Selective, Electrophilic Fluorinations Using *N*-Fluoro-*o*-benzenedisulfonimide

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The synthesis of *N*-fluoro-*o*-benzenedisulfonimide (NFOBS, **2**) and its use as an "electrophilic" fluorinating reagent with nucleophilic substrates is described and compared with that of *N*-fluorobenzenesulfonimide (NFSi, **3**). NFOBS (**2**) is prepared in three steps in 81% overall yield from commercially available *o*-benzenedisulfonic acid (**4**) and involves treatment of *o*-benzenedisulfonimide (**6**) with dilute fluorine (10% F_2/N_2). Reaction of **2** with metal enolates, silyl enol ethers, and 1,3-dicarbonyl compounds affords the corresponding α-fluoro compounds in yields up to 95%, with good control of mono- and difluorination. Fluorination of ortho-metalated aromatic compounds was achieved in modest to good yields (10–80%). While the reactivities of **2** and **3** are similar, better yields were observed with the former reagent in the fluorination of metal enolates, Grignard and lithium reagents, while **3** gave better results with the ortho-lithiated aromatic substrates. The available evidence suggests an S_N2-type mechanism for the fluorination of nucleophilic substrates by these reagents.

The development of mild and selective methods for introduction of fluorine into organic substrates is an important objective because this element exerts unique influences upon physical, chemical, and biological properties.[1-3] Although replacement of hydrogen by fluorine is often regarded as an isosteric substitution, their van der Waals radii are are quite different (1.20 vs 1.47 Å).[4] The high C–F bond strength generally protects fluorine from metabolic transformations. The ability of fluorine to function as a hydrogen-bond acceptor, together with the similarity of typical C–F and C–O bond lengths (1.39 vs 1.43 Å), suggests that replacement of hydroxyl by fluorine in bioactive compounds could result in useful analogs as well as a probe of hydrogen bonding.[1a] Moreover, vinyl fluorides (–CH=CHF) serve as important peptide mimics because they are resistant to hydrolysis[5] and the difluoromethyl group is regarded as an isopolar–isosteric replacement for C=O.[6] For these reasons, the strategic introduction of fluorine has often been used to enhance biological activity and determine mechanisms of action.

Since procedures for the regio- and stereocontrolled generation of carbanions and enolates are well established, methodology for their selective fluorination becomes increasingly important. Until quite recently, however, the selective electrophilic fluorination of enolates and carbanions was difficult because most procedures employed highly reactive, corrosive and toxic materials such as F_2, $FClO_3$, or MeC(O)OF.[3] To overcome these limitations, a range of N–F reagents with different reactivities that were safe and easy to handle without special equipment was developed.[3b,7] Important examples include dihydro *N*-fluoro-2-pyridone,[8] *N*-fluoropyridinum salts,[9] *N*-fluoroquinuclidinium salts,[10] *N*-fluorotriethylenediamine salts,[11] *N*-fluoro sulfonamides,[12,13] and *N*-fluoro sulfonimides. The *N*-fluoro sulfonimides are particularly attractive because of their high reactivity, stability, and ease of preparation. The most reactive of these reagents is *N*-fluorobis[(trifluoromethyl)sulfon]-imide (**1**) introduced in 1987 by DesMarteau et al.[14] Unfortunately this compound, which is a low-boiling liquid (bp 90–91 °C), is not readily accessible, requiring a five-step synthesis of its precursor, bis(trifluoromethanesulfonyl)imide, and the use of liquid fluorine in a special apparatus.[15] To overcome these limitations, we introduced *N*-fluoro-*o*-benzenedisulfonimide (NFOBS, **2**)[16] in 1991, and Differding and Ofner independently reported *N*-fluorobenzenesulfonimide (NFSi, **3**).[17,18] These stable, "off the shelf", easily prepared reagents are the ones of choice for the selective, electrophilic monofluorination of enolates and carbanions. In this paper we describe details of the synthesis and reactions of NFOBS (**2**),

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(1) For reviews on biologically active organofluorine compounds, see: (a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (c) Filler, R.; Kobayashi, Y., Eds. *Biomedicinal Aspects of Fluorine Chemistry*; Kodansha Ltd., Elsevier Biomedical Press: Tokyo, New York 1982. (d) *Carbon-Fluorine Compounds: Chemistry, Biochemistry and Biological Activities*, Ciba Foundation Symposium; Associated Scientific Publishers: Amsterdam 1972.

(2) *Selective Fluorination*; Welch, J. T., Ed.; ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991.

(3) For reviews on the selective fluorination of organic molecules, see: (a) Purrington, S. T.; Kagan, B. S.; Patrick, T. B. *Chem. Rev.* **1986**, *86*, 997. (b) Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505.

(4) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.

(5) Allmendinger, T.; Furet, P.; Hungerbuhler, E. *Tetrahedron Lett.* **1990**, *31*, 7297.

(6) Yang, Z.-Y.; Burton, D. J. *J. Org. Chem.* **1991**, *56*, 1037.

(7) For leading references to electrophilic fluorinating reagents, see: Resnati, G.; DesMarteau, D. D. *J. Org. Chem.* **1991**, *56*, 4925.

(8) Purrington, S. T.; Jones, W. A. *J. Org. Chem.* **1983**, *48*, 761.

(9) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563.

(10) Banks, R. E., Du Boisson, R. A.; Morton, W. D.; Tsiliopoulos, E. *J. Chem. Soc., Perkin Trans. I* **1988**, 2805.

(11) Lal, G. S. *J. Org. Chem.* **1993**, *58*, 2791.

(12) (a) Barnette, W. E. *J. Am. Chem. Soc.* **1984**, *106*, 452. (b) Lee, S. H.; Schwartz, J. *J. Am. Chem. Soc.* **1986**, *108*, 2445. (c) Diffferding, E.; Lang, R. W. *Helv. Chim. Acta* **1989**, *72*, 1248. (d) Banks, R. E.; Khazaei, A. J. *J. Fluorine Chem.* **1990**, *46*, 297.

(13) Asymmetric N–F sultam fluorinating reagents. (a) Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1988**, *29*, 6087. (b) Davis, F. A.; Zhou, P.; Murphy, C. K. *Tetrahedron Lett.* **1993**, *34*, 3971.

(14) Singh, S.; DesMarteau, D. D.; Zuberi, S. S.; Witz, M.; Huang, H. N. *J. Am. Chem. Soc.* **1987**, *109*, 7194.

(15) DesMarteau, D. D.; Witz, M. *J. Fluorine Chem.* **1991**, *52*, 7.

(16) Davis, F. A.; Han, W. *Tetrahedron Lett.* **1991**, *32*, 1631.

(17) Differding, E.; Ofner, H. *Synlett* **1991**, 187.

(18) *N*-Fluorobenzenesulfonimide (**3**) is manufactured by Allied Signal Inc. and is available from Aldrich Chemical Co.

0022-3263/95/1960-4730$09.00/0

Scheme 1

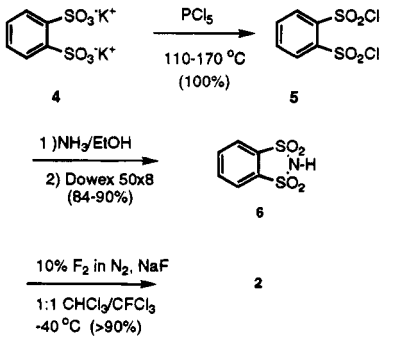
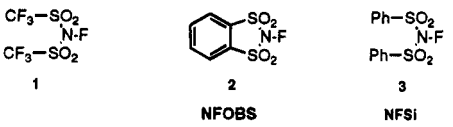


Table 1. Fluorination of *o*-Benzenedisulfonimide (6)

entry	solvent[a]	temperature (°C)	time (h)	isolated yield, %
1	$CFCl_3$	−40	2	tars
2	$CHCl_3$	−40	4	35−45[b]
3	CH_3CN	−40	4	mixture[c]
4	$CFCl_3/CHCl_3$ (1:1)	−40	2	>90
5	$CFCl_3/CHCl_3$ (1:1)[d]	−40	2	73
6	$CFCl_3/CHCl_3$ (2:1)	−40	3	56−65[a]
7	$CFCl_3/CHCl_3$ (1:2)	−40	2	50−60[a]
8	$CFCl_3/CHCl_3$ (1:1)	−40 to −10	4	32
9	$CFCl_3/CHCl_3$ (1:1)	−40 to 0	4	tars

[a] 0.02 M solutions. [b] Determined by ^{19}F NMR. [c] Ring fluorination. [d] 0.045 M solution.

comparing its reactivity with **3**, now commercially available (Aldrich).



