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The role of F–N reagent and reaction conditions on fluoro functionalisation of substituted phenols

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Abstract—The effect of steric interactions on the regioselectivity of fluorination of *para* alkyl substituted phenols was investigated and the strong effect of size of the alkyl substituent, the structure of the F–N reagent and the solvent on the site of fluorination was established. The course of reaction obeyed a second order rate equation, while the fluorination process required higher $\Delta H^{\neq}$ activation than oxidation or oxidative demethylation. Solvent polarity variations had a small effect on the rate of functionalisation, while an excellent Hammett correlation with $\rho^{+} = -2.3$ was determined.

1. Introduction

Hydroxy substituted aromatic molecules are important compounds in the chemistry of life and consequently in health chemistry, today being very popular as antioxidising, anticarcinogenic molecules, etc.[1] These molecules bear at least one hydroxy group, but the second and third substituents play important roles in their chemical reactivity. Usually at least one alkoxy group is present while the third substituent modulates the electron density of the aromatic ring. They can be classified into one of three major classes: *class A*, the most electron-rich molecules with at least one additional hydroxy or alkoxy group, preferably *para* to the hydroxyl group, have a very low oxidising potential and are very strong radical inhibitors. In *class B*, the molecule bears an sp^3 hybridized carbon atom in the *para* position, while in *class C* an sp^2 carbon atom is present at the *para* position. On the other hand, the important role of the alkoxy group (usually methoxy in the position *ortho* to the hydroxyl group) has been shown in modulation of the biological activity of various types of phenols, connected with the possibility of hydrogen bond formation between the methoxy and hydroxy groups and consequently in the geometry of the molecule and its hydrogen atom donation properties.

The fluorine atom has several times been used as a convenient substituent or modulator in the field of bioactive molecules[2] and is also very effective in the bioisosterism strategy.[3] The mild and selective introduction of a fluorine atom into organic molecules has been a specialised field of investigation in the last three decades, and various types of reagents were developed. Hydroxy substituted benzene derivatives have been used as model substrates in fluorination studies on several occasions,[4] but the effectiveness of preparation of fluoro substituted molecules also varies with the other substituents present. The course of fluorination is greatly dependent on the strong oxidation capacity of this family of reagents. In the field of mild fluorination, studies have been mainly connected with the effect of the structure of the F–L reagent[4] on the type of transformation of the organic molecule, its regioselectivity, the effect of solvent, inhibitors, etc.

Valuable information about the mechanism involved that could be provided from kinetic data (rate of reaction, activation parameters, Hammett correlations, etc.) are rare, due to the high reactivity and high sensitivity of F–L reagents (CF_3OF, CF_3COOF, $CsSO_4F$, XeF_2) to the reaction conditions (small amounts of HF, presence of water, solvent polarity, reaction of the solvent with the reagent, etc.). This type of investigation is possible with the class of F–N reagents,[5] as they are quite reactive, stable, non-explosive and selective in their fluorination of organic molecules. We have already demonstrated that the reactions of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™ F-TEDA-BF_4), a representative of the F–N class of reagent, could be easily monitored by iodometric titration.[6] F–N reagents have been

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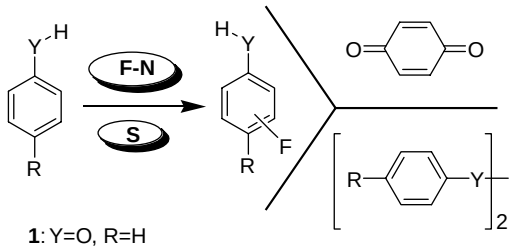
used for fluorination of aromatic molecules; however, the type of functionalisation strongly depends on the structure of the F–N reagent, the functional groups attached to the aromatic molecule and the reaction conditions (solvent e.g., acetonitrile, methanol, water, trifluoroacetic acid; catalyst and reaction temperature). The types of ring transformations observed include ring substitution, *ipso* substitution, the addition process and oxidation.[4–11]

In order to obtain further information about the course of functionalisation of aromatic molecules with the F–N type of reagents, we decided to study the effect of substituents and solvent polarity on mild functionalisation of substituted phenols with Selectfluor™ F-TEDA-BF_4, Accufluor™ NFTh (1-hydroxy-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate)) and FP-B800 (*N*-fluoro-2,6-dichloropyridinium tetrafluoroborate). Because of the importance of the substituent on the phenol in the *para* position on the course of the functionalisation with F–N reagents, we studied the effect of the alkyl group in the context of steric interactions on the one hand and leaving group properties on the other (Scheme 1).

