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Remarkable Effect of Water on Functionalization of the Phenyl Ring in Methyl-Substituted Benzene Derivatives with F-TEDA-BF_4

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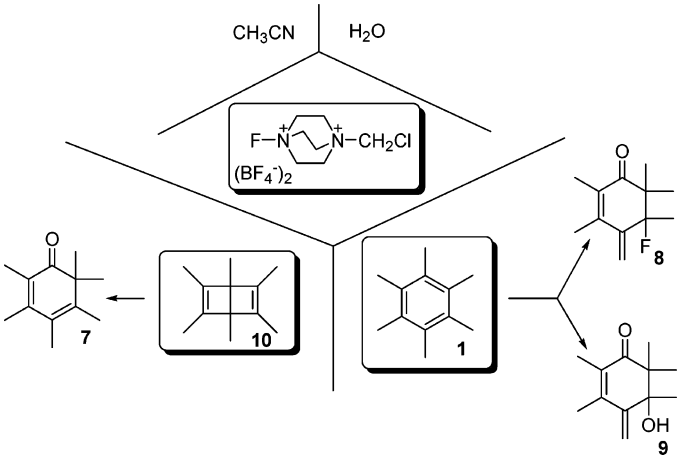

Various N−F reagents reacted with hexamethylbenzene (**1**) forming side chain substituted alkoxides or esters in protic solvents, Ritter type side chain functionalization was observed in acetonitrile in the presence of trifluoroacetic acid, while in aqueous acetonitrile solution phenyl ring transformation took place, starting with ipso attack of water and further rearrangement of the methyl group as the main process. Rearranged 2,3,4,5,6,6-hexamethylcyclohexa-2,4-dienone (**7**) was transformed to 5-fluoro-2,3,5,6,6-pentamethyl-4-methylenecyclohex-2-en-1-one (**8**) or 5-hydroxy-2,3,5,6,6-pentamethyl-4-methylenecyclohex-2-en-1-one (**9**). 1,2,3,4,5,6-Hexamethyl-bicyclo[2.2.0]hexa-2,5-diene reacted with F-TEDA-BF_4 in the presence of water and **7** was formed in high yield. Durene (**12**) followed similar ipso attack of water as **1**, but on the other hand 1,2,3,4-tetramethylbenzene displayed different regioselectivity and 2,3,4,5-tetramethylphenol was formed, further transforming to 4-fluoro-2,3,4,5-tetramethylcyclohexa-2,5-dienone. The functionalizations of methylbenzenes obeyed a second-order rate equation $v = \mathrm{d[N{-}F]/d}t = k_2[\mathrm{N{-}F}][\mathrm{substrate}]$, and $\Delta G^{\#}$ values between 77 and 94 kJ/mol were determined. The presence of water did not significantly influence $\Delta G^{\#}$ but considerably affected $\Delta S^{\#}$ and positive values were found where methyl group migration was the dominant process (9.1 J/(mol K) for **1** and 0.5 J/(mol K) for **12**). A higher reactivity of durene than mesitylene ($k_2^{\mathrm{MES}}/k_2^{\mathrm{DUR}} = 0.23$) was found, supporting the assumption that single electron transfer (SET) is the dominant process in the functionalizations of methyl-substituted benzene derivatives with F-TEDA-BF_4.

Introduction

The demands of recent decades for sustainable and ecologically friendly chemical procedures have put water at the frontier of organic chemistry,[1] and it is no longer surprising to conduct organometallic chemistry[2] or free radical functionalization[3] of organic molecules in aqueous media. The solubility of substrates and reagents in water is of crucial importance for reactions performed in the presence of water, while phase transfer catalysis was developed for systems where one substrate is