Results

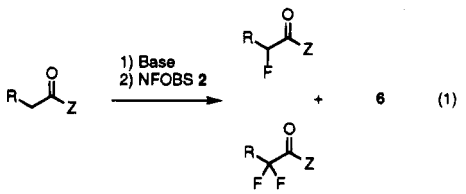
Synthesis of NFOBS. *o*-Benzenedisulfonimide (**6**), the precursor of **2**, was prepared in two steps from the commercially available dipotassium salt of *o*-benzenedisulfonic acid (**4**) using a modification of the procedure reported by Hendrickson and co-workers (Scheme 1).[19] The potassium salt **4** was converted to the disulfonyl chloride in quantitative yield by treatment with phosphorus pentachloride at 110 °C, followed by warming to 170 °C. Efficient stirring with a mechanical stirrer is crucial for good yields. Treatment of crude **5** with an ethanolic ammonia solution at 0 °C for 2 h and liberation of **6** from its ammonium salts using a Dowex 50 × 8 ion exchange resin afforded this material in 84% overall yield on a 20 g scale.

N-Fluoro-*o*-benzenedisulfonimide (**2**) was prepared in better than 90% yield by passing 10% molecular fluorine in nitrogen through a solution of **6** in a 1:1 mixture of chloroform and Freon-11 ($CFCl_3$) at −40 °C for 3−4 h. Sodium fluoride is present as an HF scavenger. As can be seen from the results summarized in Table 1, the choice of solvent, temperature, and concentration are important for optimum yields. Purrington has reported that fluorinations in $CFCl_3$ are generally more selective than in other solvents.[3a] However, tars were obtained in this solvent, whereas in $CHCl_3$ a 35−45% yield of **2** was isolated (Table 1, entries 1 and 2). In acetonitrile, aromatic ring fluorination was detected by ^{19}F NMR (entry 3). The ideal solvent system proved to be a 1:1 mixture of $CHCl_3$:$CFCl_3$, where **2** was isolated in >90% yield (entry 4). Rozen has suggested that $CHCl_3$, when added to $CFCl_3$, polarizes the fluorine molecule, enhancing its selectivity.[20] At temperatures higher than −40 °C, particularly toward the end of the reaction, yields were dramatically lower (entries 8 and 9). High concentrations of **6** also resulted in lower yields, perhaps because of the limited solubility of this substrate in the solvent system (Table 1, compare entries 4 and 5).

N-Fluoro-*o*-benzenedisulfonimide (**2**) is a white crystalline solid melting at 139−141 °C with decomposition. It is stable at room temperature for more than a year when stored in ordinary Pyrex under an inert atmosphere. Exposure of a benzene solution of **2** to the atmosphere at room temperature for 5 days resulted in less than 9% decomposition as estimated from the ^1H NMR spectrum. In C_6D_6 the ^1H NMR spectrum of NFOBS consists of two sets of multiplets at δ 6.30−6.45 and 6.62−6.75, corresponding to the aromatic protons. The fluorine absorption in the ^{19}F NMR spectrum of **2** is observed at −12 ppm upfield from $CFCl_3$, whereas those for **1** and **3** are reported at −34[14] and −37.8 ppm, respectively.

Fluorination of Enolates and Aza Enolates. The synthesis and asymmetric synthesis of α-fluoro carbonyl compounds is an area of considerable interest because these materials have important applications in studies of enzyme mechanisms, as enzyme inhibitors, and as synthons for the synthesis of organofluorine compounds.[21,22] Furthermore, this moiety is often found in bioactive compounds.[1]

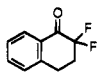
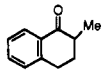
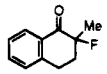
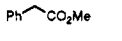
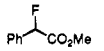
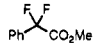
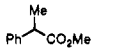
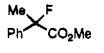
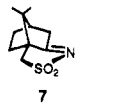
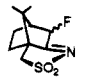
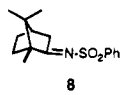
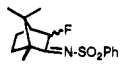
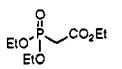
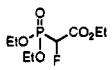
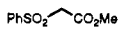
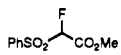
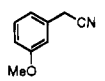
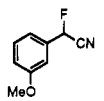
Results of the fluorination of enolates and aza enolates by NFOBS (**2**) (eq 1) are summarized in Table 2. The preformed enolates, generated by standard methods, were treated with 1.2 equiv of **2** at −78 °C and warmed to rt after 1−2 h, and the reaction was quenched with saturated NH_4Cl solution. Products were isolated by preparative TLC and identified by comparison of their spectral properties (^1H and ^{19}F NMR) with literature values. The reaction mixtures were exceptionally clean because the disulfonimide byproduct **6**, being highly water soluble, is removed during the aqueous workup. By contrast, fluorinations using NFSi (**3**) require an alkaline wash to remove the dibenzenesulfonimide [$(PhSO_2)_2NH$] byproduct.



Ketone enolates were monofluorinated in excellent yield by **2** (80 → 95%) (Table 2, entries 1, 2, and 9), and ester enolates gave somewhat lower yields (65−67%) (Table 2, entries 10 and 14). Generally the lithium and the sodium enolates afforded better yields than the potassium enolates. As a consequence of the enhanced acidity of the α-fluoro protons in 2-fluorotetralone and methyl 2-fluorophenylacetate, difluorination often competes with monofluorination. The ratio of mono- to difluorination was readily determined by integration of

(19) Hendrickson, J. B.; Okano, S.; Bloom, R. K. *J. Org. Chem.* **1969**, *34*, 3434.
(20) Rozen, S.; Gal, C.; Faust, Y. *J. Am. Chem. Soc.* **1980**, *102*, 6860.
(21) For a review on the synthesis of chiral organofluorine compounds, see: Bravo, P., Resnati, G. *Tetrahedron: Asymmetry* **1990**, *1*, 661.
(22) For a review of α-fluoro carbonyl compounds, see: Rozen, S.; Filler, R. *Tetrahedron* **1985**, *41*, 1111.

Table 2. Fluorination of Enolates USING NFOBS

entry	substrate	conditions:[a] Base/temp (°C)/time h	products isolated yield, %		(mono:di)[b]	$\delta(^{19}F)$ ($CFCl_3$)	ref
1		1.1 NaHMDS/−78 to rt/2	 87 [85][c]			−172.4	25a
2		1.1 NaHMDS/−78 to rt/1	 80		(15:1)	−189.8/	26
3		1.1 NaHMDS/0 to rt/1	35		(2:1)	−111.7	
4		1.1 LDA/−78 to rt/1	77		(17:1)		
5		1.1 KHMDS/−78 to rt/1	51		(10:3)		
6		2.1 NaHMDS/0/1 (2.2)[d]	32	48			
7		2.1 LDA/0/1 (2.2)[d]	45	55			
8		2.5 LDA/0/1 (2.7)[d]	28	63			
9		1.1 NaHMDS/−78 to rt/1	 95 [50][c]			−154.4	12c, 17, 27
10		1.1 NaHMDS/−78 to rt/2	67 [36][e]		(18:1)	−180.3	28
11		1.1 NaHMDS/0 to rt/2	 46		(7.5:1)		
12		1.1 LDA/−78 to rt/2	64		(18:1)		
13		1.1 KHMDS/−78 to rt/2	53		(16:1)		
14		1.1 NaHMDS/−78 to rt/2	 65			−151.7	25c
15	 7	1.1 NaHMDS/−78 to rt/2	45		(54:46)[f]	−179/	23
16		2.1 NaHMDS/−78 to rt/2 (2.2)[d]	 44−51			−202	
17	 8	1.1 NaHMDS/−78 to rt/2	65		(10:90)[f]	−169/	24
18		2.1 NaHMDS/−78 to rt/2 (2.2)[d]	 58−67			−189	
19		1.1 NaHMDS/−78 to 0/2	 78			−210	29
20		1.1 NaHMDS/−78 to 0/2	 86	[42][e]		−181	30
21		1.1 NaHMDS/−78 to 0/2	 67			−177	31

[a] 1.2 equiv of NFOBS (**2**) used unless otherwise noted. [b] Ratio of mono- and difluorinated products determined by ^{19}F NMR. [c] Fluorination using **3**. See ref 16. [d] Equivalents of NFOBS **2** used. [e] Fluorination using NFSi (**3**). This work. [f] Exo:endo ratio.