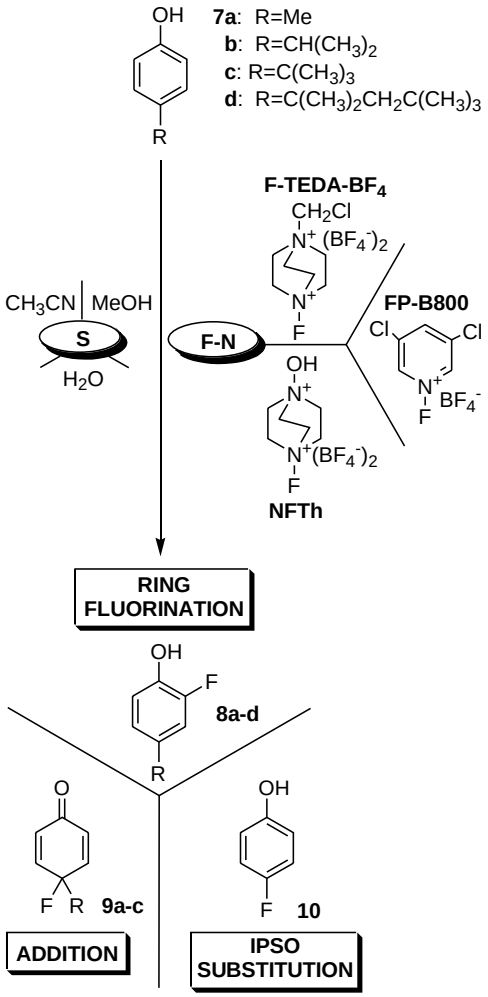


1: Y=O, R=H
2: Y=O, R=OH
3: Y=O, R=OCH_3
4: Y=O, R=$COOCH_3$
5: Y=O, R=CN
6: Y=S, R=H

Scheme 1.

2. Results and discussion

We started by investigating the effect of the bulk substituent, the structure of the reagent and the solvent on the course of functionalisation of *para* substituted phenols (Scheme 2); the effect of these three parameters is presented in Table 1. Fluorination with F-TEDA-BF_4 in acetonitrile at reflux temperature resulted in three types of product: 2-fluoro-4-alkyl-phenoles (**8**) as a result of *ortho* fluorination, 4-alkyl-4-fluoro-cyclohexa-2,5-di-enone addition products (**9**) and *ipso* substituted 4-fluoro-phenol (**10**). The alkyl substituent has an important effect on the reaction path, bulky alkyl substituents increasing *ortho* fluorination (Me: 34%, *i*Pr: 40%, *t*Bu: 60%, *t*Oct(1,1,3,3-tetramethyl-butyl): 88%) and reducing *para* attack. The structure of the alkyl group (tertiary, secondary, primary carbon atom) also has an important role in the competition between two types of functionalisation at the *para* position and is graphically presented in Figure 1.



Scheme 2.

Table 1. Effect of the structure of 4-substituted phenols, fluorination agents and solvents on reaction channels in fluoro functionalisation[a]

R subst.	Reagent	Product distribution **8**:**9**:**10** (yield (%)) in[b]	
		MeCN	MeOH
Me (**7a**)	F-TEDA-BF_4	34:66:0 (55)	100:0:0 (52)
	NFTh	41:59:0 (53)	100:0:0 (60)
	FP-B800	(<5)	
*i*Pr (**7b**)	F-TEDA-BF_4	40:60:0 (78)	62:38:0 (84)
	NFTh	47:52:0 (87)	67:33:0 (88)
	FP-B800	100:0:0 (22)	
*t*Bu (**7c**)	F-TEDA-BF_4	60:0:40 (84)	81:0:19 (83)
	NFTh	61:0:39 (92)	90:0:10 (91)
	FP-B800	63:0:36 (43)	
*t*Oct (**7d**)	F-TEDA-BF_4	88:0:12 (55)	88:0:12 (60)

[a] Reaction conditions: substrate (1 mmol), fluorinating reagent (1 mmol), solvent (10 mL), reflux temperature, 2 h.
[b] Relative distribution in percentage determined from ^{19}F NMR spectra of isolated reaction mixtures; total yield of fluorinated products was determined from ^{19}F NMR spectra of isolated reaction mixtures using octafluoronaphthalene as internal standard.

In fluoro functionalisation the regioselectivity and type of transformation were found to be dependent on both the solvent and the substituent. Methanol in comparison to acetonitrile completely changed the regioselectivity in the case of 4-methyl phenol (**7a**) where exclusive *ortho*

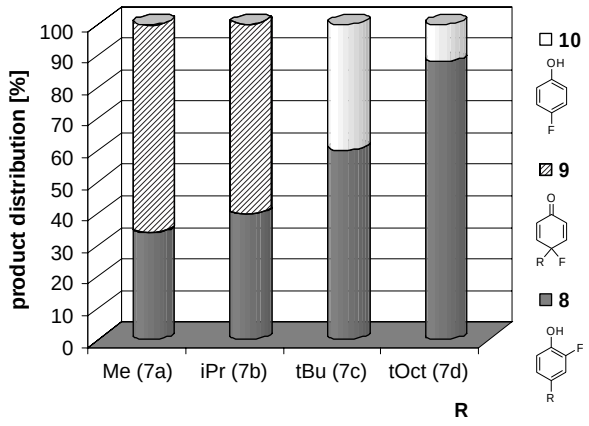


Figure 1. Effect of the alkyl substituent on reaction channels in fluorination of 4-alkyl phenols (**7a–d**) with F-TEDA-BF_4 in acetonitrile. Relative distribution in % determined from ^{19}F NMR spectra of isolated reaction mixtures. Reaction conditions: substrate (1 mmol), F-TEDA-BF_4 (1 mmol), acetonitrile (10 mL), 2 h.