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soluble in water and the other completely insoluble. Breslow and co-workers used water in combination with antihydrophobic additives as a mechanistic probe for elucidation of the structure of the transition state.[4] Mayr and co-workers found an important influence of water on the reactivity of organic molecules, enabling alkylation of aromatic molecules with benzyl halides in a water/acetonitrile mixture without the use of a Friedel−Crafts catalyst.[5] Very recently Sharpless and co-workers[6] reported the important observation that some organic molecules can react on the surface of water and often a very strong enhancement of reaction rates was noticed in this case, particularly when at least one compound involved in these reactions bears a polar group, enabling some degree of solubility (carboxylic ether, amine, etc., ...) in water. The authors also suggested that water could be a useful reaction medium for reactions where no acceleration of the rate was observed, especially in cases of exothermic reactions, due to the high heat capacity of water. This concept of organic reactions on water has been recently confirmed by Bose et al. as well.[7]

Water as a reaction medium has not been extensively used in connection with introduction of halogens into organic molecules. However, we recently reported that fluorination[8] with F-TEDA-BF_4 and iodination[9] with the I_2/H_2O_2 tandem could be effectively performed in water with various types of organic compounds.[10] To obtain some further information about the role of water in these functionalizations, we decided to study the reactions of methyl-substituted benzene derivatives which are much more hydrophobic than previously studied substrates. Hexamethylbenzene (HMB) was used several times as a convenient structural probe for elucidation of several organic reactions, because of the fact that various types of transformations strongly depending on the structure of the reagents and the reaction conditions could be observed for this organic molecule. Kochi and co-workers[11] made an important contribution in the understanding of the transformations of alkylbenzene derivatives with electron accepting reagents, while the importance of the formation of a π-complex and its further dual transformation through single electron transfer (SET) to a cation radical or a two-electron transfer to a Wheland σ-intermediate was extensively discussed over the decades.[12−15] On the other hand, tetramethylbenzene derivatives, especially durene (DUR) in relation to trimethyl-substituted benzenes (among them mesitylene, MES), have also been suggested as effective mechanistic probes for differentiation between SET or σ-ion formation, and this was intensively discussed and documented in the literature.[14,15] In general it is expected that SET is the dominant process with DUR since it is more reactive than MES. Less reactive substrates such as MES are expected to proceed by a two-electron transfer with formation of Wheland's σ-intermediate as the rate determining step.

Various fluorinating reagents have been tested on HMB. Side chain fluorinated products were formed by xenon difluoride in dichloromethane solution in the presence of HF[16] or by $CsSO_4F$ in acetonitrile,[17] while trifluoroacetic acid pentamethylphenylmethyl ester[16] was formed by XeF_2 in the presence in TFA as a catalyst. Side chain methoxylation was achieved by methyl hypofluorite (MeOF)[18] and amidation by *N*-fluoropyridinium salts,[19] while side chain amides, alkoxides, or esters were formed by F-TEDA-BF_4.[20] On the other hand, the DUR, MES tandem has often been used as a convenient probe for the elucidation of the role of the structure of reagents (XeF_2,[21] $CsSO_4F$,[22] F-TEDA,[23] *N*-fluoropyridinium salts,[19,24] HOF/MeCN,[18] etc.), solvent (MeCN, ionic liquid, etc.), catalyst, and various external nucleophiles on the course of fluorination and its mechanistic attributes.

Much valuable information about the mechanism of organic reactions can be provided from relevant kinetic data (rate of reactions, activation parameters, ...), but when dealing with fluorination reagents such as CF_3OF, CH_3OF, $CsSO_4F$, XeF_2, CF_3COOF, AcOF, F_2, etc. their high reactivity and high sensitivity to reaction conditions often cause much experimental

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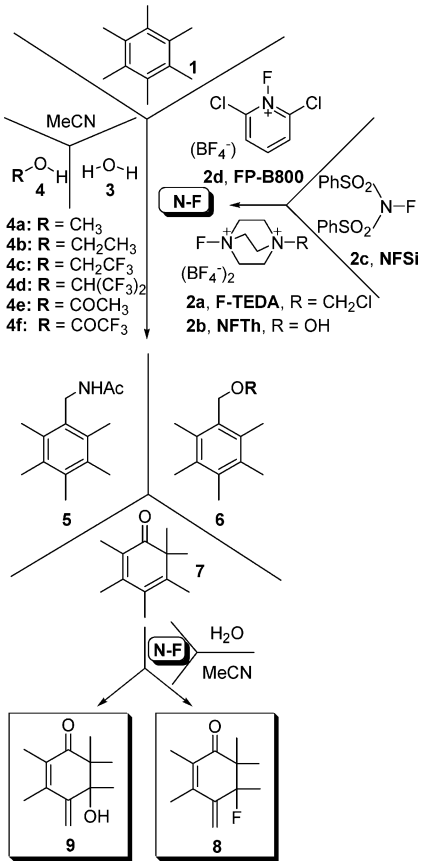
SCHEME 1



