JOC The Journal of Organic Chemistry

Article

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Comprehensive Energetic Scale for Quantitatively Estimating the Fluorinating Potential of N−F Reagents in Electrophilic Fluorinations

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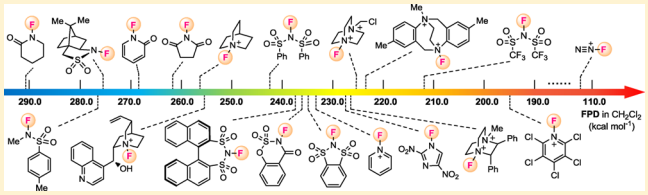
Supporting Information

ABSTRACT: Quantitative knowledge of the fluorinating strength of electrophilic N−F reagents is of crucial importance for rational design and optimization of novel reagents and new reactions. Herein, we report the first systematic computation of fluorinating potentials of 130 electrophilic N−F reagents in two commonly used solvents dichloromethane and acetonitrile in terms of the N−F bond heterolysis energies as expressed by the fluorine plus detachment (FPD) values. The calculated FPD scales of 130 N−F reagents cover a range from 112.3 to 290.4 kcal mol^{-1} and 110.9 to 278.4 kcal mol^{-1} in dichloromethane and acetonitrile, respectively. This comprehensive FPD database provides a valuable quantitative guide for studying the influence of structural variation on the fluorinating strength of the N−F reagents, opening a door to the rational design of novel reagents with appropriate fluorinating strength for specific purposes. It is demonstrated that the FPD values can reproduce the reactivity order for electrophilic N−F reagents better than other parameters.

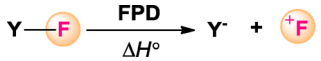


1. INTRODUCTION

Fluorine plays an amazing role in medicinal chemistry and drug design for it often causes significant improvements in bioavailability, lipophilicity, metabolic stability, or other desirable properties for drug targets.[1] In fact, roughly 20% of the known pharmaceuticals and 30% agrochemicals in the market contain fluorine atoms.[1] Fluorinated compounds are also widely used in advanced functional materials.[2] Despite their broad-spectrum utilities, organofluoro compounds are very scarce in nature.[3] Thus, enormous efforts have been devoted to the development of safe and efficient fluorinating reagents and selective synthetic methodologies for the introduction of fluorine into desired scaffolds.[4]

Among various methodologies of introducing fluorine into target molecules, electrophilic fluorination has been particularly successful and remains a very active research area.[5,6] In fact, the rapid progress of this field would not have been possible without the appearance of a wide variety of electrophilic N−F fluorinating reagents[7] (Figure 1) developed by a number of fine groups, such as Banks,[7b,8] Umemoto,[7f,9] Differding,[10] Shibata,[11] Cahard,[11c,12] and Gouverneur.[13] Unlike the O−F or other types of electrophilic fluorinating reagents,[14] these N−F reagents are generally safe and easy to handle and also cover a wide range of reactivity and so can effectively fluorinate a broad range of nucleophiles.[7] Indeed, the discovery of these N−F reagents has promoted many breakthroughs in synthetic fluorine chemistry.[4]

Although a sizable arsenal of electrophilic N−F fluorinating agents is available to organic chemists, works toward quantitative or semiquantitative understanding of their fluorinating strength are relatively scarce.[7a,15] Gilicinski et al. found a correlation between fluorinating strength of some N−F reagents and their peak reduction potentials (E_p),[15a] but accessing accurate data concerning the fluorinating strength is often precluded by experimental problems when determining the standard redox potential.[7a,15a−e] Togni et al. attempted to relate the relative electrophilic fluorinating power of N−F reagents with kinetic data based on competitive halogenations of β-keto esters, but only seven N−F reagents were investigated in the analysis.[15g] Considering that different substrates may be fluorinated by different mechanisms (e.g., S_N2 or SET)[5a−d,7a−f] and that a fluorinating power found for one substrate class (as above) may not be directly transferable to other classes, a more general and easily applicable tool for quantitatively estimating the intrinsic fluorinating strength of these reagents should be highly demanded. Actually, as early as in 1992, Christe and Dixon already followed this line by introducing a parameter named Fluorine Plus Detachment (FPD) energy (eq 1) as a



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quantitative measure of the fluorinating or oxidizing strength. However, only two N−F reagents, N_2F^+ and NF_4^+, were included in the study.[16] Though it was suggested right after in an elegant review[7a] that "it would clearly be of interest to extend these calculations to the other N−F reagents", no follow up works were found even for the most widely used reagents

Received: March 30, 2016
Published: April 27, 2016

DOI: 10.1021/acs.joc.6b00683
J. Org. Chem. 2016, 81, 4280−4289

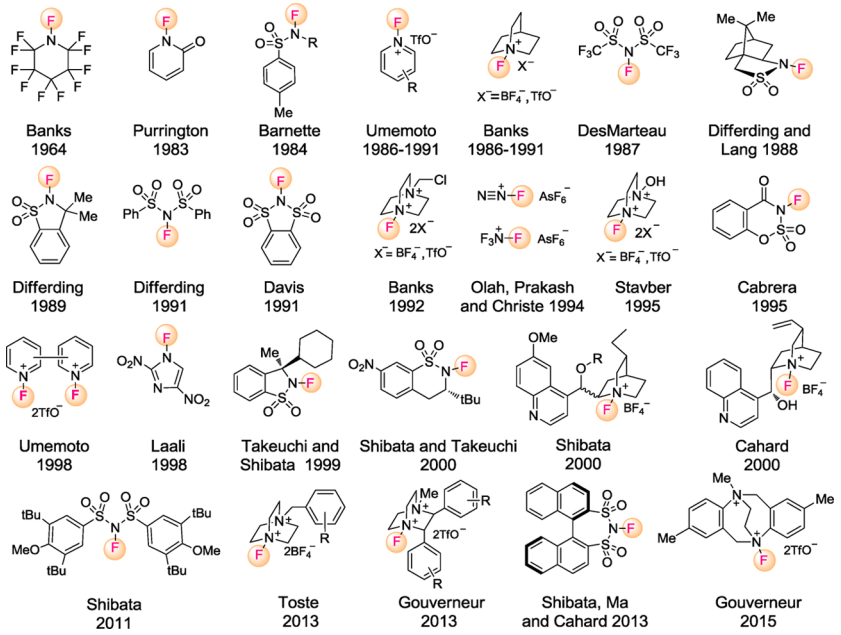


Figure 1. Typical electrophilic N−F fluorinating reagents.

like Differding's *N*-fluorobenzenesulfonimide (NFSI)[10c] and Banks' Selectfluor.[17] As a consequence, the long desired rational design and optimization of novel reagents for exploring new reactions have been largely hampered.

In the present work, we report the first systematic quantum mechanical calculation of FPD values of 130 electrophilic N−F reagents in two commonly used solvents (CH_2Cl_2 and CH_3CN). To our delight, the derived FPD values explain and predict well the reactivity order of various electrophilic fluorinating N−F reagents. Detailed discussion on structural effect and the first comprehensive FPD scale for popular N−F type electrophilic fluorinating reagents are presented. The results from this contribution lay an important groundwork for the rational design and optimization of novel N−F reagents and would contribute to future rapid development of the area of electrophilic fluorination.

2. COMPUTATIONAL METHODS

Truhlar and co-workers' M06-2X and M05-2X functionals have been shown to provide accurate predictions for main group thermochemistry.[18] Indeed, the calculated gas-phase FPD values of N_2F^+ and NF_4^+ reagents at the M06-2X/6-311++G(2d, p)//M05-2X/6-31+G(d) level of theory agree well with these obtained at the CCSD(T)/CBS level reported by Dixon and Christe.[19] In contrast, other density functionals tested such as B3LYP,[20] X3LYP,[21] BMK,[22] ωB97X-D,[23] and B2PLYP-D[24] exhibit larger deviations (see Table S1). Accordingly, the M06-2X/6-311++G(2d, p)//M05-2X/6-31+G(d) method was employed for the calculation of the FPD values. Notably, the FPD values reported here are at 298.15 K instead of at 0 K.

