor

Supramolecular arrangements involving hydrogen bonds with organic fluorine were also observed.



(1) The H,F distance ranges from 2.18 to 2.62 Å.
(2) C–H···F angle is between 120 and 176°.

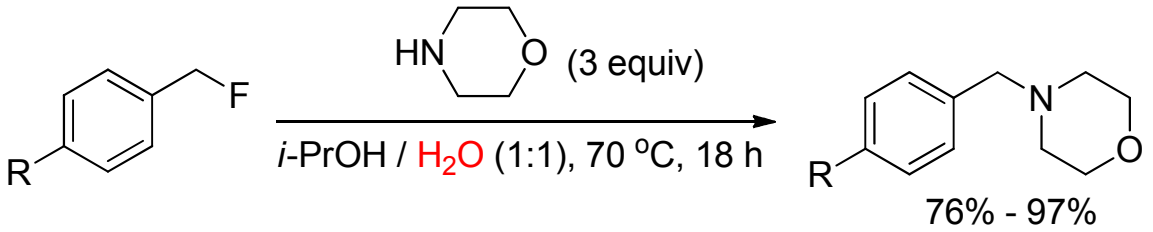
Figure 4 Packing motif of fluorinated N-benzylideneaniline

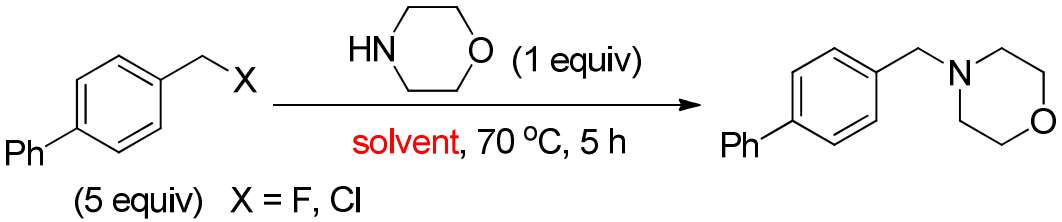
Kaur, G.; Panini, P.; Chopra, D.; Choudhury, A. R. *Cryst. Growth Des.* **2012**, *12*, 5096.

4. C(sp^3)–F as a Hydrogen-Bond Acceptor

4.1 O–H as Donor

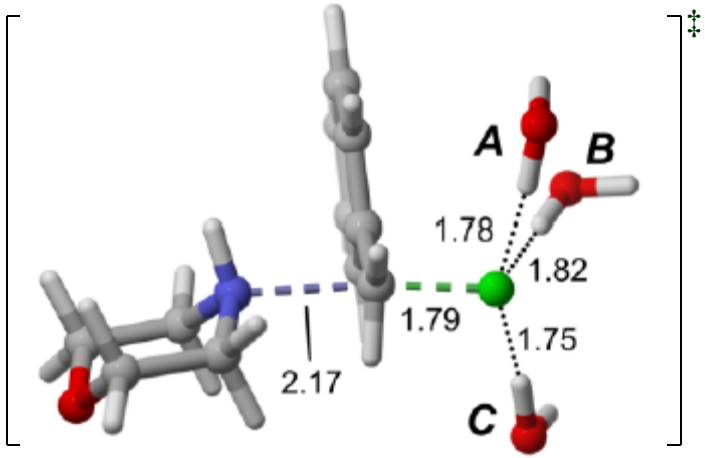
Hydrogen-bond donors could act as C–F activation agents through a similar interaction.





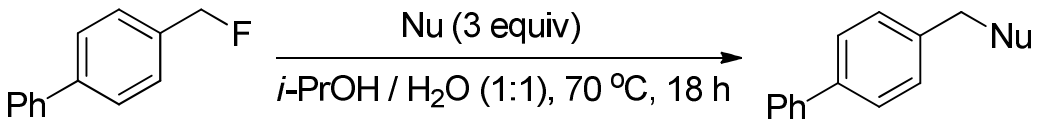
solvent	
DMF	$k_{Cl} / k_F > 49$
DMF / H_2O (1:1) (0.1 M)	k_{Cl} / k_F ~5

via

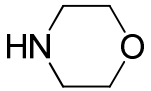
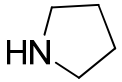
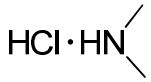
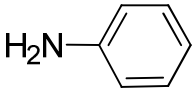
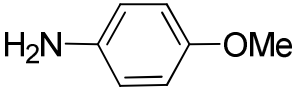
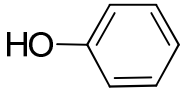
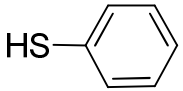
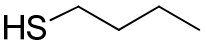


Champagne, P. A.; Pomarole, J.; Paquin, J.-F.; and et al. *Org. Lett*. **2013**, *15*, 2210.