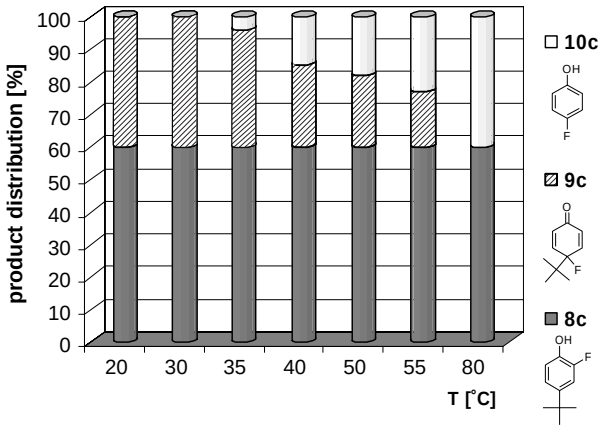
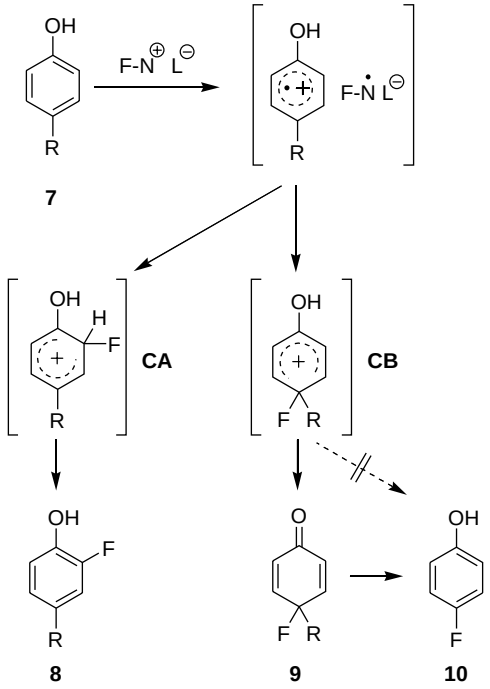


Figure 2. Effect of temperature on competition between the electrophilic substitution process, *ipso* substitution and addition functionalisation of 4-*tert*-butyl phenol (**7c**) with NFTh in acetonitrile. Relative distribution in percentage determined from ^{19}F NMR spectra of isolated reaction mixtures. Reaction conditions: substrate (1 mmol), fluorinating reagent (1 mmol), solvent (10 mL), 2–24 h (2 h for at 80 °C, 8 h at 50 and 55 °C, 24 h at 20, 30 and 35 °C).

fluorination was observed, but the effect was less pronounced with other phenols (Table 1).

Further, we investigated the effect of reagent structure on the course of functionalisation of phenols and found that the structurally similar NFTh is a comparable reagent but with higher *ortho* regioselectivity, as evident from Table 1. The pyridinium fluorinating reagent proved to be much less reactive; conversions achieved after 2 h reflux were also dependent on the substituent (5, 22, 43% for **7a**, **7b**, **7c**, respectively) with similar selectivity to F-TEDA-BF_4 and NFTh in the case of *tert*-butyl derivative **7c**, but exclusive *ortho* fluorination with *iso*-propyl derivative **7b**. As evident from Table 1 the alkyl group not only has an effect on the regioselectivity, but also on the further transformation of the intermediate formed after *para* attack. In the case of the methyl group, the hydroxyl group lost a proton and the dienone derivative **9a** was formed exclusively, but in the case of the *tert*-butyl derivative the alkyl group left the molecule giving 4-fluoro phenol (**10**). This reaction channel could be explained by the stability of the *tert*-butyl cation as a leaving group from the intermediate formed after *para* attack, or by the instability of 4-*tert*-butyl-4-fluoro-cyclohexa-2,5-dienone. To clarify the reaction pathways yielding addition or *ipso* substitution products at the *para* position, we studied the effect of temperature on fluorination of 4-*tert*-butyl phenol (**7c**) with NFTh in acetonitrile and found that the product distribution was significantly dependent on the temperature used. As evident from Figure 2, at room temperature 60% of *ortho* attack was accompanied by 40% of the addition process, yielding cyclohexadienone product **9c**.

At higher temperature (80 °C) the regioselectivity was unchanged, the amount of *ortho* attack remaining unchanged, while the cyclohexadienone product is no longer found and 40% of 4-fluoro phenol (**10**) was formed with comparably high conversions in all experiments (85–95%). Further, we studied the stability of 4-*tert*-butyl-4-fluoro-cyclohexa-2,5-dienone (**9c**) in acetonitrile or methanol under reflux and after 2 h no conversion to **10** was observed. On the other hand, when the reaction mixture obtained after fluorination of **7c** at room temperature (60% **8c**, 40% **9c**) was heated for another hour at 80 °C, the dienone product **9c** was completely converted to 4-fluorophenol (**10**). This conversion was also independently confirmed recently.[12] These experiments indicate that 4-fluorophenol (**10**) was probably formed from cyclohexadienone derivative **9** under the given reaction conditions and not by the *ipso* substitution process from the precursor carbonium ion (**CB**, Scheme 3).