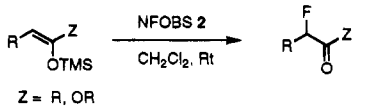
the ^{19}F NMR spectra of the crude reaction mixtures, e.g., the difluoro product absorbs at lower field than the monofluoro product. Higher temperatures and the more reactive potassium enolates enhanced difluorination. Attempts to prepare the 2,2-difluorotetralone by reaction of tetralone with excess base and **2** was only partially successful, affording this material in 63% yield along with 28% of the monofluorinated isomer (Table 2, entries 6−8).

Similar results were observed with **3**, but the yields were lower (Table 2, entries 1, 9, 10, and 20).

In an earlier study we described the fluorination of the aza enolates of (camphorsulfonyl)imine **7**[23] and *N*-phenyl-(camphorsulfonyl)imine **8**[24] with the highly reactive acetyl hypofluroite [MeC(O)OF]. Only monofluorination was observed, which we speculated was a consequence of the lower reactivity of these enolate species. Similar results were observed using NFOBS (**2**) (Table 2, entries 15−18).

α-Fluoro phosphonates, α-fluoro sulfones and α-fluoro cyanides are also available in good to excellent yields using NFOBS (Table 2, entries 19−21).

Fluorination of Silyl Enol Ethers. Fluorination of silyl enol ethers with NFOBS (**2**) gave good yields of the corresponding monofluorinated product (eq 2) (Table 3). Since silyl enol ethers are neutral species, difluorinated products were not detected. Fluorination was accomplished simply by stirring the silyl enol ether with **2** in methylene chloride. Products were isolated in the usual manner and identified by comparison with authentic samples or their spectra with literature values.

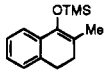
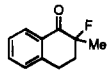


(2)

Fluorination of β-Dicarbonyl Compounds. β-Dicarbonyl compounds are also fluorinated directly on treatment with NFOBS (**2**) (eq 3). The fact that ease of fluorination increases in the order β-diketone > β-keto ester ≫ β-diester, the same order as their enol content,[33]

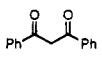
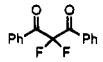
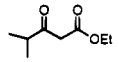
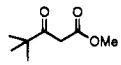
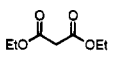
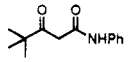
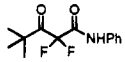
(23) Davis, F. A.; Weismiller, M. C.; Murphy, C. K.; Reddy, T. R.; Chen, B.-C. *J. Org. Chem.* **1992**, *57*, 7274.
(24) Davis, F. A.; Reddy, T. R.; Han, W. Carroll, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 1428.
(25) (a) Purrinton, S. T.; Lazaridis, N. V.; Bumgardner, C. L. *Tetrahedron Lett.* **1986**, *27*, 2715. (b) Cousseau, J.; Albert, P. *J. Org. Chem.* **1989**, *54*, 5380. (c) Purrington, S. T.; Woodard, D. L. *J. Org. Chem.* **1990**, *55*, 3423.
(26) Rozen, S.; Band, M. *Synthesis* **1985**, 665.
(27) Auer, K.; Hungerbuhler, E.; Lang, R. E. *Chimia* **1990**, *5*, 120.
(28) Differding, E.; Ruegg, G. M.; Lang, R. W. *Tetrahedron Lett.* **1991**, *32*, 1779.
(29) (a) Thenappan, A.; Burton, D. J. *Tetrahedron Lett.* **1989**, *30*, 5571. (b) Liu, R. S. H.; Matsumoto, H.; Asato, A. E.; Denny, M.; Shichida, Y.; Yoshizawa, T.; Dahlquist, F. W. *J. Am. Chem. Soc.* **1981**, *103*, 7195.
(30) Umemoto, T.; Tomizawa, G. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3625. Umemoto, T.; Tomita, K.; Kawada, T. *Jpn. Kokai Tokkyo Koho* **1987**, *62*, 207, 230.
(31) LeToureau, M. E.; McCarthy, J. R. *Tetrahedron Lett.* **1984**, *25*, 5227.
(32) Xu, Z-Q.; DesMarteau, D. D.; Gotoh, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 179.
(33) Gero, A. *J. Org. Chem.* **1954**, *19*, 469 and 1960.

Table 3. Fluorination of Silyl Enol Ethers with NFOBS 2 at rt in CH_2Cl_2

entry	silyl enol ether	time (h)	product	% yield,[a] %	$\delta(^{19}F)$ ($CFCl_3$)	ref
1		3		71	−180.3	9
2		2.5[b]		62−79[c] [46][d]	−196.9	9, 25c
3		10[b]		31−40[c]	−193.2	9
4		4		67		26
5		2.5		86		12c, 17, 27

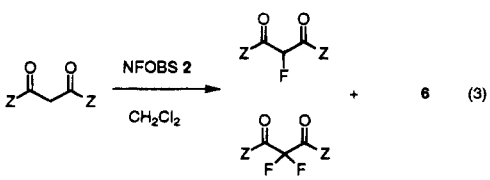
[a] Isolated yields unless otherwise noted. [b] Solvent $CDCl_3$. [c] Yields determined by ^{19}F NMR using 4-fluoroaniline as an internal standard. [d] Fluorination using NFSi (**3**). See ref 17.

Table 4. Direct Fluorination of β-Dicarbonyl Compounds with 2 at rt

entry	substrate	conditions:[a] solvent/time (h)	products yield, %		(mono:di)[b]	$\delta(^{19}F)$ ($CFCl_3$)	ref
1		CH_2Cl_2/2	52 [92][c]		(3.5:1) [3.4:1][c]	−186/−103	34
2		CH_2Cl_2/H_2O/2	85 [41][c]		(17:1) [7.2:1][c]		
3		CH_2Cl_2/8	32 [91][d]			−196	35
4		CH_2Cl_2/8	30			−191	
5		CH_2Cl_2/24	no reaction				
6		CH_2Cl_2/4	70		(6.4:1)	−187/−108	
7		CH_2Cl_2/H_2O/4	79		(16:1)		
8		CH_2Cl_2/2	0		42	−185.9/−123	
9		CH_2Cl_2/H_2O/2	<10[e]		30		

[a] 1.2 equiv of NFOBS (**2**) used. [b] Ratio of mono- and difluorinated products determined by ^{19}F NMR. [c] Fluorination carried out using 1.2−1.3 equiv of NFSi (**3**). This work. [d] Fluorination carried out using **1**. See ref 31. [e] Detected by ^{19}F NMR.

strongly suggests that the enols are reaction intermediates. Mono- and difluorination are observed (Table 4). Note that when the cosolvent is water, monofluorination increases at the expense of difluorination (Table 4, compare entries 1 and 6 with 2 and 7). DesMarteau has suggested that the acidic sulfonimide [$(RSO_2)_2NH$] byproduct promotes enolization and hence difluorination.[32] In the biphasic aqueous media, sulfonimide **6** is efficiently removed because of its water solubility. As expected, **3** gave more difluorination under these conditions because the sulfonimide byproduct has limited solubility in water (Table 4, entry 2).