inconvenience. As easy handling benchtop materials, usually with optimal stability/reactivity characteristics, N−F reagents[25] enable better conditions for kinetic investigations to be achieved. In our continued interest in the organic chemistry of N−F reagents we now report further investigations of the effect of water, the role of the solvent, and the presence of an external nucleophile on the type of functionalization (Scheme 1) and kinetic parameters of these transformations of HMB, tetramethylbenzenes, and trimethylbenzenes with the most representative members of the N−F group of reagents: 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor F-TEDA-BF_4, **2a**), 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Accufluor NFTh, **2b**), *N*-fluorobenzenesulfonimide (Accufluor NFSi, **2c**), and *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate (FP-B800, **2d**).

Results and Discussion

Because of its stabilizing effect acetonitrile was usually used as a convenient solvent for reactions where the formation of ion-radicals was expected, but the structure of the products formed strongly depended on the stability of the ion-radicals and other nucleophiles present.[26,27] As usual in the case of involvement of cation-radicals, we also observed formation of a complex reaction mixture after reaction of hexamethylbenzene (**1**) with **2a** in acetonitrile at 55 °C, detecting the presence of various monofluoro and difluoro products, and acetamido substituted derivatives, as well as their dimeric or polymeric analogues. HMB thus did not react in water with **2a** or in the presence of a 0.02% surface active compound (SAC, sodium lauryl ether sulfate, Genapol LRO). Further we studied the effects of various protic solvents (Scheme 1) and the presence of an external nucleophile on the course of functionalization of HMB with **2a**. Methyl pentamethylbenzyl ether (**6a**) was isolated in high yield after 1.5 h of reaction at 55 °C in MeOH and similar functionalization was observed with **2a** in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) thus forming ether **6d** (stabilization effect on cation-radicals has been proven several times[28,29]). Side chain functionalization also proceeded well in more acidic solvents, like acetic or trifluoroacetic acid, thus forming acetate (**6e**) or trifluoroacetate (**6f**) as the sole product in excellent yield.

The effect of acetonitrile (10 and 1 mmol of **1**) as a competitive nucleophile in protic media was investigated and the type of functionalization was found to be completely changed. In trifluoroacetic acid (TFA) *N*-pentamethylphenylmethylacetamide (**5**) was formed in excellent yield, while the acetamido derivative was accompanied by acetate (**6**) in acetic acid (**5**:**6e** = 27:73). By changing the reaction conditions so that acetonitrile (10 mL) was used as the solvent and alcohols or water were used as a nucleophile (10 mmol), high yields of side chain substituted alkyl ethers (**6a**−**d**) were obtained in the presence of methanol, ethanol, and 2,2,2-trifluoroethanol, while quite a different course was observed in the presence of water. When an equimolar amount of F-TEDA-BF_4 was used, approximately half of the HMB remain unreacted, while an enhanced amount of fluorinating reagent (**2a**) resulted in complete conversion to a new product in high yield. The product showed a strong band at 1670 cm^{-1} in its IR spectrum indicating the presence of a carbonyl group, had a molar mass 196.1269 indicating the composition $C_{12}H_{17}OF$, and one qd signal at −155.68 ppm in its ^{19}F NMR spectrum, while the disappearance of the aromatic structure was observed from its ^{13}C NMR spectrum. On the basis of the spectroscopic data we established that 5-fluoro-2,3,5,6,6-pentamethyl-4-methylenecyclohex-2-en-1-one (**8**, Scheme 1) was formed. We assumed that the reaction proceeds through the primary formation of 2,3,4,5,6,6-hexamethylcyclohexa-2,4-dienone[30] (**7**), which is further fluorinated to the final product **8**, the second step of the transformation being much faster than the first. Comparison of the reactivities of hexamethylbenzene (**1**), 1,2,3,4,5,6-hexamethylbicyclo[2.2.0]-hexa-2,5-diene (**10**, Scheme 2), and cyclohexadienone derivative (**7**) with F-TEDA-BF_4 revealed that bicyclic diene **10** reacted faster with **2a** in acetonitrile in the presence of water than HMB, and that cyclohexadienone derivative **7** was formed as the sole product, so that the reactivity is in the order **10** > **7** > **1**. The