Scheme 3.

In continuation, we investigated the kinetics of the reaction of phenol (**1**) with F-TEDA-BF_4 in water and acetonitrile, monitoring the process of transformation by iodometric titration and found that the rates of fluorination obey the

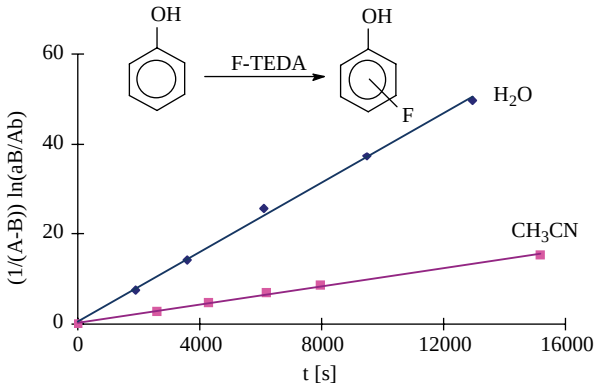


Figure 3. Effect of solvent on the reaction of phenol (**1**) with F-TEDA-BF_4 at 40 °C.

simple rate equation (Fig. 3):

$$v = \mathrm{d[F{-}N]}/\mathrm{d}t = k_2[\mathrm{F{-}N}][Y\text{-}C_3H_4\text{–}OH]$$

Table 2. Effect of solvent and reaction temperature on the second order rate constants for the functionalisation of phenol (**1**), *p*-hydroquinone (**2**), *p*-methoxyphenol (**3**), 4-methylphenol (**7a**), 4-*iso*-propylphenol (**7b**), 3-methyl-4-*iso*-propylphenol (**11a**) and 3,4,5-trimethylphenol (**11b**) with F-TEDA-BF_4

Subst.	Solvent	T (°C)	k_2 (10^{-3} M^{-1} s^{-1})[a]	$\Delta H^{\neq}$ (kJ/mol)	$\Delta S^{\neq}$ (J/mol K)
1		35	2.3		
	H_2O	40	3.9	83±1	−27±1
		45	6.5		
		35	0.63		
	MeCN	40	1.0	80±3	−49±3
		45	1.7		
2		7	21		
	H_2O	12	36	59±3	−68±8
		17	51		
		7	11		
	MeCN	12	19	68±4	−39±4
		17	30		
3		17	38		
	H_2O	22	54	58±3	−74±5
		26	81		
		19	22		
	MeCN	22	36	60±7	−70±12
		25	41		
	MeOH/	19	75		
	H_2O	22	102	73±4	−18±1
	9:1	26	137		
7a		35	4.8		
	MeCN	40	8.7	86±2	−10±0.4
		46	14		
7b		35	5.1		
	MeCN	40	8.6	85±2	−14±0.5
		46	15		
11a		15	7.9		
	MeCN	20	15	76±2	−21±0.4
		25	24		
11b		0	22		
	MeCN	2	28	70±2	−17±0.5
		5	50		

[a] An average from at least three measurements with no more than 3% relative error.

As evident from Table 2, reaction was faster in water than in acetonitrile. Oxidation of *p*-hydroquinone (**2**) with F-TEDA-BF_4 to *p*-quinone[8] also obeyed a second order rate equation, but the process was much faster than fluorination of the aromatic ring in **1** and the effect of solvent polarity less pronounced than in the fluorination process ($k_2^{\text{water}}/k_2^{\text{acetonitrile}}=1.9$ for oxidation and 3.6 for fluorination). The reactivity of the *p*-methoxy derivative (**3**), which is also converted to *p*-quinone,[8] lay in between that of hydroquinone and phenol and the effect of solvent polarity on the oxidation–demethylation process was less pronounced than in the case of the above mentioned processes (Table 2) ($k_2^{\text{water}}/k_2^{\text{acetonitrile}}=1.5$). However, transformation in methanol–water mixture (9/1) was almost twice as fast than in water alone. Introduction of a methyl group at the *para* position enhanced functionalisation in acetonitrile by a factor of 7.6 while no substantial increase was observed when the methyl group is replaced by *iso*-propyl (Table 2). A further increase in reactivity was achieved when one or two additional alkyl groups were introduced into the aromatic ring, that is, 3-methyl-4-*iso*-propylphenol (**11a**) or 3,4,5-trimethylphenol (**11b**).