Fluorination of Aromatic Compounds. Fluoroaromatic compounds are found in a broad spectrum of biologically active molecules including antibiotics, antifolates, sedatives, and estrogen receptor imaging agents.[35,36] However, efficient methodology for the selective fluorination of aromatic substrates is generally lacking; the Balz−Schiemann thermal decomposition of aryldiazonium fluoroborates is often difficult to control and requires the corresponding aniline.[37]

While NFOBS (**2**) is sufficiently reactive to directly fluorinate activated aromatics, the reaction is not selective (eq 4) (Table 5). Thus, on heating **2** with anisole at 60 °C for 10 h, a 42% yield of a 3:2 mixture of *o*- and *p*-fluoroanisoles results (Table 5, entry 3). NFSi gave lower yields (Table 5, entry 3). With 1,4-dimethoxybenzene, NFOBS gave a 48% yield of 2-fluoro-1,4-dimethoxybenzene after 6 h at 0 °C to rt (Table 5, entry 4). Benzene and toluene were not fluorinated even on refluxing with NFOBS for 12 h. While NFOBS was stable in refluxing benzene, it decomposed, turning black, in toluene. Both benzene and toluene are fluorinated by **1** with ortho fluorination predominating in the latter.[14]

Alternatively, the regiospecific synthesis of fluorinated aromatics can be accomplished by fluorination of aro-

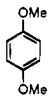
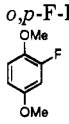
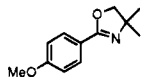
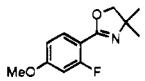
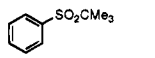
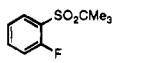
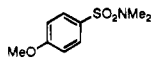
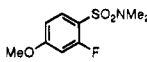
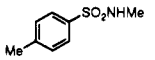
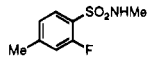
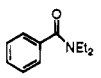
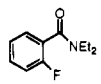
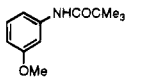
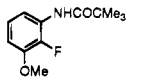
(34) Stavber, S.; Sket, B.; Zajc, B.; Zupan, M. *Tetrahedron* **1989**, *45*, 6003.

(35) Resnati, G.; DesMarteau, D. D. *J. Org. Chem.* **1991**, *56*, 4925. Thenappan, A.; Burton, D. J. *Tetrahedron Lett.* **1989**, *30*, 6113.

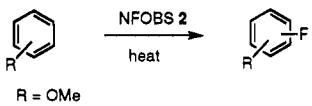
(36) For a disscussion of fluorinations of aromatic substrates and relevant citations, see: Purrington, S. T.; Woodard, D. L. *J. Org. Chem.* **1991**, *56*, 142.

(37) For reviews on fluoroaromatic and fluoroheterocyclic compounds, see: Hewitt, C. D; Silvester, M. J. *Aldrichimica Acta* **1988**, *21*, 3. Silvester, M. J. *Aldrichimica Acta* **1991**, *24*, 31.

Table 5. Fluorination of Aromatic Compounds Using NFOBS (2)

entry	substrate	conditions	products	yield,[a] %	$\delta(^{19}F)$ ($CHCl_3$)	ref
1	PhH	reflux/12 h	no reaction			
2	PhMe	reflux/12 h	decomposition			
3	PhOMe	60 °C/10 h	*o,p*-F-Ph-OMe (3:2)[b]	42[c] [33][d]	−137/123	14, 41
4		0 °C to rt/6 h		48	−144	42
5	PhMgBr	neat/0 °C to rt/2	PhF	80[c,e]	−112	12a
6		C_6D_6/0 °C to rt/2		74 [12][d]		
7	PhLi	C_6D_6/0 °C to rt/2		70 [37][f]		
8		Et_2O/0 °C to rt/2		61		
9		1 equiv of *sec*-BuLi/TMEDA/−78 °C/2		48 [78][g]	−107	
10		1 equiv of *n*-BuLi/−78 °C to rt/2		30 [74][g]	−114	
11		1 equiv of *n*-BuLi/−40 °C/2		47 [55][g]	−129	
12		2 equiv of *n*-BuLi/−40 °C/2		61−76	−113	
13		1 equiv of *sec*-BuLi/TMEDA/−78 °C/2		10[g]		
14		2.2 2 equiv of *n*-BuLi/0 °C to rt/2		0 [56][h]		

[a] Isolated yields unless otherwise noted. [b] *ortho/para* ratios. [c] Yields determined by ^{19}F NMR using 4-fluoroaniline as the internal standard. [d] Yield using **3**. See ref 17. [e] Less than 7% biphenyl was detected by GLC. [f] Fluorination using NFSi (**3**). This work. [g] Fluorination using NFSi (**3**). See ref 40. [h] Fluorination using NFSi (**3**). See ref 38.



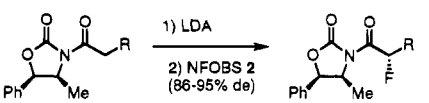
(4)

(5)

matic organometallic compounds (eq 5). For example, fluorobenzene is obtained in good yield (70−80%) on treatment of phenylmagnesium bromide or phenyllithium with **2** (Table 5, entries 5−8). Best yields were obtained in benzene. Similarly, treatment of ortho-lithiated aromatic substrates, generated by reaction of directed metalation group aromatics (DMG) with alkyllithiums, with NFOBS afforded the corresponding ortho-fluorinated compounds in modest to good yields (Table 5, entries 5 and 9−14).[38,39] In these examples, however, NFSi (**3**) gave better yields. Snieckus et al. recently reported that fluorination of ortho-lithiated diethylbenzamide gave a ca. 10% yield of *o*-fluoro diethylbenzamide (entry 13),[40] and with **3**, sulfonation ($PhSO_2$) rather than fluorination was observed.[37] All attempts to fluorinate lithio-*N*-*tert*-butyl-*m*-methoxybenzamide with **2** failed, but with **3** the desired product was isolated in 56% yield (Table 5, entry 14).[38]

Discussion

Characteristic of the N−F fluorinating reagents, fluorine is attached to an excellent leaving group. Despite this feature, a two-step electron transfer (ET) mechanism, in addition to the direct nucleophilic attack S_N2 mechanism for fluorine transfer, has been considered because of the high enthalpy for formation of F^-. In support of the S_N2 mechanism, Differding and co-workers recently reported that rearranged products were not detected in the fluorination of citronellic ester enolate with **3**. This suggests that radical intermediates, expected of the ET reaction pathway, were not involved.[43] The similarity in yields of fluorobenzene on treatment of phenyllithium or phenylmagnesium bromide with **2**, along with the fact that less than 7% biphenyl was detected, provides additional support for the S_N2 mechanism (Table 5, entries 5−8). Finally, the high de's (86−97%) observed in the diastereoselective fluorination of chiral imide enolates with **2** also seems incompatible with a radical mechanism of fluorine transfer (eq 6).[44,45] Thus, all of the available evidence supports a nucleophilic S_N2-type mechanism for transfer of fluorine from **2** and **3** to organometallic species. However, an ET mechanism involving very fast combination of radical/radical anion pairs within a solvent cage cannot be rigorously excluded.