Geometry optimizations, vibrational frequencies, and thermal energy corrections were performed with the M05-2X functional[18] in conjunction with the standard 6-31+G(d)[25] basis set. The SMD solvation model[26] was used to account for the effects of dichloromethane and acetonitrile solutions. To obtain more accurate electronic energies, single-point energy calculations were performed at the SMD-M06-2X/6-311++G(2d, p) level of theory with the M05-2X/6-31+G(d) optimized structures.[27] The spin state of each structure is a singlet except for that of F^+, which is triplet.[28] Structures were generated using CYLview.[29] All calculations were carried out with GAUSSIAN 09 packages.[30]

3. RESULTS AND DISCUSSION

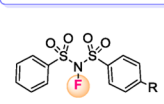
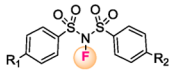
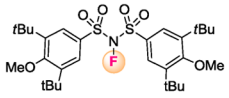
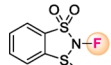
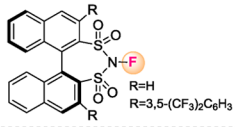
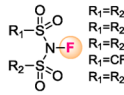
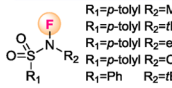
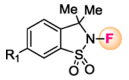
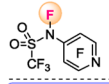
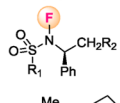
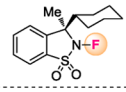
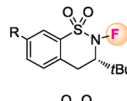
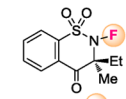
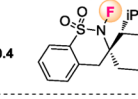
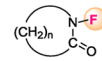
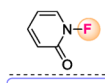
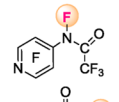
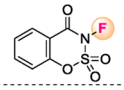
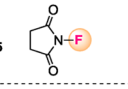
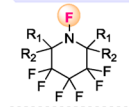
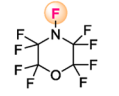
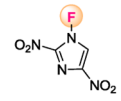
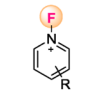
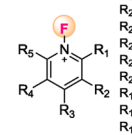
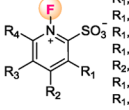
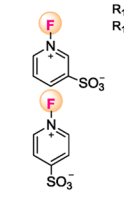
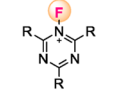
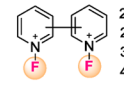
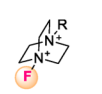
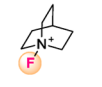
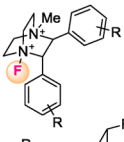
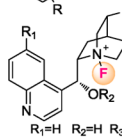
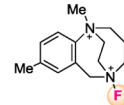
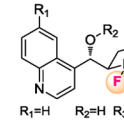
The calculated FPD values for 130 N−F reagents in dichloromethane and acetonitrile solutions at the (SMD) M06-2X/6-311++G(2d, p)//M05-2X/6-31+G(d) level of theory are presented in Table 1. To elucidate the effects of structural variations on the FPD values, these N−F reagents are grouped into six families: (1) *N*-fluorosulfonimides (**A1a**−**A6d**), (2) *N*-fluorosulfonamides (**B1a**−**B9**), (3) *N*-fluorocarboxamides (**C1a**−**C6**), (4) *N*-fluoro heterocycles (**D1a**−**D3**), (5) *N*-fluoropyridiniums (**E1a**−**E6d**), and (6) *N*-fluoroammoniums (**F1a**−**F8**). Examination of Table 1 reveals that the FPD values of 130 N−F reagents cover a range from 112.3 kcal mol^{-1} for N_2F^+ reagent (**F7**)[31] to 290.4 kcal mol^{-1} for *N*-Fluorocarboxamide reagent (**C1b**)[32] in dichloromethane, a narrowing in the range of values (110.9−278.4 kcal mol^{-1}) in acetonitrile. In the following discussion, we focus mainly on the FPD values in dichloromethane and comment the corresponding values in acetonitrile when necessary.

3.1. FPDs of *N*-Fluorosulfonimides (A1a-A6d). The calculated FPD values for Differding's NFSI (**A1a**),[10c] one of the most popular fluorinating reagents, in dichloromethane and acetonitrile are 242.4 and 229.6 kcal mol^{-1}, respectively. This indicates that electrophilic fluorine transfer from NFSI should be more favorable in a high dielectric solvent than in a low dielectric solvent. Consistent with experimental observations that the fluorinating reactivity of NFSI could be enhanced by electron-withdrawing substituents on the aromatic ring and depressed by electron-donating substituents,[5e,11b,33] the FPD values of substituted NFSI reagents increase as the substituent changes from electron-withdrawing to electron-donating groups. In particular, plot of FPDs of *para*- and *meta*-substituted NFSI against the Hammett substituent parameters obtained an excellent correlation with a correlation coefficient r = 0.993 (Figure 2), meaning that the effects of multiple substituents at the *para*- and *meta*-positions have a good linear additivity.

The FPD value of cyclic *N*-fluoro-*o*-benzenedisulfonimide (NFOBS: **A2**) is smaller than that of NFSI by 6.6 kcal mol^{-1} in

DOI: 10.1021/acs.joc.6b00683
J. Org. Chem. 2016, 81, 4280−4289

Table 1. Calculated FPD Values (kcal mol^{-1}) of N−F-Type Electrophilic Fluorine Sources in Dichloromethane and Acetonitrile Solutions

F$^+$ Source			FPD in CH_2Cl_2	FPD in CH_3CN
A. *N*-Fluorosulfonimides				
	R=H	A1a	242.4	229.6
	R=OMe	A1b	244.2	231.2
	R=Me	A1c	243.4	230.3
	R=F	A1d	241.8	229.1
	R=Cl	A1e	241.1	228.4
	R=Br	A1f	240.9	228.3
	R=CN	A1g	239.0	226.7
	R=NO_2	A1h	238.1	226.2
	R_1=R_2=OMe	A1i	245.8	232.5
	R_1=R_2=Me	A1j	244.3	231.1
	R_1=R_2=*t*Bu	A1k	244.2	231.4
	R_1=R_2=F	A1l	241.1	228.6
	R_1=R_2=Cl	A1m	239.8	227.4
	R_1=R_2=Br	A1n	239.5	227.2
	R_1=R_2=OCF_3	A1o	238.7	226.6
	R_1=R_2=CF_3	A1p	237.4	225.3
	R_1=F R_2=NO_2	A1q	237.6	225.8
	R_1=R_2=NO_2	A1r	234.3	222.8
		A1s	246.7	236.2
		A2	235.8	224.2
	R=H	A3a	239.6	227.7
	R=3,5-$(CF_3)_2C_6H_3$	A3b	237.8	226.9
	R_1=R_2=Me	A4a	241.0	230.0
	R_1=R_2=F	A4b	208.2	196.7
	R_1=R_2=CF_3	A4c	211.8	200.5
	R_1=CF_3 R_2=C_4F_9	A4d	212.4	201.2
	R_1=R_2=C_4F_9	A4e	212.7	201.2
	n=2	A5a	216.1	204.8
	n=3	A5b	211.5	200.2
	n=4	A5c	211.3	200.1
	n=1	A6a	235.0	223.7
	n=2	A6b	239.5	228.7
	n=3	A6c	243.9	233.0
	n=4	A6d	245.5	234.5
B. *N*-Fluorosulfonamides				
	R_1=*p*-tolyl R_2=Me	B1a	276.3	264.4
	R_1=*p*-tolyl R_2=*t*Bu	B1b	278.0	265.8
	R_1=*p*-tolyl R_2=exo-2-norbornyl	B1c	275.4	263.7
	R_1=*p*-tolyl R_2=CH_2*t*Bu	B1d	276.1	264.0
	R_1=Ph R_2=*t*Bu	B1e	277.1	264.9
	R_1=H	B2a	270.4	258.3
	R_1=NO_2	B2b	265.4	254.1
		B3	229.2	218.4
	R_1=H R_2=H	B4a	275.6	264.1
	R_1=H R_2=Me	B4b	275.7	264.2
	R_1=Cl R_2=H	B4c	269.1	257.6
	R_1=OMe R_2=H	B4d	274.4	262.8
	R_1=Me R_2=H	B5a	276.4	264.4
	R_1=*p*-tolyl R_2=H	B5b	272.1	260.1
	R_1=*p*-tolyl R_2=OAc	B5c	269.6	257.0
		B6	272.6	260.4
	R=H	B7a	273.6	261.7
	R=NO_2	B7b	269.1	257.9
		B8	266.7	255.0
		B9	272.7	261.1
C. *N*-Fluorocarboxamides				
	n=3	C1a	284.5	272.6
	n=4	C1b	290.4	278.4
	n=5	C1c	289.4	277.4
	n=6	C1d	290.3	278.4
		C2	268.4	256.5
		C3	237.3	226.7
		C4	237.3	225.5
	n=2	C5a	237.5	226.7
	n=3	C5b	237.8	226.9
		C6	262.7	251.2
D. *N*-Fluoro Heterocycles				
	R_1=R_2=F	D1a	241.6	229.3
	R_1=CF_3 R_2=F	D1b	242.0	230.1
	R_1=R_2=CF_3	D1c	249.1	237.7
		D2	243.2	231.0
		D3	228.8	218.6
E. *N*-Fluoropyridiniums				
	R=H	E1a	233.4	230.0
	R=*p*-OMe	E1b	236.0	232.0
	R=*p*-Me	E1c	235.3	231.7
	R=*p*-F	E1d	229.5	226.4
	R=*p*-Cl	E1e	228.4	225.4
	R=*p*-CF_3	E1f	226.1	223.6
	R=*p*-CN	E1g	224.8	222.4
	R=*p*-NO_2	E1h	222.5	220.3
	R=*o*-CN	E1i	218.0	215.1
	R=*m*-CN	E1j	223.2	220.9
	$R_{2,3,4}$=H $R_{1,5}$=Me,	E1k	239.1	234.9
	$R_{2,3,4}$=H $R_{1,5}$=CH_2OMe	E1l	232.1	229.3
	$R_{2,3,4}$=H $R_{1,5}$=CH_2OAc	E1m	228.2	224.8
	$R_{2,3,4}$=H $R_{1,5}$=COOMe	E1n	213.9	210.2
	$R_{2,3,4}$=H $R_{1,5}$=Cl	E1o	208.0	204.2
	$R_{2,3,4}$=H $R_{1,5}$=CN	E1p	202.6	200.2
	$R_{1,3,5}$=H $R_{2,4}$=Cl	E1q	219.7	216.9
	$R_{1,3,5}$=H R_2=CF_3 R_4=Cl	E1r	218.9	216.3
	$R_{1,3,5}$=H $R_{2,4}$=CF_3	E1s	217.0	215.1
	$R_{2,4}$=H $R_{1,3,5}$=Me	E1t	240.9	236.6
	$R_{1\text{-}5}$=Cl	E1u	195.3	191.8
	$R_{1,4}$=H	E2a	238.3	228.7
	$R_{1,3,4}$=H R_2=Me	E2b	240.2	230.6
	$R_{1,3,4}$=H R_2=Et	E2c	240.7	230.9
	$R_{1,3,4}$=H R_2=*t*Bu	E2d	240.6	230.4
	$R_{1,2,4}$=H R_4=Me	E2e	241.2	231.4
	$R_{2,3,4}$=H R_1=CF_3	E2f	231.4	222.3
	$R_{1,2,4}$=H R_3=CF_3	E2g	231.2	222.0
	$R_{1,2,4}$=H R_4=CF_3	E2h	224.7	215.0
	$R_{2,4}$=H R_1=Cl R_3=CF_3	E2i	224.6	215.5
	$R_{1,3}$=H $R_{2,4}$=Me	E2j	242.9	233.1
	$R_{1,3}$=H $R_{2,4}$=CF_3	E2k	218.6	209.9
		E3	238.7	230.2
		E4	238.5	230.2
	R=H	E5a	213.2	210.6
	R=Cl	E5b	189.4	186.2
	2,2'-bisFP	E6a	211.2	213.6
	2,4'-bisFP	E6b	214.7	217.0
	3,3'-bisFP	E6c	220.5	223.0
	4,4'-bisFP	E6d	221.7	224.1
F. *N*-Fluoroammoniums				
	$R=CH_2Cl$	F1a	225.5	229.8
	R=OH	F1b	222.3	226.8
	R=F	F1c	218.9	223.8
	R=Me	F1d	228.1	232.1
	R=CH_2CH_3	F1e	228.6	233.1
	R=CH_2CF_3	F1f	224.8	230.0
	R=$CH_2C_6F_5$	F1g	225.9	230.4
	R=CH_2[3,5-$(CF_3)_2C_6H_3$]	F1h	226.5	231.5
		F4	256.2	252.9
		F7	112.3	110.9
	R=H	F2a	226.3	230.1
	R=*o*-Me	F2b	227.7	230.1
	R=*p*-CF_3	F2c	222.4	227.7
	R_1=H R_2=H R_3=$CHCH_2$	F5a	254.3	249.2
	R_1=OMe R_2=H R_3=$CHCH_2$	F5b	253.9	248.8
	R_1=OMe R_2=4-ClC_6H_4CO R_3=C_2H_5	F5c	249.6	247.6
		F8	153.0	150.9
		F3	223.6	225.3
	R_1=H R_2=H R_3=$CHCH_2$	F6a	253.3	249.5
	R_1=OMe R_2=H R_3=$CHCH_2$	F6b	252.7	249.2
	R_1=OMe R_2=Ac R_3=C_2H_5	F6c	250.7	248.0