Important information about the course of functionalisation of aromatic molecules with the F–N type of reagents could be obtained from the activation parameters, but up to now no such data were available for this kind of reagent. We therefore investigated the activation parameters for all three types of transformations on the phenyl ring and also studied the effect of solvent. It is evident that the highest activation enthalpy is required for fluorination, while for oxidation and oxidative demethylation almost the same $\Delta H^{\neq}$ was established, the activation enthalpy increasing in methanol–water solution for the transformation of **3**. As also evident from Table 2, differences in activation entropies that were observed in both the type of functionalisation and in the effect of solvent on the geometry of the process are important. In the fluorination process, a decrease of solvent polarity was reflected in a lowering of activation entropy, while the opposite effect was observed in oxidation (−68± 8 J/mol K for water and −39±4 J/mol K for acetonitrile). The most interesting case is the oxidation–demethylation process where differences between water and acetonitrile were not so pronounced, but the transition state in the presence of methanol must be much less ordered than in the case of water. Introduction of a methyl group in phenyl ring increased the activation enthalpy of fluoro functionalisation in acetonitrile and caused significant changes in activation entropies (−49 J/mol K for **1**, −10 for **7a**; Table 2). Further introduction of alkyl groups (**11a**, **11b**) decreased activation enthalpies and changed activation entropies.

Important information about the nature of the intermediate in the functionalisation of the aromatic molecule could be obtained by using solvents with various dielectric constants or by using mixtures of solvents for which the Grunwald–Winstein *Y* values have already been determined;[13] very large variations were observed for acetonitrile–water solutions.[14] Unfortunately, reactions with F–N type of reagents are solvent dependent, where small changes could completely halt the process or alter its course. Functionalisation of substituted phenols with F-TEDA-BF_4 proceeded very well in acetonitrile or water, and fortunately

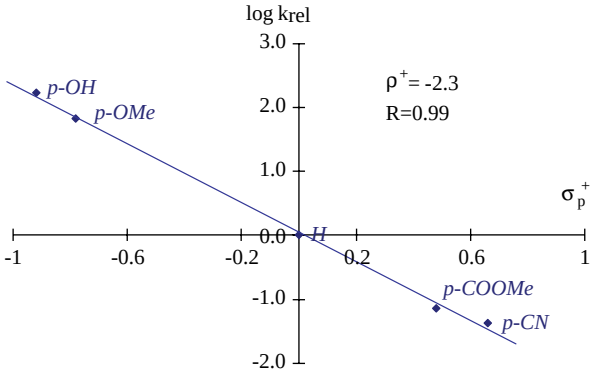
Table 3. Effect of solvent polarity (Y_{benzyl}) on the second order rate constants for the reactions of phenol (**1**), *p*-hydroquinone (**2**), *p*-methoxyphenol (**3**) and 3-methyl-4-*iso*-propyphenol (**11a**) with F-TEDA-BF_4 in acetonitrile–water solutions[a]

Solvent[b]	Y_{benzyl}[c]	k_2 (10^{-3} M^{-1} s^{-1})			
		1	**2**	**3**	**11a**
90An	−1.45	1.8	63	40	29
80An	−0.35	1.5	51	29	20
60An	0.81	1.3	42	19	15
40An	1.74	1.7	38	23	
20An	2.72	2.8	43	35	

[a] Reactions at 40 °C for **1**, at 17 °C for **2**, at 22 °C for **3** and at 25 °C for **11a**.
[b] % v/v of acetonitrile in water solution.
[c] Values from Ref. 14.

acetonitrile–water mixtures have a very large range of *Y* values.[14] However, as evident from Table 3, variation of *Y* in the range of 4.17 units had only a small effect on second order rate processes for functionalisation of phenol (**1**), *p*-hydroquinone (2), *p*-methoxyphenol (**3**) and 3-methyl-4-*iso*-propylphenol (**11a**). The small effect of solvent polarity on the second order rate constants indicated a small change in the polarity of the rate determining transition state in comparison to the reactants.

Hammett correlations have several times been used in investigating the effect of substituents on the transformation of aromatic molecules.[15] A very good kinetic correlation with σ_p^+ has been demonstrated in the reactions of *para* substituted phenols with peroxynitrite ($ONOO^-$), in spite of the fact that functionalisation (nitration or hydroxylation) occurred at the position meta to the substituent.[16] We undertook a similar investigation, although reactions with phenols bearing electron withdrawing groups give complex reaction mixtures, fluoro substituted products not being the major ones, while in the case of a hydroxyl substituent, a high yield oxidation process took place and oxidation followed by demethoxylation giving *p*-quinone was observed with *p*-methoxyphenol (**3**).



Y	σ_p^+	k_2 [$M^{-1}s^{-1}$]	log $k_{rel.}$
p-OH (**2**)	-0.92	2.8	2.24
p-OMe (**3**)	-0.78	1.1	1.83
H (**1**)	0	1.6×10^{-2}	0.00
p-COOMe (**4**)	0.48	1.2×10^{-3}	-1.14
p-CN (**5**)	0.66	7.1×10^{-4}	-1.36

Figure 4. Hammett correlation plot (log k_{rel}/σ_p^+) for the functionalisation of *para* substituted phenols (**1–5**) with F-TEDA-BF_4 at 70 °C in acetonitrile.