(6)

The results summarized in Tables 2−5 for the selective fluorination of nucleophilic substrates by **2** and **3** indicate

(38) For results of a preliminary study, see: Snieckus, V.; Deaubieu, F., Mobri, K.; Han, W.; Murphy, C. K.; Davis, F. A., *Tetrahedron Lett.* **1994**, *35*, 3465.
(39) For a review on directed ortho metalation, see: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
(40) Silva, S. O.; Reed, J. N.; Billedeau, R. J.; Wang, X.; Norris, D. J.; Snieckus, V. *Tetrahedron* **1992**, *48*, 4863.
(41) Dugan, C. H.; Van Wazer, J. R. *A Compilation of F NMR Chemical Shifts*; Wilrey Interscience: New York, 1970.
(42) Glennon, R. A.; Young, R.; Benington, F. *J. Med. Chem.* **1982**, *25*, 1163.
(43) Differding, E.; Ruegg, G. M. *Tetrahedron Lett.* **1991**, *32*, 3815.
(44) Davis, F. A.; Han, W. *Tetrahedron Lett.* **1992**, *33*, 1153.
(45) Details of the diastereoselective fluorination of chiral enolates with NFOBS will be described in detail elsewhere.

similar reactivities, but **2** gave better yields for the fluorination of enolates (Table 2) and lithium and Grignard reagents (Table 5). On the other hand, **3** gave significantly higher yields for the fluorination of ortholithiated aromatic substrates (Table 5). The major structural difference between the two reagents appears to be that **2** is cyclic and **3** is acyclic. This would be expected to translate into higher reactivity for **2** because approach of the nucleophile is sterically favored and the cyclic sulfonyl array makes **6** a better leaving group than $[PhSO_2]_2NH$.

Recently, however, two studies attempted to correlate the reduction potentials (E_p) of **1**–**3**, which behave electrochemically as one-electron oxidants, with their reactivities.[46,47] The reported E_p values for **1**–**3** are +0.18,[46] −0.78,[46] and −0.54[47] vs SCE, respectively, and suggest that **3** is more reactive than **2**. While **1** has the largest E_p value and is clearly the most reactive, the relationship between reactivity and the E_p values of **2** and **3** are less clear. Here, as mentioned earlier, steric factors may play a role in their reactivity. Furthermore, it is interesting to note that the ^{19}F NMR chemical shifts of these reagents imply that fluorine in **2** (−12 ppm) is considerably more "electrophilic" than in **1** (−34 ppm) or **3** (−37.8 ppm). While the factors influencing ^{19}F chemical shifts are complicated, in a similar series of compounds the chemical shift can often be correlated with the apparent electron density at the fluorine.[48] Thus, the relationship between redox potentials, ^{19}F NMR chemical shifts, and reactivity of these N−F reagents remains unclear. Efforts are underway to clarify this point.

In summary, the reagents of choice for the electrophilic fluorination of nucleophilic substrates, carbanions, enolates, enols, and silyl enol ethers are *N*-fluoro-*o*-benzenedisulfonimide (NFOBS, **2**) and *N*-fluorobenzenesulfonimide (NFSi, **3**).

Experimental Section

General Procedure. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution and referenced to TMS. ^{19}F NMR spectra were recorded in ppm (δ) upfield from $CFCl_3$ (δ = 0 ppm). THF was freshly distilled under nitrogen from a purple solution of sodium and benzophenone. CH_2Cl_2 was dried over CaH_2, and all reagents and solvents were purchased from Aldrich Chemical Co. and used without further purification unless otherwise noted.

Substrates were purchased from Aldrich and used without additional purification unless otherwise noted. Silyl enol ethers (Table 3) were prepared in the standard way by trapping of the corresponding lithium or sodium enolates with trimethylsilyl chloride.[49] *tert*-Butyl phenyl sulfone,[50] 2-(4-methoxylphenyl)-4,4-dimethyl-2-oxazolidinone,[51] and *N*,*N*-dimethyl(4-methoxyphenyl)-*p*-toluenesulfonamide[52] were prepared as previously described.

Fluorination was carried out in the apparatus recommended by Matheson Gas Products for the handling of dilute concentrations of F_2/N_2. For a related apparatus, see ref 36. *Caution: fluorine is a poisonous, corrosive gas which is a powerful oxidant.*

o-Benzenedisulfonyl Chloride (5). In a 250 mL three-necked round-bottomed flask equipped with a mechanical stirrer, a 125 mm Teflon stirring blade, a Safe Lab stirring bar, and thermometer inlet was placed 31.4 g (0.1 mol) of *o*-benzenedisulfonic acid, dipotassium salt (**4**) [Aldrich]. Phosphorus pentachloride, 52 g (0.25 mol, 2.5 equiv) was added portionwise with stirring, and the resultant solid mixture was heated at 110 °C for 10 min. The temperature was monitored by stopping the stirring and inserting the thermometer into the reaction mixture. The temperature was raised to 170 °C in 10 min, and the liquefied mixture was stirred for 30 min. The solution was allowed to cool to ca. 50 °C and poured onto 100 g of crushed ice in a 500 mL beaker. The solid precipitate was filtered, washed with ice water (3 × 100 mL), and dried under vacuum to give 27.4 g (99.7%) of *o*-benzenedisulfonyl chloride (**5**) as a white solid, mp 142–144 °C [lit.[53] mp 143–144 °C].

o-Benzenedisulfonimide (6). A 3.4 M NH_3 solution was prepared by bubbling NH_3 gas through 600 mL of EtOH in a 1 L round-bottomed flask at 0 °C until the weight of the flask increased by 34 g. In a separate 2 L two-necked round-bottomed flask equipped with a magnetic stirring bar and a 250 mL addition funnel was placed 27.4 g (0.1 mol) of *o*-benzenedisulfonyl chloride (**160**) in 500 mL of benzene. The solution was cooled to 0 °C in an ice bath, and the freshly prepared NH_3/EtOH solution was added dropwise with stirring. The resultant mixture was stirred at room temperature for 2 h, the precipitated NH_4Cl was removed by filtration, and the solvent was removed on a rotary evaporator to give a white solid which was dissolved in 200 mL of water. The solution was filtered and the filtrate passed through a 300 g column of Dowex 50 × 8 ion-exchange resin. The column was washed with 200 mL of water, and the combined aqueous portions were evaporated on the rotary evaporator to give 18 g (84%) of *o*-benzenedisulfonimide (**6**) as a white solid, mp 192–194 °C [lit.[18] mp 195–186 °C]: ^1H NMR (C_6D_6) δ 6.65 (m, 2 H), 6.94 (m, 2 H); ^{13}C NMR ($CDCl_3$) 122.2, 134.7, 139.0 ppm.

***N*-Fluoro-*o*-benzenedisulfonimide (2).** In an oven-dried 2 L two-necked round-bottomed flask fitted with a S+P Teflon adapter with Teflon inlet and outlet tubes, the latter attached to a soda lime tower, and a magnetic stirring bar were placed 10.0 g (0.045 mol) of *o*-benzenedisulfonimide (**1**), 800 mL of Freon 11 ($CFCl_3$), and 800 mL of dry $CHCl_3$. The mixture was stirred at room temperature until the solids dissolved, and 18.9 g (10 equiv) of NaF (dried under high vacuum overnight) was added. The reaction mixture was cooled to −40 °C (dry ice–acetonitrile), and nitrogen gas was passed through the mixture until the reaction system reached equilibrium (i.e. the flow rate of N_2 is constant at about 60 mL/min). The nitrogen gas flow was stopped, and diluted fluorine, 10% F_2 in N_2 (Matheson), was passed into the reaction mixture at a flow rate of 70–90 mL/min until the reaction was complete as monitored by NMR (4–5 h). The diagnostic features of the ^1H NMR specturm in C_6D_6 is the growth of two sets of aromatic proton multiplets at δ 6.29, 6.60 for **2** and the loss of two sets of multiplets at δ 6.37, 6.85 for **6**. After the reaction was complete, the fluorine flow was stopped and the reaction system was purged with nitrogen gas for 1 h to remove excess fluorine. The reaction mixture was filtered, the solid residue was washed with 800 mL of $CHCl_3$, and the combined filtrates were washed with water (2 × 500 mL) and brine (3 × 500 mL) and dried ($MgSO_4$). Removal of solvent afforded the crude product (9.8 g) as a slightly yellow solid which on washing with diethyl ether (100 mL) gave 9.7 g (90%) of *N*-fluoro-*o*-benzenedisulfonimide (**2**) as a white solid, mp 138–141 °C, of sufficient purity for further use. An analytically pure sample was prepared by crystallization from *n*-hexane/ether (5:1): mp 139–141 °C; IR (KBr) 1213 (SO_2) cm^{-1}; ^1H NMR(C_6D_6) δ 6.30–6.45 (m 2H), 6.62–6.75 (m 2H); ^{13}C NMR ($CDCl_3$) δ 124.2, 135.4, 135.9; ^{19}F NMR ($CFCl_3$ in $CDCl_3$) δ −12; EI-MS *m/z* 237 (M^+), 140 ($C_6H_4SO_2^+$), 76 ($C_6H_4^+$). Anal. Calcd for $C_6H_4FNO_4S_2$: C, 30.38; H, 1.70. Found: C, 30.78; H, 1.92.