Table 1 SN_2 reaction of 4-phenylbenzyl fluoride (**1a**) with N-, O-, S- and C- nucleophiles.

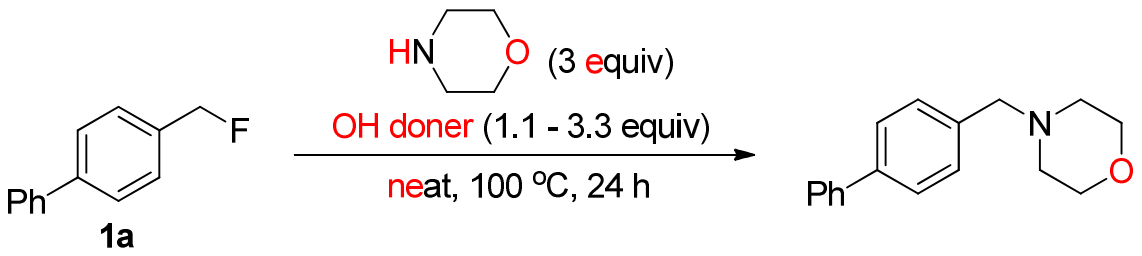


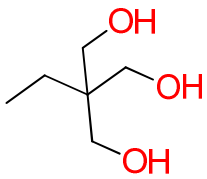
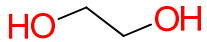
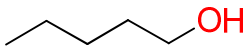
1a **2, 11-19**

Entry	Nu	Product	Yield [%][a]
1		**2**	96
2		**11**	98
3		**12**	73
4[b]		**13**	97
5[c]		**14**	77
6[c]		**15**	96
7[d]		**16**	36
8		**17**	88
9		**18**	64
10[e]	*n*-$Bu_4N^+CN^-$	**19**	13

[a] Yields after purification by flash chromatography. [b] 3 equiv of DBU was also added. [c] Reaction was performed at 90 °C for 48 h. [d] 3 equiv of NaOH was also added. [e] 10 equiv. of the n-$Bu_4N^+CN^-$ was used.

Table 2 Substitution of **1a** with morpholine musing different OH donors



Entry	OH doner	Equivalents	Conversion [%][a]
1		1.1	96[b]
2		1.1	91
3		1.65	97[b]
4		1.1	67[b]
5[b]		3.3	96[b]

[a] Determined by ^{1}H NMR analysis of the crude mixture.
[b] Average of two experiments.

Champagne, P. A.; Drouin, M.; Legault, C. Y.; Audubert, C.; Paquin, J.-F. *J. Fluorine Chem.* **2014**, in press; DOI: 10.1016/j.jfluchem.2014.08.018