DOI: 10.1021/acs.joc.6b00683
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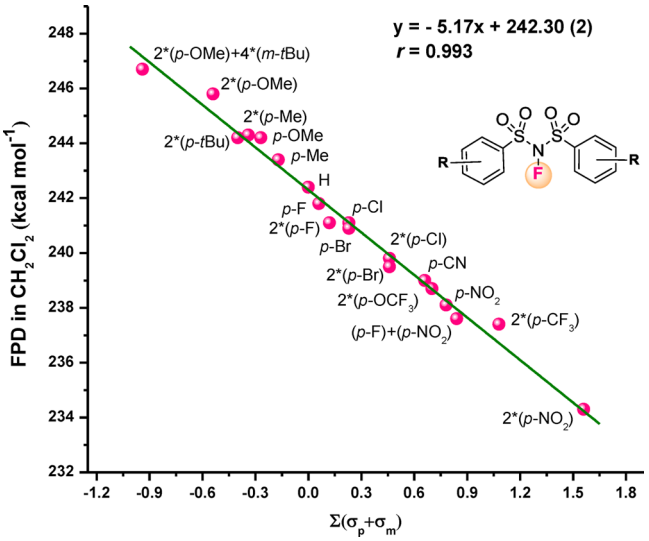

Figure 2. Plot of FPD values of *para*- and *meta*-substituted *N*-fluorobenzenesulfonimides against the Hammett substituent parameters σ_p and σ_m.

dichloromethane, in good agreement with Davis and co-worker's experimental finding that NFOBS was more reactive than NFSI.[34] Interestingly, the FPD value of the chiral NFSI analogue **A3a**, recently developed by Shibata, Ma, Cahard, and co-workers,[11c] falls between those of NFSI and NFOBS. The introduction of two 3,5-bis(trifluoromethyl)phenyl groups at the 3,3′-positions of the reagent **A3a** causes a decrease in the FPD value by 1.8 kcal mol^{-1} in dichloromethane.

Replacement of two phenyl rings of NFSI with two methyl groups leads to a decrease in FPD by 1.4 kcal mol^{-1} in dichloromethane as seen for Me-NFSI[35] (**A4a**: 241.0 kcal mol^{-1}). This trend is perhaps counterintuitive as one might predict that the resulting anion after fluorine loss could be better stabilized by the phenyl group than by the methyl group. A closer inspection into the optimized structures (Figure 3)

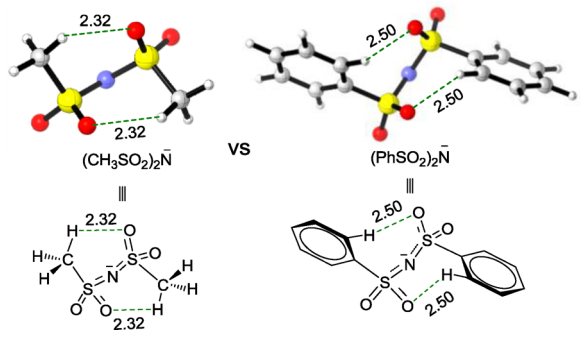

Figure 3. Stabilizing C−H···O hydrogen-bonding interactions in the structure of $(CH_3SO_2)_2N^-$ and $(PhSO_2)_2N^-$ (bond lengths in angstroms).

reveals that stabilizing C−H···O hydrogen bonding interactions[36] exist in $(CH_3SO_2)_2N^-$ and such interactions should be much weaker in $(PhSO_2)_2N^-$ as indicated by longer C−H···O distances. This factor appears to be the determinant for a lower FPD value of Me-NFSI as compared to that of NFSI. Indeed, Shibata and co-workers recently reported that Me-NFSI is more effective than NFSI for the fluorination of active methines.[11d] Notably, the stabilizing C−H···O hydrogen bonding interactions could be attenuated in highly polar acetonitrile solution, leading to similar FPD values for Me-NFSI and NFSI in acetonitrile. Replacing the methyl groups of Me-NFSI with strongly electron-withdrawing F and CF_3 enhances the ability to transfer an electrophilic fluorine by about 33 and 29 kcal mol^{-1} as seen for DesMarteau's $(FSO_2)_2N-F$ (**A4b**) and $(CF_3SO_2)_2N-F$ (**A4c**),[37] respectively. Increasing the fluoroalkyl chain length does not affect the FPDs of *N*-fluoroperfluoroalkylsulfonimides much ($(CF_3SO_2)_2N-F$: 211.8 vs $(C_4F_9SO_2)_2N-F$: 212.7 kcal mol^{-1}).

As a result of the different electronic properties between the perfluoroalkyl and the alkyl group, the FPDs of DesMarteau's cyclic *N*-fluoroperfluoroalkylsulfonimides (**A5a−A5c**)[7a] and their hydrocarbon analogues (**A6a−A6d**)[35] display different trends as the ring enlargements. The FPDs of cyclic *N*-fluoroperfluoroalkylsulfonimides (**A5a−A5c**) gradually decrease from 216.1 to 211.3 kcal mol^{-1}, while FPDs of their hydrocarbon analogues (**A6a−A6d**) steadily increase from 235.0 to 245.5 kcal mol^{-1}.

3.2. FPDs of *N*-Fluorosulfonamides (B1a−B9). The FPDs of Barnette's *N*-fluoro-*N*-alkylsulfonamides (**B1a−B1e**)[38] cover a range from 275.4 to 278.0 kcal mol^{-1} in dichloromethane, meaning that these reagents are at least 33 kcal mol^{-1} less favorable to transfer an electrophilic fluorine than NFSI. Differding and Lang's *N*-fluorosultam reagent (**B2a**)[10b] was predicted to be 5.9 kcal mol^{-1} more likely to transfer an electrophilic fluorine than Barnette's reagent (**B1a**). Incorpration of a nitro group on the aromatic ring of *N*-fluorosultam (**B2a**) leads to an increase in electrophilic reactivity by 5.0 kcal mol^{-1}. The FPD value of Banks' perfluoro-[*N*-fluoro-*N*-(4-pyridyl)methanesulfonamide] (**B3**) is 13.2 kcal mol^{-1} lower than that of NFSI, explaining the experimental observation that this reagent could fluorinate anisole under mild condition.[39]

The FPD values for Differding and Lang's *N*-fluorocamphorsultams (**B4a** and **B4b**), the first enantioselective fluorinating reagents,[10a] are around 276 kcal mol^{-1}, which is actually close to that of Barnette's reagent (**B1c**). Introduction of two electron-withdrawing Cl atoms on the camphor skeleton enhances the reactivity toward transferring an electrophilic fluorine by 6.5 kcal mol^{-1} as seen for Davis' reagent (**B4c**).[40] Computational analysis showed that the FPDs of *N*-fluorotosyl and mesyl derivatives (**B5a−B5c**),[41] *N*-Fluorosultams (**B6**,[42] **B7a−7b**,[43] **B8**[44]), and spiro *N*-fluorosultam (**B9**)[45] cover a narrow range from 266.7 to 276.4 kcal mol^{-1} in dichloromethane.