General Procedure for Monofluorination of Keto and Ester Enolates with NFOBS (2) and NFSi (3). A representative procedure is described for the preparation of 2-fluoro-

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2-methyl-1-tetralone. For reactions using enolates generated from KHMDS, LiHMDS, or LDA, a similar procedure was followed. The ratios of monofluorinated and difluorinated products was determined by ^{19}F NMR analysis of the crude mixture on the basis of integration. These results are summarized in Table 2.

2-Fluoro-2-methyl-1-tetralone.[17,27] In a 25 mL oven-dried two-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar was placed 3 mL of freshly distilled THF. The reaction flask was cooled to −78 °C (dry ice−acetone) and 0.55 mL (0.55 mmol, 1.1 equiv) of NaHMDS was added followed by the dropwise addition of 0.08 g (0.5 mmol) of 2-methyl-1-tetralone in 2 mL of THF. The reaction mixture was stirred at −78 °C for 10 min, warmed to 0 °C for 0.5 h, and cooled to −78 °C. A solution of 0.154 g (0.65 mmol, 1.3 equiv based on the ketone) of **2** (or **3**) in 5 mL of THF was added dropwise, and the mixture was stirred at rt for 2 h. Upon completion, as monitored by TLC (30% ether in hexane), the reaction was quenched with 1 mL of saturated aqueous NH_4Cl solution and diluted with 10 mLof diethyl ether. The aqueous layer was extracted with diethyl ether (2 × 5 mL), and the combined ether extracts were washed with H_2O (2 × 10 mL) and brine (2 × 10 mL) and dried ($MgSO_4$). Concentration in vacuo gave an oil which was purified by preparative TLC (hexane/Et_2O, 7:3) or flash chromatography (hexane/EtOAc, 7:1) to give 0.085 g (96%) of 2-fluoro-2-methyl-1-tetralone as an oil: ^{19}F NMR ($CDCl_3$) δ −154.4 (m). Its spectral properties were in agreement with literature values.[17,27]

2-Fluorophenylpropanone: yield 87%; ^{19}F NMR ($CDCl_3$) δ −172.4 (m); ^1H NMR ($CDCl_3$) δ 1.55 (dm, 3 H, J = 23 Hz), 5.48 (dm, 1 H, J = 50 Hz), 7.35 (m, 5 H) [lit.[25a] ^1H NMR ($CDCl_3$) δ 1.58 (dm, 3 H, J = 22 Hz), 5.6 (dm, 1 H, J = 50 Hz), 7.2−7.5 (m, 5 H)].

2-Fluoro-1-tetralone: yield 80%; mp 39−41 °C; ^{19}F NMR ($CDCl_3$) δ −189.8 (m); ^1H NMR ($CDCl_3$) δ 5.2 (dm, 1 H, J = 48 Hz) for the α-proton [lit.[34] mp 38−40 °C; ^{19}F NMR ($CDCl_3$) δ −192].

Methyl α-fluorobenzeneacetate: yield 67%; ^{19}F NMR ($CDCl_3$) δ −179 (d, J = 52.8 Hz); ^1H NMR ($CDCl_3$) δ 5.77 (d, 1 H, J = 50.2 Hz) for the α-proton [lit.[54] ^{19}F NMR ($CDCl_3$) δ −174.4 (d, J = 48 Hz); ^1H NMR ($CDCl_3$) δ 5.80 (d, 1 H, J = 50 Hz) for the α-proton].

Methyl α-fluoro-α-methylbenzeneacetate: yield 65%; ^{19}F NMR ($CDCl_3$) δ −151.7; ^1H NMR ($CDCl_3$) δ 1.9 (d, 3 H, J = 23 Hz), 3.7 (s, 3 H), 7.2−7.5 (m, 5 H) [lit.[25c] ^1H NMR δ 1.87 (d, 3 H, J = 22.5 Hz), 3.70 (s, 3 H), 7.22−7.46 (m, 5 H)].

Triethyl α-fluorophosphonoacetate: yield, 78% (oil); ^{19}F NMR ($CDCl_3$) δ −210 (d, J = 70.5 Hz); ^1H NMR ($CDCl_3$) δ 5.2 (d, 1 H, J = 48 Hz) for the α-proton [lit.[29] ($CDCl_3$) δ −212.4 (d, J = 68 Hz); ^1H NMR ($CDCl_3$) δ 5.34 (d, 1 H, J = 49 Hz) for the α-proton].

Methyl α-fluoro-α-(phenylsulfonyl)acetate: yield 86% (oil); ^{19}F NMR ($CDCl_3$) δ −181.1 (d, J = 52.9 Hz); ^1H NMR ($CDCl_3$) δ 3.84 (s, 3 H), 5.6 (d, 1 H, J = 52 Hz), 7.6 (m, 2 H), 7.75 (m, 1 H), 7.93 (d, 2 H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 53.8, 95.3 and 99.0 (J = 231.7 Hz), 129.4, 129.7, 134.4, 135.3, 161.1 and 161.9 (J = 22 Hz) [lit.[29] ^{19}F NMR ($CDCl_3$) δ −180.2 (d, J = 50 Hz)].

α-Fluoro-α-(2-methylphenyl)acetonitrile: yield 67% (oil); ^{19}F NMR ($CDCl_3$) δ −176.5 (d, J = 52.7 Hz); ^1H NMR ($CDCl_3$) δ 6.4 (d, 1 H, J = 48 Hz) for α-proton [lit.[31] ^{19}F NMR ($CFCl_3$ in $CDCl_3$) δ −176 ppm (d, J = 46.8 Hz)].

General Procedure for the Fluorination of Silyl Enol Ethers. Ethyl 2-Fluoro-2-phenylacetate. In a 50 mL single necked flask equipped with a magnetic stirring bar and rubber septum with inlet and outlet needles was placed 0.12 g (0.5 mmol) of the corresponding silyl enol ether in 10 mL of CH_2Cl_2 under an argon atmosphere. To the reaction mixture at rt was added dropwise 0.18 g (0.75 mmol, 1.5 equiv based on the silyl enol ether) of NFOBS (**2**) in 20 mL of CH_2Cl_2. After being stirred for 3 h, the reaction mixture was diluted with diethyl ether, washed with brine (1 × 10 mL), and dried over anhydrous $MgSO_4$. The oily residue was purified by preparative TLC (ethyl acetate/hexane 1:9) to give 0.064 g (71%) of ethyl 2-fluoro-2-phenylacetate: ^{19}F NMR ($CDCl_3$) δ −180.5 (d, J = 52 Hz); ^1H NMR ($CDCl_3$) δ 5.75 (d, 1 H, J = 51 Hz) for the α-proton [lit.[35] ^{19}F NMR ($CDCl_3$) δ −180.4 (d, J = 48 Hz)].

2-Fluorocyclohexanone: yield 70% as determined by ^{19}F NMR (4-fluoroaniline as the internal standard); ^{19}F NMR (relative to $CFCl_3$) δ −188 (dm, J = 50.2 Hz) [lit.[55] ^{19}F NMR (relative to $CFCl_3$) δ −187].