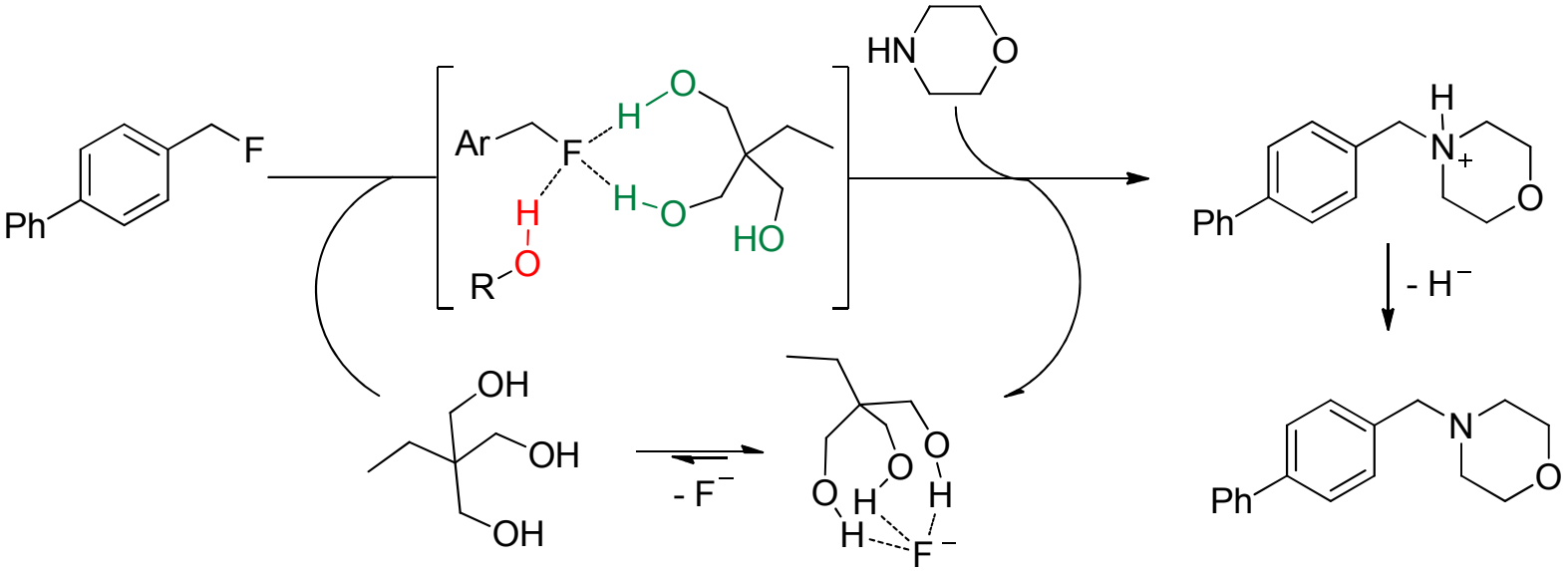


Figure 5 Improved proposed mechanism (R–O–H represents an alcohol from another triol molecule)

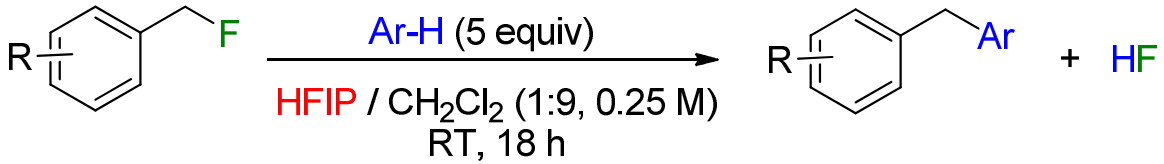
Three OH groups around the fluorine atom at the transiton-state are better to activate the C–F bond, *but only two of them can originate from a single triol molecule.*

Champagne, P. A.; Drouin, M.; Legault, C. Y.; Audubert, C.; Paquin, J.-F. *J. Fluorine Chem.* **2014**, in press; DOI: 10.1016/j.jfluchem.2014.08.018

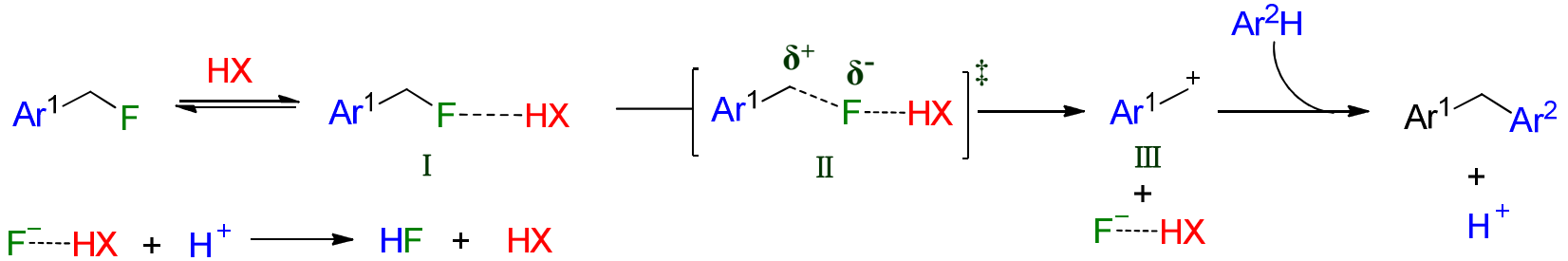
4. C(sp^3)–F as a Hydrogen-Bond Acceptor

4.1 O–H as Donor

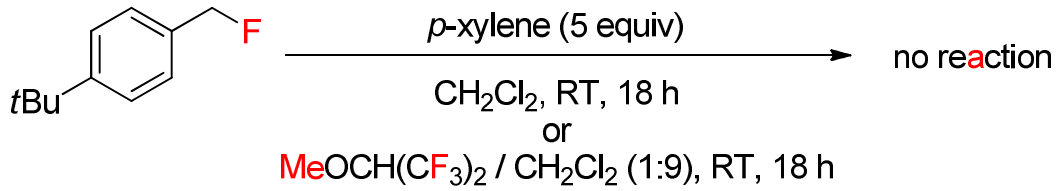
The activation and nucleophilic substitution of benzylic fluorides by using C–F···H–O hydrogen bonds.