3.3. FPDs of *N*-Fluorocarboxamides (C1a−C6). The largest FPD values calculated in this study are those of Satyamurthy's *N*-fluorolactams[32] (**C1a−C1d**: from 284.5 to 290.4 kcal mol^{-1}), suggesting that the least tendency of these reagents is to transfer an electrophilic fluorine. Because of the additional driving force gained from the recovery of aromaticity after loss an electrophilic fluorine, Purrington's 1-fluoro-2-pyridone reagent[46] (**C2**) was found to be 16.1 kcal mol^{-1} more favorable to transfer an electrophilic fluorine than Satyamurthy's *N*-fluorolactam reagent (**C1a**). Almost identical FPD values were found for Banks' perfluoro-[*N*-fluoro-*N*-(4-pyridyl)acetamide] (**C3**),[47] Cabrera's *N*-fluorooxathiazinone dioxide (**C4**),[48] and Yagupol'skii's *N*-fluoroperfluorosuccinimide (**C5a**) and *N*-fluoroperfluoroglutarimide (**C5b**),[49] suggesting that they should have fluorinating powers similar to each other. Replacing four fluorine atoms in *N*-fluoroperfluorosuccinimide (**C5a**) with hydrogen atoms causes

DOI: 10.1021/acs.joc.6b00683
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a increase in FPD value by 25 kcal mol^{-1} as seen for Huang's *N*-fluorosuccinimide reagent (**C6**).[50]

3.4. FPDs of *N*-Fluoro Heterocycles (D1a–D3). *N*-Fluoroperfluoropiperidine (**D1a**) is actually the first *N*-F compound reported to act as an electrophilic fluorinating agent.[51] Computational analysis showed that *N*-fluoroperfluoropiperidine (**D1a**) is 1.6 kcal mol^{-1} more favorable to deliver an electrophilic fluorine than its morpholine analogue (**D2**).[51b] Replacement of α-fluorines in *N*-fluoroperfluoropiperidine with the trifluoromethyl groups increases the FPDs as seen for reagents **D1b** and **D1c**.[52] The FPD of Laali's *N*-fluoro-2,4-dinitroimidazole (**D3**)[53] is 228.8 kcal mol^{-1}, meaning that this reagent is 12.8 kcal mol^{-1} more favorable to deliver a positive fluorine as compared to Banks' *N*-fluoroperfluoropiperidine (**D1a**).

3.5. FPDs of *N*-Fluoropyridinium Salts (E1a–E6d). The FPD values of Umemoto's *N*-fluoropyridinium salts (**E1a–E1u**),[9a–d,f,54] the so-called power-variable fluorinating agents, are in the range of 195.3 to 240.9 kcal mol^{-1} in dichloromethane. A good linear correlation was obtained between the calculated FPDs of *para*- and *meta*-substituted *N*-fluoropyridiniums and the Hammett substituent constants σ_p and σ_m (Figure 4), offering a useful tool to fine-tuning their fluorinating

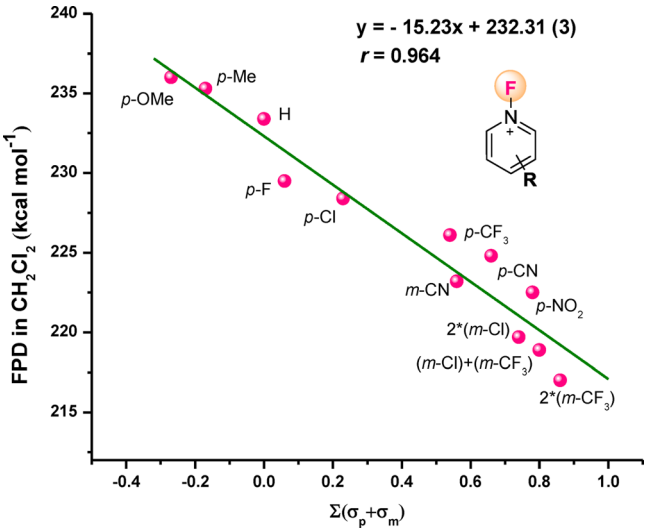

Figure 4. Plot of FPD values of *N*-fluoropyridiniums against the Hammett substituent parameters σ_p and σ_m.

power. For popular *ortho*-, *meta*-, and *para*-substituted *N*-fluoropyridinium reagents, the counteranion-bound system, and *N*,*N*-difluorobipyridinium isomers, their FPD values are in parallel with the relative fluorinating power order observed by Umemoto et al. (Figure 5).[7f,9c] This further corroborates the fact that the FPD parameter can be used as a quantitative measure of the intrinsic fluorinating strength.[16] Among these *N*-fluoropyridiniums, 1-fluoro-2,4,6-trichloro-1,3,5-triazinium (**E5b**)[55] shows the smallest FPD value (189.4 kcal mol^{-1}). Indeed, this reagent could even fluorinate nitrobenzene.[55a]

3.6. FPDs of *N*-Fluoroammonium Salts (F1a–F8). The calculated FPD value of Banks' Selectfluor (**F1a**)[17] is 225.5 kcal mol^{-1} in dichloromethane. Replacing the CH_2Cl moiety with more powerful electron-withdrawing substituents such as OH and F decreases the FPD value by 3.2 and 6.6 kcal mol^{-1} as seen for reagents **F1b**[56] and **F1c**,[57] while substitution with electron-donating Me and Et groups increases the FPD value by 2.6 and 3.1 kcal mol^{-1} as seen for reagents **F1d** and **F1e**,[17] respectively. Notably, the calculated FPD values for Toste et al.'s recently developed Selectfluor derivatives[58] (**F1g** and **F1h**) are in fact larger than that of Selectfluor by 0.4 and 1.0 kcal mol^{-1}, respectively. This could be attributed to a weaker electron-withdrawing inductive ability of pentafluorphenyl and 3,5-bis(trifluoromethyl)phenyl than that of chlorine.[59] Indeed, a plot of FPD values versus field/inductive parameters (*F*)[59] gave a linear relationship for doubly quarternized *N*-fluoro-1,4-bicyclo[2.2.2]octane derivatives, allowing their FPD values to be fine-tuned by the quaternizing group R (Figure 6).

Gouverneur et al. recently reported a new class of chiral Selectfluor N–F reagents (**F2a–F2c**), which has led to the successful development of asymmetric fluorocarbocyclization reactions.[13d] Computational analysis showed that reagent **F2c** is 3.1 kcal mol^{-1} more electrophilic than Selectfluor in dichloromethane. More recently, the same group developed a novel N–F reagent (**F3**) derived from the ethano-Tröger's base.[13e] The FPD value of this reagent is 223.6 kcal mol^{-1}, which is 1.9 kcal mol^{-1} below that of Selectfluor. Notably, the FPD values of all these dicationic N–F reagents in the low polar dichloromethane are smaller than those in the high polar acetonitrile, suggesting that electrophilic fluorine transfer from dicationic N–F reagents should be more favorable in a low dielectric solvent. This trend is strikingly different from the situation for neutral and monocationic N–F reagents.

In line with previous observations that the monocationic N–F reagents are significantly less reactive than the dicationic N–F reagents, the FPD value of Banks' *N*-fluoroquinuclidinium (**F4**)[60] is ca. 30 kcal mol^{-1} larger than that of Selectfluor in dichloromethane. The FPD values for cinchona alkaloid derived *N*-fluoroammoniums (**F5a–F6c**), reported simultaneously and independently by Shibata[11a,61] and Cahard,[12] are in the range from 249.6 to 254.3 kcal mol^{-1}. Very similar FPD values obtained for *N*-fluorocinchonidinium (**F5a**) and *N*-fluorocinchoninium (**F6a**) (as well as for *N*-fluoroquininium (**F5b**) and *N*-fluorocinquinidinium (**F6b**)) indicate that the stereochemistry at the C_8/C_9 centers has little influence on the electrophilic of these reagents. Interestingly, the esterification of the 9-OH with electron-withdrawing 4-chlorobenzoyl and acetyl groups enhances the electrophilic by 4.3 and 2.0 kcal mol^{-1}, respectively, as seen for Shibata's *N*-fluorodihydroquininium 4-chlorobenzoate (**F5c**) and *N*-fluorodihydroquinidinium acetate (**F6c**).[11a] The lowest FPD values of N–F reagents calculated in this study are those for N_2F^+ (**F7**: 112.3 kcal mol^{-1}) and NF_4^+ (**F7**:153.0 kcal mol^{-1}). Indeed, Olah, Prakash, and Christe reported that the two reagents could directly electrophilic fluorinate methane.[31]

3.7. Correlation between FPD Values and pK_a Data. Previously, Umemoto and co-workers have found that the electrophilic fluorination reactivity of *N*-fluoropyridinium salts correlates with the pK_a values of the corresponding pyridines.[54c] It would be of great value to test whether the correlation could be extended to other N–F fluorinating reagents. Indeed, plotting the calculated FPD values of N–F reagents against the corresponding experimental pK_a values[62] yields a good linear relationship with a regression coefficient r = 0.988 (Figure 7). This offers a good opportunity for future design of new N–F fluorinating reagents because substantial pK_a data have already been accumulated in past decades.[62,63]