As evident from Figure 4 an excellent correlation with σ_p^+ with a value of $\rho^+ = -2.3$ was established. It is interesting that the correlation was excellent in spite of the fact that different types of phenyl ring functionalisation were involved. The similar behaviour of *para* substituted phenols on functionalisation as in the case of nitration and hydroxylation could be explained by the formation of cation radicals after one electron transfer from the aromatic nucleus to the F–N reagent, while further reactions resulted in various types of product. Formation of cation radicals has also been confirmed by UV and ESR spectroscopy in halogenations with N–X reagents (NBS, NCS, …) of electron-rich aromatic molecules.[17,18] Effective transformation of cation radicals to fluoro substituted products in our case was best achieved when alkyl groups (**7**, **11**) are present at position four.

Two reaction channels resulting after fluorine attack at position 2 or 4 giving fluoro carbonium ions are presented in Scheme 3 (**CA** and **CB**). As evident from an independent experiment, 4-fluorophenol (**10**) was formed from cyclohexadienone derivative **9** at higher temperature as was observed with substrates bearing a substituted tertiary carbon atom (i.e., in the case of the *tert*-butyl derivative **7c**).

3. Conclusion

In summarizing our observations, we can state that steric interactions and reaction conditions strongly influenced the regioselectivity of fluorination of *para* alkyl substituted phenols with F–N reagents. The site of fluorination depended on the size of the substituent, the structure of the F–N reagent and the solvent. In MeCN, the methyl group favoured attack at the *para* position (66%), while bulky alkyl substituents like *t*Bu or the 1,1,3,3-tetramethyl-butyl (*t*Oct) group caused a change of the regioselectivity and *ortho* fluorination (60 and 88%) was found to be dominant. On the other hand, analogous reactions in MeOH resulted in exclusive fluorination of the position two in the case of 4-methylphenol, and predominant fluorofunctionalisation at the same position in the case of other 4-alkyl-substituted phenols. The structure of the alkyl substituents also influenced the type of fluorofunctionalisation, since attack at the *para* position resulted in the addition process thus forming 4-fluoro-4-alkyl-cyclohexa-2,5-dienone derivatives **9**, while the substitution process resulting in formation of 2-fluoro-4-alkylphenol derivatives **8** followed *ortho* attack. Reactions of F-TEDA-BF_4 with phenol derivatives bearing electron withdrawing substituents (**4**, **5**) resulted in complex reaction mixtures, while *p*-hydroquinone (**2**) and *p*-methoxyphenol were transformed to *p*-quinone. Kinetic studies on the transformation of *para* substituted phenols with F-TEDA-BF_4 carried out in water, acetonitrile or water–acetonitrile mixtures at various temperatures established that the course of the reaction obeyed the simple rate equation $v = d[F\text{–}N]/dt = k_2[F\text{–}N][Y\text{-}C_6H_4\text{–}OH]$ for all types of transformations. Higher $\Delta H^{\neq}$ activation was required for the fluorination process ($\Delta H^{\neq}$: 80–83 kJ/mol) than for oxidation ($\Delta H^{\neq}$: 59–68 kJ/mol) or oxidative demethylation ($\Delta H^{\neq}$: 58–73 kJ/mol). A very pronounced effect of solvent polarity on activation entropies was observed in all three types of functionalisation (fluorination,

oxidation, oxidative demethylation), but the effect depended on the type of transformation. In order to obtain more insight into the nature of the rate determining step in transformations of *para* substituted phenols with F-TEDA-BF_4, Grunwald–Winstein correlation analysis carried out and since only a small effect of solvent polarity variation on reaction rates was established we can presume that the polarity of the rate determining state is not so different from the reactants. On the basis of the excellent Hammett correlation plot obtained for reactions of *para* substituted phenols with with F-TEDA-BF_4 ($\rho^+ = -2.3$; $R = 0.99$) we can also anticipate similar nature of the key intermediate of these reactions, although the type of products strongly depended on the substituents.

4. Experimental

Melting points were determined on a Büchi 535 apparatus. ^{1}H NMR spectra were recorded on a Varian EM 360L at 60 MHz or on a Varian INOVA 300 spectrometer at 300 MHz, and ^{13}C NMR spectra on the same instrument at 76 MHz. Chemical shifts are reported in parts per million from TMS as the internal standard. ^{19}F NMR spectra were recorded on a Varian EM 360L at 56.4 MHz and chemical shifts are reported in parts per million from CCl_3F as internal standard. IR spectra were recorded on a Perkin-Elmer 1310 spectrometer. Standard KBr pellet procedures were used to obtain IR spectra of solids, while a film of neat material was used to obtain IR spectra of liquid products. Mass spectra were obtained on an Autospec Q instrument under electron impact (EI) conditions at 70 eV. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN analyzer or obtained from Mikranalytisches Labor Pascher, Germany. 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)[19] (Selectfluor™ F-TEDA-BF_4; Air Products) was crystallised from an acetonitrile–methanol mixture and dried in a vacuum at 20 °C. 1-Fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate) (Accufluor™ NFTh, 50% w/w on Al_2O_3) was received as a gift from Allied Signal and used as obtained. *N*-Fluoro-2,6-dichloropyridinium tetrafluoroborate (FP-B800) was received from Chichibu Onoda Cement Corp., Japan, and also used as obtained. Other starting materials were obtained from commercial sources. Acetonitrile and methanol were purified by distillation and stored over molecular sieves.