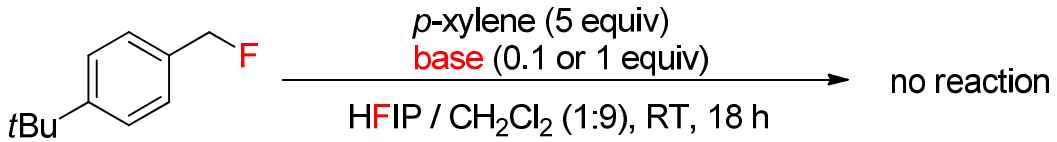


HFIP: $(CF_3)_2CHOH$ (*a stronger hydrogen-bond donor than water*)

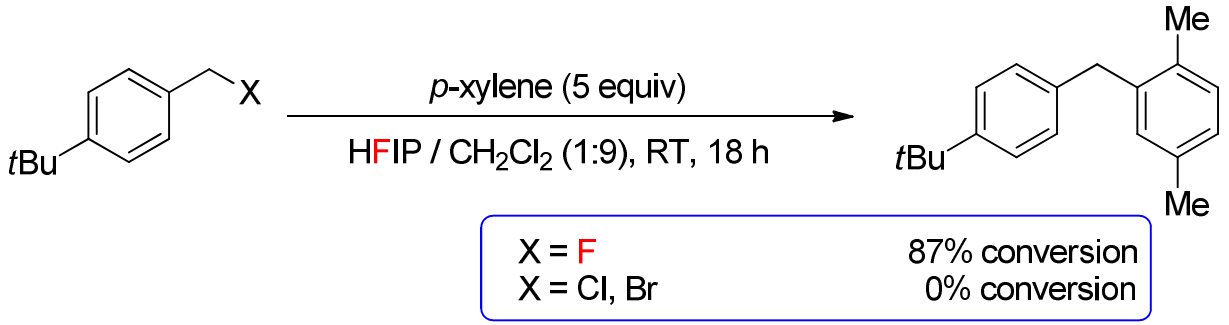


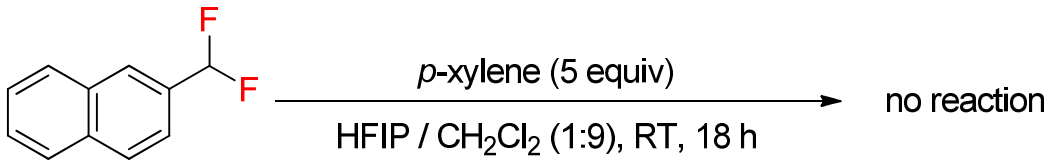
Champagne, P. A.; Benhassine, Y.; Desroches, J.; Paquin, J.-F. *Angew. Chem. Int. Ed.* **2014**, *53*, 13835–13839.





base = $NaHCO_3$ or 2,6-di-tert-butyl-4-methylpridine)



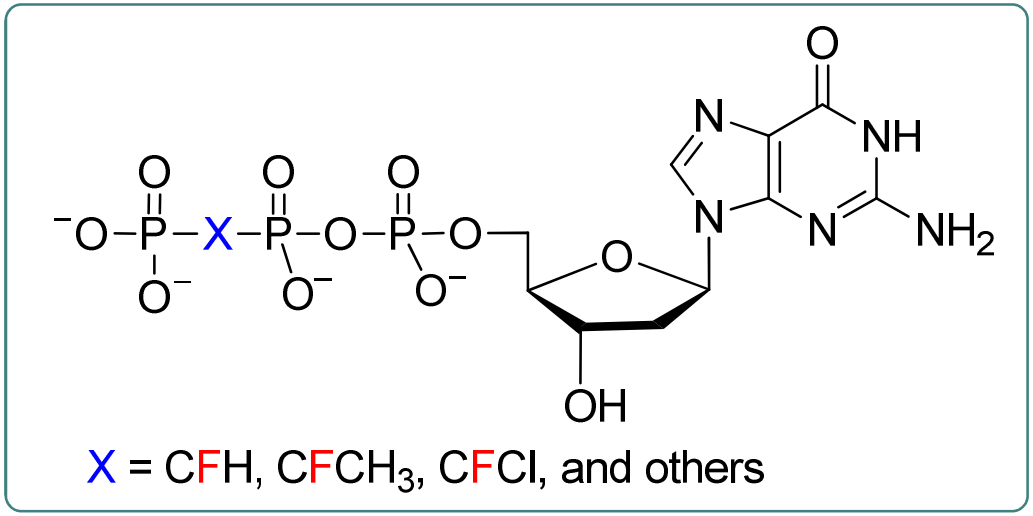


Champagne, P. A.; Benhassine, Y.; Desroches, J.; Paquin, J.-F. *Angew. Chem. Int. Ed.* **2014**, *53*, 13835–13839.