3.8. FPD Scale for Representative Electrophilic N–F Fluorinating Reagents. For a better comparison, we compiled a FPD scale for selected representative electrophilic

DOI: 10.1021/acs.joc.6b00683
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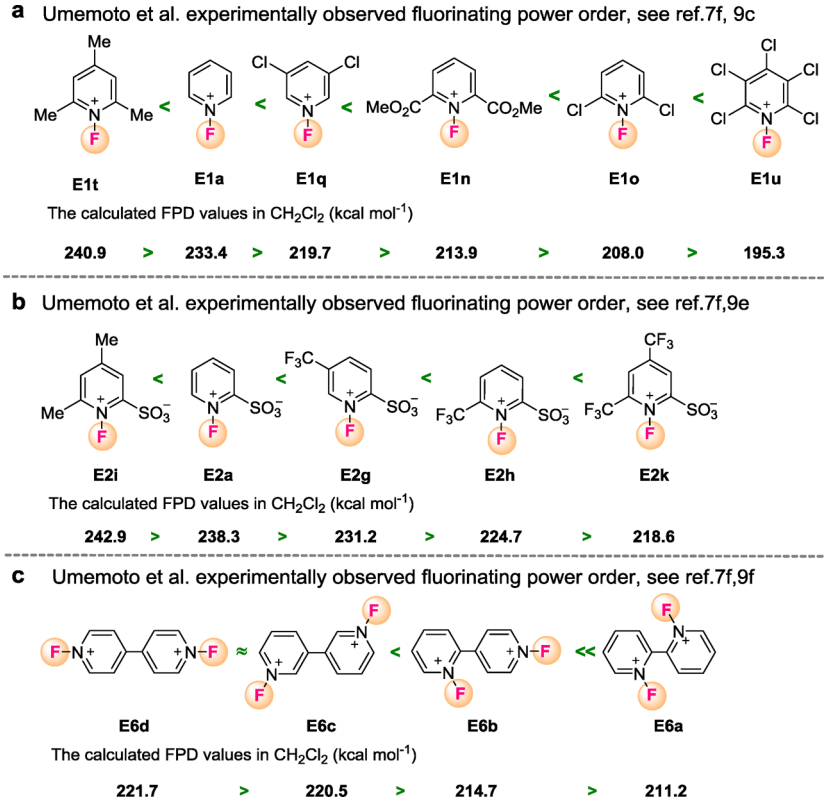

Figure 5. Comparison between calculated FPDs and experimental fluorinating power (increasing FPD values signify decreasing fluorinating power).

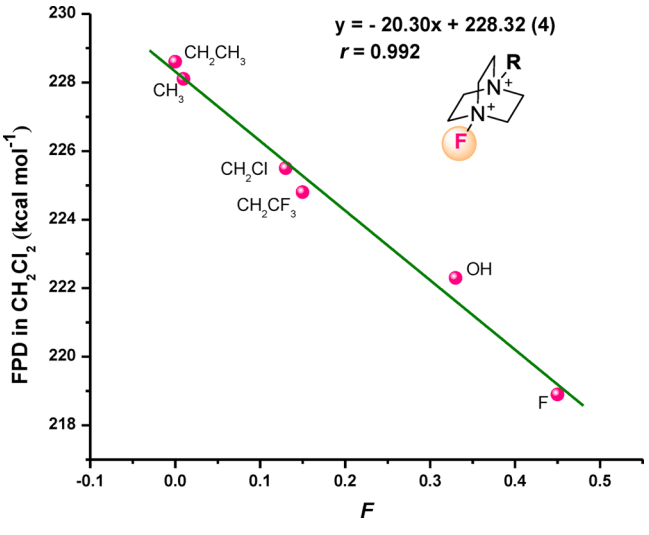

Figure 6. Plot of FPD values of doubly quarternized *N*-fluoro-1,4-bicyclo[2.2.2]octane derivatives against the field/inductive parameters (*F*).

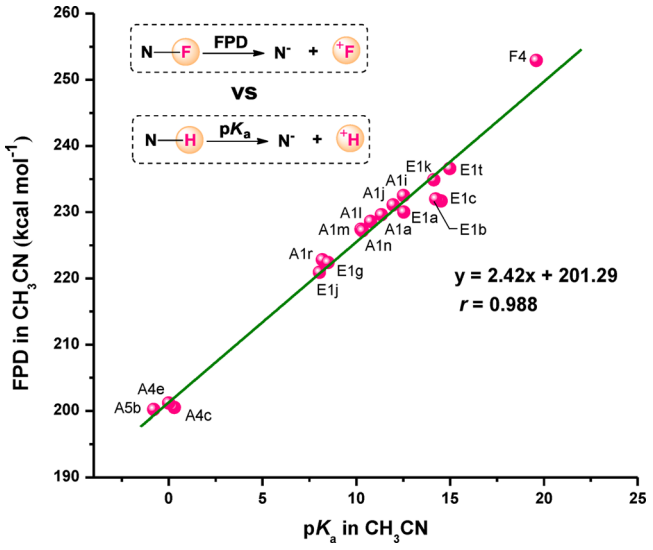

Figure 7. Plot of calculated FPD values of electrophilic N−F fluorinating reagents against corresponding experimental pK_a values in acetonitrile.

N−F reagents in Figure 8.[64] To further demonstrate the value of the FPD scale, we applied it to analyzing electrophilic fluorination reactions and found that the FPD data can better reproduce the reactivity order of electrophilic N−F reagents than other parameters.

The discovery of *N*-fluoroammonium salts of the cinchona alkaloids as effective enantioselective fluorinating reagents by Shibata and co-workers[11a,61] and Cahard and co-workers[12] represents a landmark in the field of enantioselective electrophilic fluorination. *N*-Fluoroammonium salts of the cinchona alkaloids can be either formed in situ[6a,11a,61,65] or isolated as stable chiral fluorinating reagents.[12,66] In each case, fluorine transfer from achiral fluorinating reagents such as Selectfluor, NFSI, and NFBSI to the quinuclidine nitrogen of cinchona alkaloids is actually the key prerequisite.[5e] We found that the FPD values can well rationalize these transfer fluorination processes, whereas the widely used peak reduction potentials (E_p)[15a] appear to be misleading (Figure 9). According to the calculated FPD values, the fluorinating power of both NFSI and NFBSI exceeds those of cinchona alkaloid derivatives by at least 11.4 kcal mol^{-1} in acetonitrile, suggesting that these transfer

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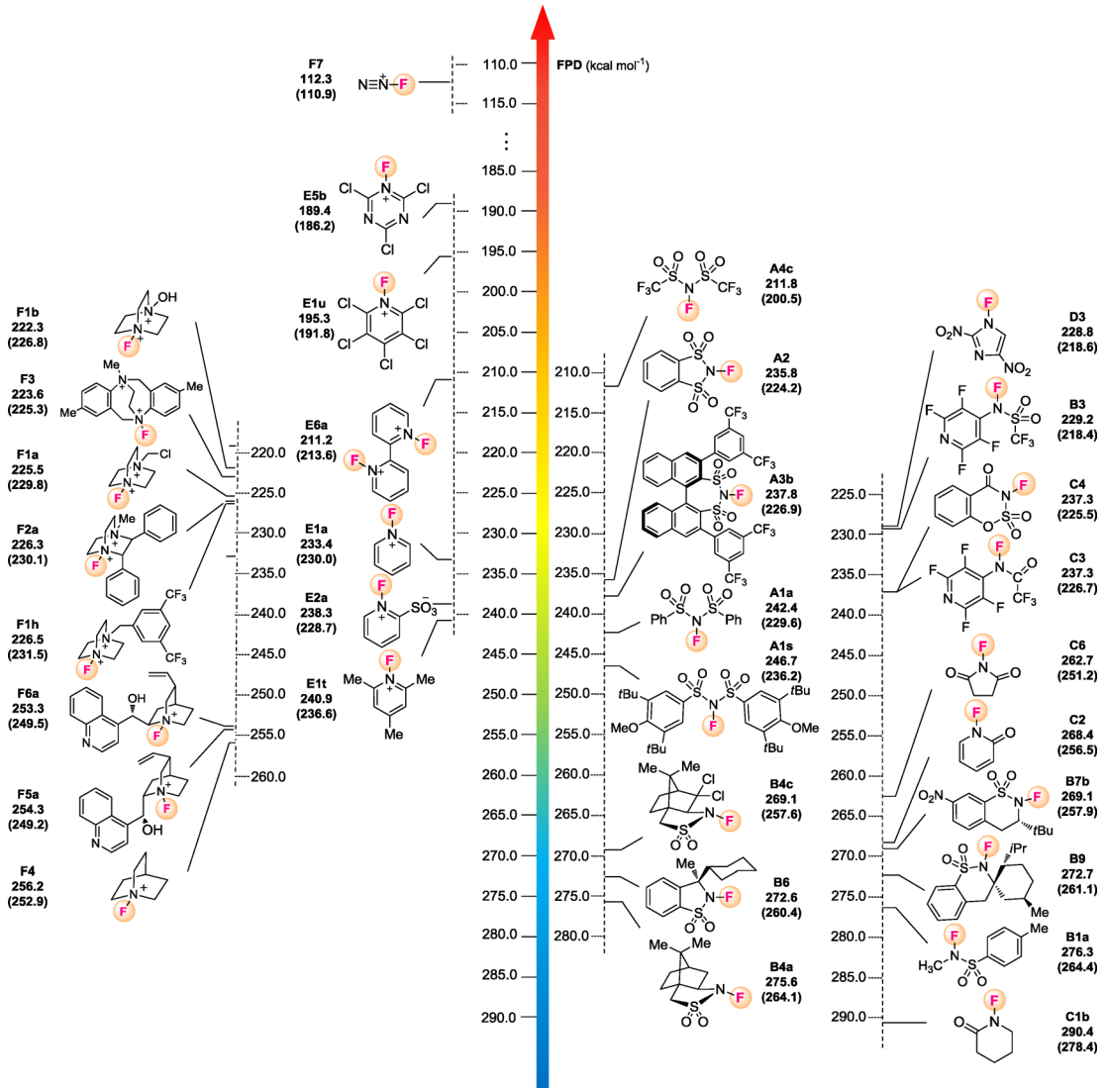

Figure 8. FPD values for representative electrophilic fluorinating reagents in dichloromethane and acetonitrile (in parentheses).