α-Fluoro-γ-butyrolactone: yield 40% as determined by ^{19}F NMR (4-fluoroaniline as the internal standard); ^{19}F NMR (relative to $CFCl_3$) δ −159.8 (dm, J = 50.2 Hz); ^1H NMR ($CDCl_3$) δ 5.1 (dm, 1 H, J = 50.3 Hz) for the α-proton [lit.[25c,54] ^{19}F NMR (relative to $CFCl_3$) δ −162; ^1H NMR ($CDCl_3$) δ 5.18 (dm, 1 H, J = 52 Hz) for the α-proton].

General Procedure for the Direct Fluorination of Active Methylene Compounds. In a 50 mL single necked flask equipped with a rubber septum with inlet and outlet needles was placed 0.134 g (0.6 mmol) of dibenzoylmethane in 10 mL of CH_2Cl_2 at rt. Added dropwise with stirring was a solution of 0.19 g (0.78 mmol, 1.3 equiv) of NFOBS (**2**) in 10 mL of CH_2Cl_2. After 2 h, the reaction mixture was diluted with 10 mL of diethyl ether, washed with H_2O (1 × 10 mL) and brine (10 mL), and dried ($MgSO_4$). Removal of solvent gave the crude products which were purified by preparative TLC (1:1 n-hexane:CH_2Cl_2).

Fluorodibenzoylmethane: yield 52%; mp 67−68 °C; ^{19}F NMR (relative to $CFCl_3$) δ −187.3 (d, J = 50 Hz); ^1H NMR ($CDCl_3$) δ 6.5 (d, 1 H, J = 52 Hz) for the α-proton [lit.[34] mp 65−67 °C; ^{19}F NMR ($CDCl_3$) δ −185.7 (d, J = 48 Hz); ^1H NMR ($CDCl_3$) δ 6.4 (d, 1 H, J = 48 Hz) for the α-proton].

Difluorodibenzylmethane: yield 15%; mp 54−55 °C; ^{19}F NMR (relative to $CFCl_3$) δ −103.2 (s) [lit.[34] mp 56−57 °C; ^{19}F NMR ($CDCl_3$) δ −102 (s)].

A similar procedure was followed when CH_2Cl_2−H_2O (2 mL of H_2O in 10 mL of methylene chloride) was used as the solvent.

Ethyl α-fluoro-α-isobutyrylacetate: yield 32%, ^{19}F NMR ($CDCl_3$) δ −196.1 (d, J = 52.8 Hz); ^1H NMR ($CDCl_3$) δ 5.8 (d, 1 H, J = 52 Hz) for the α-proton [lit.[35] ($CDCl_3$) δ −196.3 (d, J = 50 Hz)].

Methyl 2-fluoro-4,4-dimethyl-3-oxopentanoate: yield 30% oil; IR (neat) 1767 and 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.2−1.3 (s, 9 H), 3.8−3.9 (s, 3 H), 5.3−5.7 (d, 1 H, J = 50 Hz); ^{13}C NMR ($CDCl_3$) δ 25.8, 43.7, 53.0, 87.4 and 90.6 (J = 197.7 Hz), 165.0 and 165.4 (J = 24.1 Hz), 204.6 and 204.9 (J = 18.3 Hz); ^{19}F NMR ($CDCl_3$) δ −191.1. Anal. Calcd for $C_8H_{13}FO_3$: C, 54.53; H, 7.44. Found: C, 54.90; H, 7.75.

***N*-Phenyl-2-Fluoro-4,4-dimethyl-3-oxopentonamide:** yield 70%; mp 84−86 °C; IR (KBr) 1723 and 1695 (C=O), 3317 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27−1.33 (s, 9 H), 5.53−5.83 (d, 1 H,J = 50 Hz), 7.09−7.23 (t, 1 H, J = 8.5 Hz), 7.27−7.39 (t, 2 H, J = 9 Hz), 7.47−7.61 (d, 2 H, J = 9 Hz), 7.94−8.08 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.9, 44.7, 87.2 and 90.3 (J = 199.2 Hz), 120.0, 125.2, 129.1, 136.2, 160.0 and 162.3 (J = 24.9 Hz), 194.1 and 194.9 (J = 19.2 Hz); ^{19}F NMR ($CDCl_3$) δ −186.7. Anal. Calcd for $C_{13}H_{16}FNO_2$: C, 65.80; H, 6.80. Found: C, 65.45; H, 7.21.

***N*-Phenyl-2,2-difluoro-4,4-dimethyl-3-oxopentanamide:** yield 70%; mp 91−92 °C; IR (KBr) 1698 and 1730 (C=O), 3314 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30−1.39 (s, 9 H), 7.16−7.28 (t, 1 H, J = 7.3 Hz), 7.30−7.45 (t, 2 H, J = 7.3 Hz), 7.51−7.62 (d, 2 H, J = 7.3 Hz), 7.90−8.07 (s, 1 H); ^{13}C NMR ($CDCl3$) δ 25.7, 44.1, 106.1 and 110.4 and 114.7 (J = 270.6 Hz), 120.2, 125.7, 129.1, 135.6, 159.0 and 159.4 and 159.9 (J = 26.7 Hz), 202.6 and 202.9 and 203.3 (J = 24.8 Hz); ^{19}F NMR ($CDCl_3$) δ −108.2. Anal. Calcd for $C_{13}H_{15}F_2NO_2$: C, 61.17; H, 5.93. Found: C, 61.39; H, 6.33.

4,4-Difluoro-3-methyl-1-phenyl-2-pyrazolin-5-one: yield 42%; mp 142−144 °C; IR (KBr) 1735 (C=O), 1875 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.2−2.4 (s, 3 H), 7.1−7.3 (m, 1 H), 7.4−7.6 (m, 2 H), 7.7−8.0 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.4, 104.4 and 108.5 and 112.6 (J = 257.4Hz), 119.0, 126.9, 130.2, 138.4, 153.4 and 154.0 and 154.5 (J = 24.5 Hz), 161.4 and 162.0 and 162.5 (J = 36.8 Hz); ^{19}F NMR ($CDCl_3$) δ −122.9. Anal. Calcd for $C_{10}H_8F_2N_2O$: C, 57.14; H, 3.84. Found: C, 57.34; H, 3.99.

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General Procedure for Fluorination of Phenylmagnesium Bromide and Phenyllithium. In a 25 mL oven-dried two-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar were placed 0.20 g (0.84 mmol) of NFOBS (**2**) (or NFSi, **3**) in 10 mL of deuterated benzene. After the reaction flask was cooled to 0 °C, 0.23 mL (0.7 mmol) of phenylmagnesium bromide (3 M solution in diethyl ether) or 0.39 mL (0.7 mmol) of phenyllithium was added. The reaction mixture was stirred at 0 °C for 5 min and warmed to room temperature, and the reaction was quenched with 0.2 mL of a saturated NH_4Cl solution. A solution of 0.050 g (0.45 mmol) of 4-fluoroaniline in 2 mL of deuterated benzene was added as the internal reference and the yield of fluorobenzene determined by ^{19}F NMR analysis on 0.5 mL of this mixture by integration of the product resonance with the internal standard. ^{19}F NMR for fluorobenzene ($CDCl_3$): δ −112.6 (s) [lit.[12a] ($CDCl_3$) δ −113.2 (s)].

2-Fluoro-1,4-dimethoxybenzene. In a dry 25 mL two-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar was placed 0.097 g (0.7 mmol) of 1,4-dimethoxybenzene. The reaction flask was cooled to 0 °C, and a solution of 0.24 g (1.05 mmol, 1.5 equiv) of NFOBS (**2**) in 5 mL of $CHCl_3$ was added. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 6 h. After removal of solvent, preparative TLC purification (ethyl acetate/hexane, 1:1) afforded 0.039 g (45%) of 2-fluoro-1,4-dimethoxylbenzene as an oil; ^{19}F NMR (relative to $CFCl_3$) δ −144; ^1H NMR δ 3.6 (s, 3 H), 3.8 (s, 3 H), 6.2−6.5 (m, 2 H), 6.9 (m, 1 H) [lit.[42] ^{19}F NMR δ −144.8].