4. C(sp^3)–F as a Hydrogen-Bond Acceptor

4.2 N–H as Donor

Hydrogen bonds to fluorine could effectively alter binding properties of chiral fluorinated molecules.



X = CFH, the fluorine is located at 3.1 Å to the guanidinium nitrogen, hinting at an N^+–H···F interaction.

Figure 5 General structure of modified deoxyguanosine triphosphate (dGTP)

Only one diastereomer was present in the crystal of the ternary complex, when monofluorinated analogues were used.

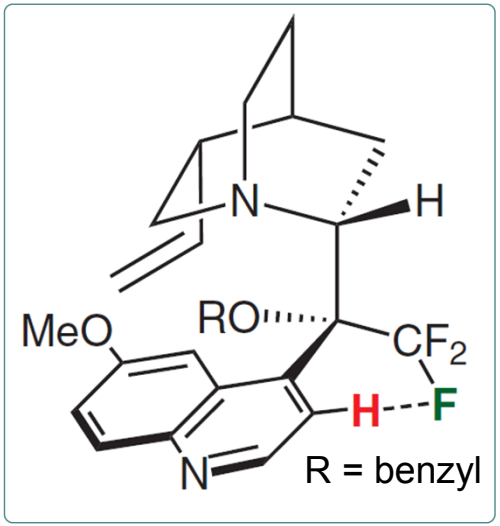
Batra, V. K.; Pedersen, L. C.; McKenna, C. E. and et al. *J. Am. Chem. Soc.* **2010**, *132*, 7617.

4. C(sp^3)–F as a Hydrogen-Bond Acceptor

4.3 C(sp^2)– H as Donor

(1) NMR spectroscopic and coupling constants validate the syn-closed structure.

(2) The syn-closed conformation was lower in energy than the anti-closed conformation in chloroform.



(1) The H,Fdistance is 2.26 Å.
(2) C–H···F angle is 130°.

Figure 6 9-Dehydro-9-(trifluoromethyl)-9-epiquinidine derivative with observed C–H···F contact

Prakash, G. K. S.; Wang, F.; Rahm, M.; Shen, J.; Ni, C.; Haiges, R.; Olah, G. A. *Angew. Chem. Int. Ed.* **2011,** *50*, 11761.

4.4 C(sp^3)–H as Donor

Hydrogen-bond donation from C(sp^3)–H is just as difficult to evidence as its sp^2 equivalent in experimental studies.

(1) The C–H···F hydrogen bond becomes stronger with increasing electron-donating ability of Y substituent.
(2) A shorter H···F distance, longer C–F bonds, and shorter C–H bonds.

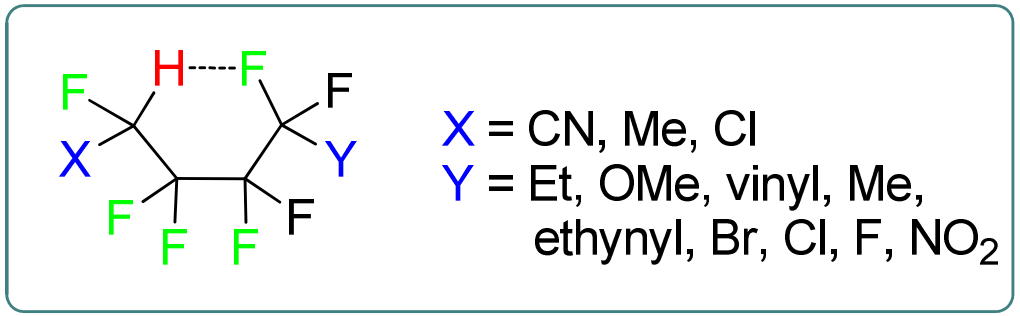


Figure 6 Model system used for investigating group effects on the H···F interaction

Lu, N.; Ley, R. M.; Negishi, E.-i.; and et al. *J. Phys. Chem. A* **2013**, *117*, 8256.

Summary and Perspective

(1) Even though hydrogen bonds involving organic fluorine is a weak interaction, convincing evidence of its existence has been given and various applications have been found.

(2) A number of studies rely on insufficient evidence to determine the presence of such hydrogen bonds.

(3) Future endeavors should focus on demonstrating its power to enhance reactivity and/or selectivity in practical systems.

Thanks for your attention!