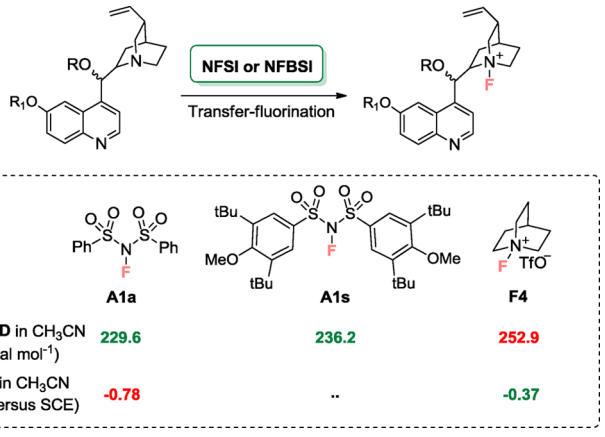

Figure 9. FPD values and peak reduction potentials (E_p)[15a] for achiral N−F fluorinating reagents in acetonitrile and transfer fluorination of the cinchona alkaloids.

fluorination processes are thermodynamically very favorable processes. Although the E_p values for *N*-fluoroammonium salts of the cinchona alkaloids have not yet been reported, it is safe to assume that their E_p values should be close to that of Banks' *N*-fluoroquinuclidinium triflate.[15a] The E_p value of *N*-fluoroquinuclidinium triflate in acetonitrile is −0.37 V,[6a] which is 0.41 V more positive than that of NFSI (Figure 9), thus resulting in a relative fluorinating power order that is inconsistent with experiments.

Very recently, Gouverneur et al. reported that Umemoto's *N*-fluoro-2,3,4,5,6-pentachloropyridinium triflate (**E1u**) could readily transfer fluorination of the ethylene-bridged Tröger's base (**F3′**) to prepare the novel N−F reagent **F3**, while no reaction occurred for Banks' Selectfluor (Figure 10).[13e] Accordingly to the FPD values, the fluorinating power should increase in the order: Banks' Selectfluor (**F1a**: 225.5 kcal mol^{-1}) < Gouverneur's reagent (**F3**: 223.6 kcal mol^{-1}) < Umemoto's *N*-fluoro-2,3,4,5,6-pentachloropyridinium (**E1u**: 191 kcal mol^{-1}), thus well rationalizing the observed transfer fluorination. On the other hand, ^{19}F chemical shifts were found to be incapable of predicting the outcomes observed by Gouverneur and co-workers.

4. CONCLUSION

In summary, we have addressed a fundamental question in the field of electrophilic fluorination. The long-awaited FPD values of 130 electrophilic N−F reagents in dichloromethane and

DOI: 10.1021/acs.joc.6b00683
J. Org. Chem. 2016, 81, 4280−4289

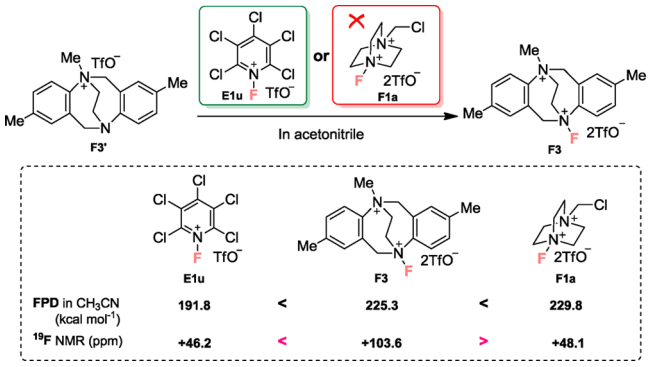

Figure 10. FPD values and ^{19}F chemical shifts[13e] for N−F reagents in acetonitrile and relevant transfer fluorinations.

acetonitrile were obtained by density functional theory, and the first FPD scale for popular electrophilic N−F reagents has been established. Such huge data sets provide a detailed quantitative view of the effects of structural alternations on the fluorinating strength of N−F reagents, paving the way to the rational design of novel reagents with suitable fluorinating strength for desired applications. A good correlation has been found between the FPD values of N−F reagents and the corresponding pK_a values of the acids, offering a powerful avenue for estimating the fluorinating strength of a novel N−F reagent. The FPD values can better reproduce the reactivity order for electrophilic N−F reagents than other parameters such as peak reduction potentials (E_p) and ^{19}F chemical shifts. This contribution lays an important foundation for the rational design and optimization of novel reagents and new reactions, and would contribute to future rapid development of the chemistry of electrophilic fluorination.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00683.

Table S1, complete citation for ref 30, and optimized geometries of all computed species (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Basic Research Program of China (973 Program, 2012CB821600), the Natural Science Foundation of China (NSFC, Grant Nos. 21390400 and 21402099), the Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), the State Key Laboratory on Elemento-organic Chemistry, and the Fundamental Research Funds for the Central Universities. X.-S.X. thanks Prof. X. Li, Dr. J.-D., Yang, and Mr. C. Yang at Nankai University for helpful discussions.

■ REFERENCES

(1) (a) Mueller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Acena, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422.

(2) (a) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *Chem. Soc. Rev.* **2011**, *40*, 3496. (b) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2013. (c) Tirotta, I.; Dichiarante, V.; Pigliacelli, C.; Cavallo, G.; Terraneo, G.; Bombelli, F. B.; Metrangolo, P.; Resnati, G. *Chem. Rev.* **2015**, *115*, 1106. (d) Preshlock, S.; Tredwell, M.; Gouverneur, V. *Chem. Rev.* **2016**, *116*, 719.

(3) (a) Dong, C. J.; Huang, F. L.; Deng, H.; Schaffrath, C.; Spencer, J. B.; O'Hagan, D.; Naismith, J. H. *Nature* **2004**, *427*, 561. (b) O'Hagan, D.; Deng, H. *Chem. Rev.* **2015**, *115*, 634.

(4) For general reviews, see: (a) Ma, J. A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. (b) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (c) Tredwell, M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 11426. (d) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (e) Xu, X. H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731. (f) Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 3216. (g) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765. (h) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826. (i) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.* **2015**, *115*, 9073. (j) Campbell, M. G.; Ritter, T. *Chem. Rev.* **2015**, *115*, 612.

(5) For reviews on electrophilic fluorination, see: (a) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431. (b) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31. (c) Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192. (d) Tredwell, M.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 26. (e) Shibata, N.; Ishimaru, T.; Nakamura, S.; Toru, T. *J. Fluorine Chem.* **2007**, *128*, 469. (f) Pacheco, M. C.; Purser, S.; Gouverneur, V. *Chem. Rev.* **2008**, *108*, 1943. (g) Lin, J.-H.; Xiao, J.-C. *Tetrahedron Lett.* **2014**, *55*, 6147. (h) Wolstenhulme, J. R.; Gouverneur, V. *Acc. Chem. Res.* **2014**, *47*, 3560.

(6) For selected examples on electrophilic fluorination, see: (a) Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4157. (b) Paull, D. H.; Scerba, M. T.; Alden-Danforth, E.; Widger, L. R.; Lectka, T. *J. Am. Chem. Soc.* **2008**, *130*, 17260. (c) Wilkinson, S. C.; Lozano, O.; Schuler, M.; Pacheco, M. C.; Salmon, R.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 7083. (d) Lozano, O.; Blessley, G.; Martinez del Campo, T.; Thompson, A. L.; Giuffredi, G. T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 8105. (e) Yamamoto, T.; Suzuki, Y.; Ito, E.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2011**, *13*, 470. (f) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681. (g) Erb, J.; Paull, D. H.; Dudding, T.; Belding, L.; Lectka, T. *J. Am. Chem. Soc.* **2011**, *133*, 7536. (h) Li, F.; Nie, J.; Wu, J.-W.; Zheng, Y.; Ma, J.-A. *J. Org. Chem.* **2012**, *77*, 2398. (i) Lee, S. Y.; Neufeind, S.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 8899. (j) Zhao, J. F.; Duan, X. H.; Yang, H.; Guo, L. N. *J. Org. Chem.* **2015**, *80*, 11149. (k) Buckingham, F.; Kirjavainen, A. K.; Forsback, S.; Krzyczmonik, A.; Keller, T.; Newington, I. M.; Glaser, M.; Luthra, S. K.; Solin, O.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2015**, *54*, 13366. (l) Egami, H.; Asada, J.; Sato, K.; Hashizume, D.; Kawato, Y.; Hamashima, Y. *J. Am. Chem. Soc.* **2015**, *137*, 10132.