4.1. Fluorination of phenols (7) with 'F–N' reagents; general procedure

To a solution of substrate **7** (1 mmol) in 10 mL of solvent (MeCN, MeOH or CH_2Cl_2) 1 mmol of fluorinating agent (F-TEDA-BF_4, NFTh or FP-B800 was added, the reaction mixture stirred at reflux temperature until the fluorinating agent was consumed (KI starch paper). The reaction solvent was removed under reduced pressure, the crude reaction mixture dissolved in 50 mL of dichloromethane, washed with water (20 mL), dried over Na_2SO_4, the solvent evaporated, the reaction mixture analyzed by ^{1}H and ^{19}F NMR spectroscopy and the relative distribution of products was determined. The amount of fluorinated products present in the reaction mixture was determined from ^{19}F NMR spectra using octafluoronaphthalene (OFN) as internal standard. Pure compounds were isolated by column chromatography and identified on the basis of spectroscopic data and elemental combustion analysis or high resolution MS spectroscopy, while in the case of known compounds comparison with literature data was made. Sufficient purity of all compounds was determined by ^{1}H NMR spectroscopy.

4.1.1. 2-Fluoro-4-methyl-phenol (8a).[20] Reaction conditions: F-TEDA-BF_4/MeOH/reflux/2 h: 120 mg crude reaction mixture (contained 65 mg of **8a**, determined by OFN), column chromatography (SiO_2/CH_2Cl_2) gave 43 mg (34%) of oily product.

4.1.2. 2-Fluoro-4-isopropyl-phenol (8b). Reaction conditions: F-TEDA-BF_4/MeOH/reflux/2 h: 135 mg crude reaction mixture (contained 80 mg of **8b**, determined by OFN), column chromatography (SiO_2/$CHCl_3$) gave 65 mg (42%) of brown oily product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, $J=6.9$ Hz, 6H, Me), 2.83 (heptet, $J=6.9$ Hz, 1H, CH), 3.79 (d, $J=2.3$ Hz, 1H, OH), 6.87–6.89 (m, 1H, ArH), 6.90–6.92 (m, 1H, ArH), 6.94–6.95 (m, 1H, ArH); ^{13}C NMR (76 MHz, $CDCl_3$) δ 24.0 (CH_3), 33.3 (CH), 113.3 (d, $J=$ 17.4 Hz, ArCH), 116.9 (d, $J=1.3$ Hz, ArCH), 122.4 (d, $J=$ 2.3 Hz, ArCH), 141.2 (d, $J=14.2$ Hz, ArCOH), 142.0 (d, $J=4.9$ Hz, ArC), 150.9 (d, $J=237.2$ Hz, ArCF); ^{19}F NMR (56.4 MHz, $CDCl_3$) δ −141.0 (m); MS (EI, 70 eV) *m/z* 154 (30, M^+), 139 (100), 109, 91; high resolution MS: *m/z* 154.079503 (calcd for $C_9H_{11}FO$ *m/z* 154.079393).

4.1.3. 2-Fluoro-4-*tert*-butyl-phenol (8c)[8] Reaction conditions: F-TEDA-BF_4/MeOH/reflux/4 h: 141 mg crude reaction mixture (contained 113 mg of **8c**, determined by OFN), column chromatography (SiO_2/$CHCl_3$) gave 75 mg (45%) of oily product.

4.1.4. 2-Fluoro-4-(1,1,3,3-tetramethyl-butyl)-phenol (8d). Reaction conditions: F-TEDA-BF_4/MeOH/reflux/4 h: 177 mg crude reaction mixture (contained 118 mg of **8d**, determined by OFN), column chromatography (SiO_2/CH_2Cl_2) gave 75 mg (33%) of light brown crystalline product, mp 59–60 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (s, 9H, *t*Bu), 1.32 (s, 6H, $2CH_3$), 1.68 (s, 2H, CH_2), 5.12 (s, 1H, OH), 6.90 (m, 1H, ArH), 7.01 (m, 1H, ArH), 7.06 (m, 1H, ArH); ^{13}C NMR (76 MHz, $CDCl_3$) δ 31.6 (CH_3), 31.7 (CH_3), 32.3 (C), 38.1 (C), 56.9 (CH_2), 113.4 (d, $J=18.4$ Hz, ArCH), 116.3 (d, $J=$ 2.1 Hz, ArCH), 122.2 (d, $J=3.0$ Hz, ArCH), 140.7 (d, $J=$ 14.7 Hz, ArCOH), 143.5 (d, $J=4.7$ Hz, ArC), 150.6 (d, $J=$ 235.6 Hz, ArCF); ^{19}F NMR (56.4 MHz, $CDCl_3$) δ −141.6 (m); MS (EI, 70 eV) *m/z* 224 (5, M^+), 153 (100), 57 (35); high resolution MS: *m/z* 224.158320 (calcd for $C_{14}H_{21}FO$ *m/z* 224.157644). Anal. Calcd for $C_{14}H_{21}FO \cdot 1/4H_2O$ C, 73.49; H, 9.47. Found: C, 73.34; H, 9.26.