***o/p*-Fluoroanisole.** A similar procedure was employed for the fluorination of anisole in $CDCl_3$ with the following exceptions: (a) the reaction mixture was stirred in $CDCl_3$ at 60 °C for 10 h, b) the yield and ratios of *o/p*-flluoroanisoles were determined by ^{19}F NMR on the crude mixture by addition of 0.02 g (0.18 mmol) of 4-fluoroaniline in 2 mL of $CDCl_3$ as the internal standard. The total volume was measured and ^{19}F NMR was taken using 0.5 mL of the above mixture as previously described.[13] NMR yield of fluoroanisole 42%. ^{19}F NMR ($CDCl_3$): δ −137 (ortho)/−123 (para) [lit.[14] (relative to $CFCl_3$) −137 (ortho)/−122 (para)].

Directed Ortho Metalation Mediated Fluorination of Aromatic Compounds. A General Procedure Is Illustrated for the Preparation of *N*-Methyl-2-fluoro-4-methylbenzenesulfonamide. In an oven-dried 50 mL two-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar was placed 0.093 g (0.5 mmol) of *N*-methyl-*p*-toluenesulfonamide (Aldrich) in 10 mL of THF. The reaction mixture was cooled to −78 °C, and 2.63 mL (1.05 mmol, 2.1 equiv) of *n*-BuLi was added. After 45 min at this temperature, a solution of 0.143 g (0.6 mmol) of NFOBS (**2**) in 10 mL of THF was added dropwise. The resultant mixture was stirred for 2 h at −78 °C, and the reaction was quenched with 1.0 mL of a saturated NH_4Cl solution. Following dilution with 20 mL of ether, the mixture was washed with brine (10 mL) and dried ($MgSO_4$). Preparative TLC purification (ethyl acetate/hexane 3:7) afforded 0.062 g (61%) of *N*-methyl-2-fluoro-4-methylbenzenesulfonamide: mp 85−88 °C; IR (KBr) 3306 (NH), 1333 and 1210 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.4−2.5 (s, 3 H), 2.6−2.8 (d, 3 H, J = 4.3 Hz), 4.5−4.9 (broad, 1 H), 6.9−7.2 (m, 2 H), 7.7−7.9 (t, 1 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 29.3, 117.1 and 117.4 (J = 21 Hz), 123.4 and 123.6 (J = 14 Hz), 125.1, 130.5, 146.5 and 146.7 (J = 9 Hz), 156.5 and 160.5 (J = 253 Hz); ^{19}F NMR ($CDCl_3$) δ −112.6. Anal. Calcd for $C_8H_{10}FNO_2S$: C, 47.29; H, 4.96. Found: C, 47.11; H 4.65.

When TMEDA was employed, 0.058 g (0.5 mmol) of freshly distilled TMEDA was added prior to the addition of *n*-BuLi.

***N,N*-Dimethyl-2-Fluoro-4-methoxybenzenesulfonamide.** In an oven-dried 50 mL two-necked round-bottomed flask fitted with an argon bubbler, a rubber septum, and a magnetic stirring bar was placed 0.100 g (0.465 mmol) of *N,N*-dimethyl(4-methoxyphenyl)-*p*-toluenesulfonamide in 10 mL of THF. The reaction mixture was cooled to −78 °C, and 0.223 mL (0.558 mmol, 1.2 equiv) of *n*-BuLi was added. After 45 min at this temperature, a solution of 0.132 g (0.558 mmol) of NFOBS (**2**) in 10 mL of THF was added dropwise. The resultant mixture was stirred for 2 h at −78 °C, and the reaction was quenched with 1.0 mL of saturated NH_4Cl solution. Normal workup procedures afforded 0.051 g (47%) of *N,N*-dimethyl-2-fluoro-4-methoxybenzenesulfonamide as an oil: IR (neat) 1359 and 1187 (SO_2NR_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.8−2.9 (s, 6 H), 2.9−3.0 (s, 3 H), 6.6−6.8 (m, 2 H), 7.9−8.0 (d, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 45.1, 55.7, 107.7 and 108.1 (J = 28 Hz), 123.8 and 124.0 (J = 15 Hz), 134.1, 148.5, 156.6 and 156.8 (J = 8 Hz), 165.7 and 169.9 (J = 294 Hz); ^{19}F NMR ($CDCl_3$) δ −129. Anal. Calcd for $C_9H_{12}FNO_3S$: C, 46.35; H, 5.15. Found: C, 46.66; H 4.99.

***tert*-Butyl 2-Fluorophenyl Sulfone.** In an oven-dried 50 mL two-necked round-bottomed flask with an argon bubbler, a rubber septum, and a magnetic stirring bar was placed 0.100 g (0.505 mmol) of *tert*-butyl phenyl sulfone[50] in 10 mL of THF. The reaction mixture was cooled to −78 °C, and 0.24 mL (0.606 mmol, 1.2 equiv) of *n*-BuLi was added. After 45 min at this temperature, a solution of 0.143 g (0.606 mmol) of NFOBS (**2**) in 10 mL of THF was added dropwise. After 1.5 h at this temperature, the mixture was warmed to room temperature over 0.5 h. At this time the reaction was quenched with 1.0 mL of a saturated NH_4Cl solution. Normal workup procedures afforded 0.033 g (30%) of *N-tert*-butyl-2-fluorobenzenesulfonamide as a colorless oil: IR (neat) 1310 and 1135 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (s, 9 H), 7.2−7.3 (t, 1H, J = 7.4 Hz), 7.3−7.4 (t, 1 H, J = 6.8 Hz), 7.6−7.7 (m, 1 H), 7.9−8.0 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.4, 61.1, 117.7 and 118.0 (J = 20 Hz), 124.4 and 124.6 (J = 14 Hz), 128.7, 130.4, 133.7 and 133.9 (J = 8 Hz), 136.3 and 140.1 (J = 266 Hz); ^{19}F NMR ($CDCl_3$) δ −114. Anal. Calcd for $C_{10}H_{13}FO_2S$: C, 55.55; H, 6.02. Found: C, 55.37; H 5.80.

2-(2-Fluoro-4-methoxyphenyl)-4,4-dimethyl-2-oxazolidinone. In an oven-dried 50 mL two-necked, round-bottomed flask with an argon bubbler, a rubber septum, and a magnetic stirring bar was placed 0.100 g (0.488 mmol) of 2-(4-methoxyphenyl)-4,4-dimethyl-2-oxazolidinone[51] in 10 mL of THF. The reaction mixture was cooled to −78 °C and treated with 89 μL (0.577 mmol, 1.18 equiv) of TMEDA, followed by 0.400 mL (0.577 mmol, 1.18 equiv) of *sec*-BuLi. The reaction mixture was then warmed to −20 °C slowly and stirred for 1 h at this temperature. The mixture was then cooled back to −78 °C, and a solution of 0.139 g (0.586 mmol) of NFOBS (**2**) in 10 mL of THF was added dropwise. After 2 h at this temperature, the reaction was quenched with 1 mL of a saturated NH_4Cl solution. Normal workup procedures afforded 0.055 g (48%) of 2-(2-fluoro-4-methoxyphenyl)-4,4-dimethyl-2-oxazolidinone as a colorless oil: IR (neat) 1642 (C=N) and 1151 (C−O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (s, 6 H), 3.8−3.9 (s, 1 H), 4.0−4.1 (s, 1H), 6.6−6.8 (m, 1 H), 6.8−7.0 (d, 1 H, J = 6.9 Hz), 7.7−7.8 (m, 1 H), 7.8−7.9 (d, 1 H, J = 8.9); ^{13}C NMR ($CDCl_3$) δ 28.3, 55.3, 67.8, 78.8, 101.3 and 101.6 (J = 21 Hz), 102.4 and102.7 (J = 23 Hz), 110.0, 113.6, 129.9 and 130.1 (J = 8 Hz), 131.9 and 136.8 (J = 246); ^{19}F NMR ($CDCl_3$) δ −107. Anal. Calcd for $C_{12}H_{14}FNO_2S$: C, 61.80; H, 6.01. Found: C, 61.55; H 5.77.1

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