(7) For reviews, see: (a) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737. (b) Banks, R. E. *J. Fluorine Chem.* **1998**, *87*, 1. (c) Kiselyov, A. S. *Chem. Soc. Rev.* **2005**, *34*, 1031. (d) Baudoux, J.; Cahard, D. In *Organic Reactions*; Denmark, S. E., Ed.; Wiley: Hoboken, 2007; Chapter 2, pp 347−672. (e) Prakash, G. K. S.; Wang, F. Flourishing Frontiers in Organofluorine Chemistry. In *Organic Chemistry Breakthroughs and Perspectives*; Ding, K., Dai, L.-X., Eds.; Wiley-VCH: Weinheim, 2012. (f) Umemoto, T. *J. Fluorine Chem.* **2014**, *167*, 3. (g) Serguchev, Y. A.; Ponomarenko, M. V.; Ignat'ev, N. V. *J. Fluorine Chem.* **2016**, *185*, 1.

(8) Banks, R. E.; Besheesh, M. K.; MohialdinKhaffaf, S. N.; Sharif, I. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2069.

(9) (a) Umemoto, T.; Kawada, K.; Tomita, K. *Tetrahedron Lett.* **1986**, *27*, 4465. (b) Umemoto, T.; Tomita, K. *Tetrahedron Lett.* **1986**,

DOI: 10.1021/acs.joc.6b00683
J. Org. Chem. 2016, 81, 4280−4289

27, 3271. (c) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563. (d) Umemoto, T.; Harasawa, K.; Tomizawa, G.; Kawada, K.; Tomita, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1081. (e) Umemoto, T.; Tomizawa, G. *J. Org. Chem.* **1995**, *60*, 6563. (f) Umemoto, T.; Nagayoshi, M.; Adachi, K.; Tomizawa, G. *J. Org. Chem.* **1998**, *63*, 3379.

(10) (a) Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1988**, *29*, 6087. (b) Differding, E.; Lang, R. W. *Helv. Chim. Acta* **1989**, *72*, 1248. (c) Differding, E.; Ofner, H. *Synlett* **1991**, *1991*, 187.

(11) (a) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728. (b) Yasui, H.; Yamamoto, T.; Ishimaru, T.; Fukuzumi, T.; Tokunaga, E.; Akikazu, K.; Shiro, M.; Shibata, N. *J. Fluorine Chem.* **2011**, *132*, 222. (c) Zhu, C. L.; Maeno, M.; Zhang, F. G.; Shigehiro, T.; Kagawa, T.; Kawada, K.; Shibata, N.; Ma, J. A.; Cahard, D. *Eur. J. Org. Chem.* **2013**, *2013*, 6501. (d) Fukushi, K.; Suzuki, S.; Kamo, T.; Tokunaga, E.; Sumii, Y.; Kagawa, T.; Kawada, K.; Shibata, N. *Green Chem.* **2016**, *18*, 1864.

(12) (a) Cahard, D.; Audouard, C.; Plaquevent, J. C.; Roques, N. *Org. Lett.* **2000**, *2*, 3699. (b) Mohar, B.; Baudoux, M.; Plaquevent, J. C.; Cahard, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4214.

(13) (a) Teare, H.; Robins, E. G.; Arstad, E.; Luthra, S. K.; Gouverneur, V. *Chem. Commun.* **2007**, 2330. (b) Teare, H.; Robins, E. G.; Kirjavainen, A.; Forsback, S.; Sandford, G.; Solin, O.; Luthra, S. K.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 6821. (c) Stenhagen, I. S. R.; Kirjavainen, A. K.; Forsback, S. J.; Jorgensen, C. G.; Robins, E. G.; Luthra, S. K.; Solin, O.; Gouverneur, V. *Chem. Commun.* **2013**, *49*, 1386. (d) Wolstenhulme, J. R.; Rosenqvist, J.; Lozano, O.; Ilupeju, J.; Wurz, N.; Engle, K. M.; Pidgeon, G. W.; Moore, P. R.; Sandford, G.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 9796. (e) Pereira, R.; Wolstenhulme, J.; Sandford, G.; Claridge, T. D.; Gouverneur, V.; Cvengros, J. *Chem. Commun.* **2016**, *52*, 1606.

(14) (a) Rozen, S. *Chem. Rev.* **1996**, *96*, 1717. (b) Rozen, S. *Acc. Chem. Res.* **2005**, *38*, 803.

(15) (a) Gilicinski, A. G.; Pez, G. P.; Syvret, R. G.; Lal, G. S. *J. Fluorine Chem.* **1992**, *59*, 157. (b) Differding, E.; Bersier, P. M. *Tetrahedron* **1992**, *48*, 1595. (c) Andrieux, C. P.; Differding, E.; Robert, M.; Saveant, J. M. *J. Am. Chem. Soc.* **1993**, *115*, 6592. (d) Girina, G. P.; Fainzil'berg, A. A.; Feoktistov, L. G. *Russ. J. Electrochem.* **2000**, *36*, 162. (e) Oliver, E. W.; Evans, D. H. *J. Electroanal. Chem.* **1999**, *474*, 1. (f) Fainzil'berg, A. A.; Faustov, V. I. *Russ. J. Org. Chem.* **2001**, *37*, 755. (g) Toullec, P. Y.; Devillers, I.; Frantz, R.; Togni, A. *Helv. Chim. Acta* **2004**, *87*, 2706.

(16) Christe, K. O.; Dixon, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 2978.

(17) Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Soc., Chem. Commun.* **1992**, 595.

(18) (a) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157. (b) Zhao, Y.; Truhlar, D. G. *Chem. Phys. Lett.* **2011**, *502*, 1.

(19) Grant, D. J.; Wang, T.-H.; Vasiliu, M.; Dixon, D. A.; Christe, K. O. *Inorg. Chem.* **2011**, *50*, 1914.

(20) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785.

(21) Xu, X.; Goddard, W. A. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 2673.

(22) Boese, A. D.; Martin, J. M. L. *J. Chem. Phys.* **2004**, *121*, 3405.

(23) Chai, J. D.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615.

(24) Schwabe, T.; Grimme, S. *Phys. Chem. Chem. Phys.* **2007**, *9*, 3397.

(25) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(26) (a) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378. For selected recent examples using the SMD model, see: (b) Yang, Y. F.; Cheng, G. J.; Liu, P.; Leow, D.; Sun, T. Y.; Chen, P.; Zhang, X. H.; Yu, J. Q.; Wu, Y. D.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 344. (c) Xue, X.-S.; Wang, Y.; Yang, C.; Ji, P.; Cheng, J.-P. *J. Org. Chem.* **2015**, *80*, 8997. (d) Xu, X.; Zheng, J.; Truhlar, D. G. *J. Am. Chem. Soc.* **2015**, *137*, 8026. (e) Zhang, L.; Wang, Y.; Yao, Z. J.; Wang, S.; Yu, Z. X. *J. Am. Chem. Soc.* **2015**, *137*, 13290.

(27) In highly polar acetonitrile solution, geometry optimizations for all species were directly conducted in solution.

(28) It should be pointed out that cationic fluorine has only been observed spectroscopically in the gas phase; there is no evidence supporting the existence of the fluoronium ion in solution.

(29) Legault, C. Y. CYLview, 1.0b; Université de Sherbrooke: Sherbrooke, 2009; http://www.cylview.org.

(30) Frisch, M. J.; et al. *Gaussian 09, revision B.01*; Gaussian, Inc.: Wallingford, CT, 2009.

(31) Olah, G. A.; Hartz, N.; Rasul, G.; Wang, Q.; Prakash, G. K. S.; Casanova, J.; Christe, K. O. *J. Am. Chem. Soc.* **1994**, *116*, 5671.

(32) Satyamurthy, N.; Bida, G. T.; Phelps, M. E.; Barrio, J. R. *J. Org. Chem.* **1990**, *55*, 3373.

(33) (a) Zhang, Y.; Yang, X. J.; Xie, T.; Chen, G. L.; Zhu, W. H.; Zhang, X. Q.; Yang, X. Y.; Wu, X. Y.; He, X. P.; He, H. M. *Tetrahedron* **2013**, *69*, 4933. (b) Chen, G.; Chen, F.; Zhang, Y.; Yang, X.; Yuan, X.; Wu, F.; Yang, X. *J. Fluorine Chem.* **2012**, *133*, 155. (c) Wang, F. J.; Li, J.; Hu, Q. Y.; Yang, X. J.; Wu, X. Y.; He, H. M. *Eur. J. Org. Chem.* **2014**, *2014*, 3607.

(34) (a) Davis, F. A.; Han, W. *Tetrahedron Lett.* **1991**, *32*, 1631. (b) Davis, F. A.; Han, W.; Murphy, C. K. *J. Org. Chem.* **1995**, *60*, 4730.

(35) Bohlmann, R. DE 4313664 1994.

(36) For selected reviews on C−H···O interactions, see: (a) Takahashi, O.; Kohno, Y.; Nishio, M. *Chem. Rev.* **2010**, *110*, 6049. (b) Johnston, R. C.; Cheong, P. H.-Y. *Org. Biomol. Chem.* **2013**, *11*, 5057. For examples, see: (c) Yang, H.; Wong, M. W. *J. Am. Chem. Soc.* **2013**, *135*, 5808. (d) Xue, X. S.; Li, X.; Yu, A.; Yang, C.; Song, C.; Cheng, J. P. *J. Am. Chem. Soc.* **2013**, *135*, 7462.