4.1.5. 4-Fluoro-4-methyl-cyclohexa-2,5-dienone (9a).[21] Reaction conditions: F-TEDA-BF_4/MeCN/reflux/2 h: 102 mg crude reaction mixture (contained 46 mg of **9a**, determined by OFN), column chromatography (SiO_2/CH_2Cl_2) gave 33 mg (26%) of dense oily product.

4.1.6. 4-Fluoro-4-isopropyl-cyclohexa-2,5-dienone (9b).[10] Reaction conditions: F-TEDA-BF_4/MeCN/reflux/2 h: 125 mg crude reaction mixture (contained 72 mg of **9b**,

determined by OFN), column chromatography (SiO_2/CH_2Cl_2) gave 48 mg (31%) of dense oily product.

4.1.7. 4-*tert*-Butyl-4-fluoro-cyclohexa-2,5-dienone (9c).[12] Reaction conditions: NFTh/MeCN/20 °C/24 h: 160 mg crude reaction mixture (contained 59 mg of **9c**, determined by OFN), column chromatography (SiO_2/CH_2Cl_2) gave 49 mg (29%) of yellow crystals, mp 63.1–63.4 °C; ^{1}H NMR (60 MHz, CCl_4) δ 1.1 (d, $J=19$ Hz, 9H), 6.3 (d, $J=13$ Hz, 2H), 7.0 (dd, $J=17$, 13 Hz, 2H); ^{19}F NMR (56.4 MHz, CCl_4) δ −165.3 (m); MS (EI, 70 eV) *m/z* 168 (M^+, 21%), 153 (75), 135 (65), 125 (35), 107 (25), 91 (12), 83 (15), 57 (100); high resolution MS: *m/z* 168.0957 (calcd for $C_{10}H_{13}FO$: 168.0950).

4.1.8. 4-Fluorophenol (10).[22] Reaction conditions: 4-*tert*-butyl-phenol/NFTh/MeCN/reflux/2 h: 170 mg crude reaction mixture (contained 38 mg of **10**, determined by OFN), column chromatography (SiO_2/CH_2Cl_2) gave 25 mg (18%) of crystalline product, mp 46 °C (lit.[22] 43–45 °C).

4.2. Determination of second rate order constants and acti vation parameters for functionalisation of phenol (1), *p*-hydroquinone (2), *p*-methoxyphenol (3), 4-methylphenol (7a), 4-*iso*-propylphenol (7b)3-methyl-4-*iso*-propylphenol (11a) and 3,4,5-trimethylphenol (11b) with F-TEDA-BF_4

To 40 mL of a thermostatted acetonitrile solution of substrate (0.3, 0.6, 0.9, 1.2, 1.8 mmol), 20 mL of a thermostatted solution of F-TEDA-BF_4 (0.66 mmol) was added and stirred at various temperatures. The progress of F-TEDA-BF_4 consumption was monitored by iodometric titration. Second order rate constants were calculated from

$$1/(A-B)\ln(Ba/Ab) = k_2 t \quad (1)$$

and a linear relationship was found. The effect of solvent on second order rate constants for the functionalisation of **1**, **2**, **3**, **7a**, **7b**, **11a** and **11b** with F-TEDA-BF_4 is presented in Table 2 and Figure 3. Rate constants are averages from at least three measurements with no more than 3% relative error. Further we investigated the effect of temperature on k_2; a linear correlation was found and activation parameters were calculated by linear regression from

$$\ln(k_2/T) = \ln(k_B/h) + \Delta S^{\neq}/R - \Delta H^{\neq}/RT \quad (2)$$

Second order rate constants for Hammett correlation studies for the reaction of substrates **4** and **5** with F-TEDA-BF_4 were determined in acetonitrile at 70 °C, while k_2 for substrates **1**, **2** and **3** under the same reaction conditions were calculated from Eq. 2 and the results are presented in Figure 4.

4.3. The effect of solvent polarity on second order rate con stants for functionalisation of phenol (1), *p*-hydroquinone (2), *p*-methoxyphenol (3) and 3-methyl-4-*iso*-propylphenol (11a)

1.2 mmol of substrate was dissolved in 40 mL of various acetonitrile–water mixtures (acetonitrile–water = 34+6; 28+12; 16+24; 10+30; 4+36; 0+40), thermostatted at 40 °C for **1**, 17 °C for **2**, at 22 °C for **3** and at 25 °C for **11a**, 20 mL of a thermostatted acetonitrile solution containing 0.6 mmol F-TEDA-BF_4 was added and stirred. The progress of F-TEDA-BF_4 consumption was monitored by iodometric titration. The results are presented in Table 3.

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