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

(38) Barnette, W. E. *J. Am. Chem. Soc.* **1984**, *106*, 452.

(39) Banks, R. E.; Khazaei, A. *J. Fluorine Chem.* **1990**, *46*, 297.

(40) (a) Davis, F. A.; Zhou, P.; Murphy, C. K. *Tetrahedron Lett.* **1993**, *34*, 3971. (b) Davis, F. A.; Zhou, P.; Murphy, C. K.; Sundarababu, G.; Qi, H.; Han, W.; Przeslawski, R. M.; Chen, B.-C.; Carroll, P. J. *J. Org. Chem.* **1998**, *63*, 2273.

(41) Takeuchi, Y.; Satoh, A.; Suzuki, T.; Kameda, A.; Dohrin, M.; Satoh, T.; Koizumi, T.; Kirk, K. L. *Chem. Pharm. Bull.* **1997**, *45*, 1085.

(42) Takeuchi, Y.; Suzuki, T.; Satoh, A.; Shiragami, T.; Shibata, N. *J. Org. Chem.* **1999**, *64*, 5708.

(43) (a) Takeuchi, Y.; Liu, Z.; Satoh, A.; Shiragami, T.; Shibata, N. *Chem. Pharm. Bull.* **1999**, *47*, 1730. (b) Shibata, N.; Liu, Z.; Takeuchi, Y. *Chem. Pharm. Bull.* **2000**, *48*, 1954.

(44) Takeuchi, Y.; Liu, Z.; Suzuki, E.; Shibata, N.; Kirk, K. L. *J. Fluorine Chem.* **1999**, *97*, 65.

(45) Liu, Z.; Shibata, N.; Takeuchi, Y. *J. Org. Chem.* **2000**, *65*, 7583.

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

(47) Banks, R. E.; Besheesh, M. K.; Tsiliopoulos, E. *J. Fluorine Chem.* **1996**, *78*, 39.

(48) Cabrera, I.; Appel, W. K. *Tetrahedron* **1995**, *51*, 10205.

(49) Yagupol'skii, Y. L.; Savina, T. I. *Zh. Org. Khim.* **1981**, *17*, 1330.

(50) Yang, Y.; Su, C.; Huang, X.; Liu, Q. *Tetrahedron Lett.* **2009**, *50*, 5754.

(51) (a) Banks, R. E.; Williamson, G. E. *Chem. Ind.(London)* **1964**, 1864. (b) Banks, R. E.; Murtagh, V.; Tsiliopoulos, E. *J. Fluorine Chem.* **1991**, *52*, 389.

(52) Banks, R. E.; Besheesh, M. K.; Lawrence, N. J.; Tovell, D. J. *J. Fluorine Chem.* **1999**, *97*, 79.

(53) Laali, K. K.; Tanaka, M.; Forohar, F.; Cheng, M.; Fetzer, J. C. *J. Fluorine Chem.* **1998**, *91*, 185.

(54) (a) Umemoto, T.; Tomizawa, G. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3625. (b) Umemoto, T.; Tomita, K. *J. Fluorine Chem.* **1987**, *35*, 14. (c) Umemoto, T.; Harasawa, K.; Tomizawa, G.; Kawada, K.; Tomita, K. *J. Fluorine Chem.* **1991**, *53*, 369.

(55) (a) Banks, R. E.; Besheesh, M. K.; Fraenk, W.; Klapötke, T. M. *J. Fluorine Chem.* **2003**, *124*, 229. (b) Schleyer, P. v. R.; Buzek, P.; Klapoetke, T. M.; Tornieporth-Oetting, I. C.; Broschag, M.; Pickardt, J. *Inorg. Chem.* **1993**, *32*, 1523. (c) Broschag, M.; Klapötke, T. M.; Tornieporth-Oetting, I. C. *Inorg. Chim. Acta* **1993**, *205*, 167.

DOI: 10.1021/acs.joc.6b00683
J. Org. Chem. 2016, 81, 4280−4289

(d) Broschag, M.; Klapötke, T. M.; Schulz, A.; Tornieporth-Oetting, I. C.; Umbach, P.; White, P. S. *Z. Anorg. Allg. Chem.* **1994**, *620*, 1132. (e) Schulz, A.; Klapötke, T. M. *J. Organomet. Chem.* **1994**, *480*, 195. (f) Fraenk, W.; Klapötke, T. M.; Banks, E.; Besheesh, M. K. *J. Fluorine Chem.* **2001**, *108*, 87.
(56) Stavber, S.; Zupan, M.; Poss, A. J.; Shia, G. A. *Tetrahedron Lett.* **1995**, *36*, 6769.
(57) (a) Banks, R. E.; Besheesh, M. K. *J. Fluorine Chem.* **1995**, *74*, 165. (b) Umemoto, T.; Nagayoshi, M. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2287.
(58) Shunatona, H. P.; Frueh, N.; Wang, Y.-M.; Rauniyar, V.; Toste, F. D. *Angew. Chem., Int. Ed.* **2013**, *52*, 7724.
(59) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
(60) (a) Banks, R. E.; Du Boisson, R. A.; Tsiliopoulos, E. *J. Fluorine Chem.* **1986**, *32*, 461. (b) Banks, R. E.; Du Boisson, R. A.; Morton, W. D.; Tsiliopoulos, E. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2805. (c) Banks, R. E.; Sharif, I. *J. Fluorine Chem.* **1988**, *41*, 297.
(61) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001.
(62) Internet Bond-Energy Databank Home Page. http://ibond.nankai.edu.cn or http://ibond.chem.tsinghua.edu.cn (accessed Nov 14, 2015).
(63) For computational and experimental studies on N−H pK_a values, see: (a) Fu, Y.; Liu, L.; Li, R.-Q.; Liu, R.; Guo, Q.-X. *J. Am. Chem. Soc.* **2004**, *126*, 814. (b) Li, J. N.; Fu, Y.; Liu, L.; Guo, Q. X. *Tetrahedron* **2006**, *62*, 11801. (c) Leito, I.; Raamat, E.; Kutt, A.; Saame, J.; Kipper, K.; Koppel, I. A.; Koppel, I.; Zhang, M.; Mishima, M.; Yagupolskii, L. M.; Garlyauskayte, R. Y.; Filatov, A. A. *J. Phys. Chem. A* **2009**, *113*, 8421. (d) Kutt, A.; Rodima, T.; Saame, J.; Raamat, E.; Maemets, V.; Kaljurand, I.; Koppel, I. A.; Garlyauskayte, R. Y.; Yagupolskii, Y. L.; Yagupolskii, L. M.; Bernhardt, E.; Willner, H.; Leito, I. *J. Org. Chem.* **2011**, *76*, 391. (e) Kaljurand, I.; Lilleorg, R.; Murumaa, A.; Mishima, M.; Burk, P.; Koppel, I.; Koppel, I. A.; Leito, I. *J. Phys. Org. Chem.* **2013**, *26*, 171. (f) Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. *Angew. Chem., Int. Ed.* **2013**, *52*, 11569. (g) Ni, X.; Li, X.; Wang, Z.; Cheng, J.-P. *Org. Lett.* **2014**, *16*, 1786. (h) Kögel, J. F.; Linder, T.; Schröder, F. G.; Sundermeyer, J.; Goll, S. K.; Himmel, D.; Krossing, I.; Kütt, K.; Saame, J.; Leito, I. *Chem. - Eur. J.* **2015**, *21*, 5769. (i) Li, Z.; Li, X.; Ni, X.; Cheng, J.-P. *Org. Lett.* **2015**, *17*, 1196. (j) Ni, X.; Li, X.; Cheng, J.-P. *Org. Chem. Front.* **2016**, *3*, 170. (k) Yang, C.; Xue, X. S.; Li, X.; Cheng, J. P. *J. Org. Chem.* **2014**, *79*, 4340.
(64) It should be pointed out that, like the cases for (trifluoromethyl) thio cation-donating ability (Tt^+DA),[64a] trifluoromethyl cation-donating ability (TC^+DA),[64b] and halenium affinity (HalA)[64c] scales that recently appeared, the FPD parameter describes a thermodynamic property of the reagent and may be well applied under thermodynamically controlled conditions. (a) Li, M.; Guo, J.; Xue, X.-S.; Cheng, J.-P. *Org. Lett.* **2016**, *18*, 264. (b) Li, M.; Xue, X.-S.; Guo, J.; Wang, Y.; Cheng, J.-P. *J. Org. Chem.* **2016**, *81*, 3119. (c) Ashtekar, K. D.; Marzijarani, N. S.; Jaganathan, A.; Holmes, D.; Jackson, J. E.; Borhan, B. *J. Am. Chem. Soc.* **2014**, *136*, 13355.
(65) (a) Shibata, N.; Ishimaru, T.; Suzuki, E.; Kirk, K. L. *J. Org. Chem.* **2003**, *68*, 2494. (b) Fukuzumi, T.; Shibata, N.; Sugiura, M.; Nakamura, S.; Toru, T. *J. Fluorine Chem.* **2006**, *127*, 548. (c) Lam, Y.-H.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 9556.
(66) Baudequin, C.; Loubassou, J.-F.; Plaquevent, J.-C.; Cahard, D. *J. Fluorine Chem.* **2003**, *122*, 189.

DOI: 10.1021/acs.joc.6b00683
J. Org. Chem. 2016, 81, 4280−4289