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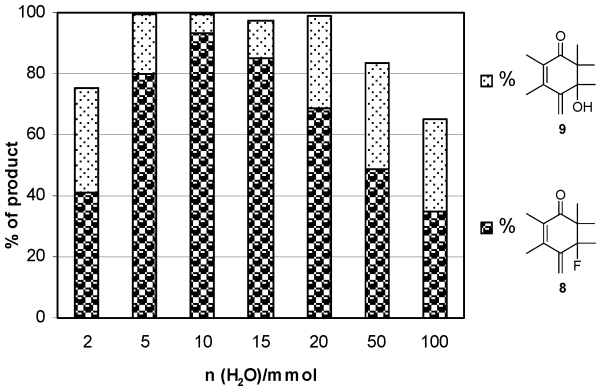
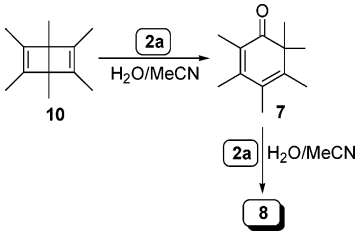


FIGURE 1. Effect of the concentration of water on functionalization of HMB (**1**) with F-TEDA-BF_4 (**2a**). Reagents and conditions: 1 mmol of HMB (**1**), 2 mmol of **2a**, 10 mL of acetonitrile, 2 (5, 10, 15, 20, 50, 100) mmol of water, $T = 55$ °C, reaction time 1.5 h.

SCHEME 2



independent reaction of dienone derivative **7** with **2a** readily resulted in **8** so that assumption of this reaction pathway for the transformation of HMB to **8** with F-TEDA-BF_4 in MeCN in the presence of water appears to be reasonable.

The changes in the course of functionalization of HMB in water in comparison to methanol stimulated us to investigate the role of the effect of the amount of water on the formation of fluoro-substituted product **8**. From Figure 1 it is evident that formation of **8** strongly depended on the amount of water present and dropped to 30% in the presence of a 100-fold molar excess of water, while F-TEDA-BF_4 consumption was complete. Careful analysis confirmed the formation of a new product, which on the basis of spectroscopic data and comparison with the literature[31] was identified as 5-hydroxy-2,3,5,6,6-pentamethyl-4-methylenecyclohex-2-en-1-one (**9**). Hydroxy-substituted derivative **9** was also formed in substantial quantity with a lower amount of water (2 mmol), while the highest amount of **8** was obtained when 10 mmol of water was used.

Rozen and co-workers[18] observed unusually high regioselectivity in fluorination of methyl pentamethylbenzyl ether **6a** with CH_3OF, while the formation of 1,2-bismethoxymethyl-3,4,5,6-tetramethylbenzene (**11a**) was ascribed to ipso attack of the methoxy moiety at position one in methyl pentamethylbenzyl ether. To evaluate the course of side chain functionalization of HMB with F-TEDA-BF_4 we performed a similar experiment and found that **6a** was regioselectivily transformed with **2a** in the presence of methanol to 1,2-bismethoxymethyl-3,4,5,6-tetramethylbenzene (**11a**) as the sole product. Similar high regioselectivity was also observed in the conversion of the ethoxy derivative **6b** to 1,2-diethoxy derivative **11b** in the presence of ethanol (Scheme 3). The important role of the nucleophile on side chain versus ring functionalization observed in the reaction of HMB with **2a**

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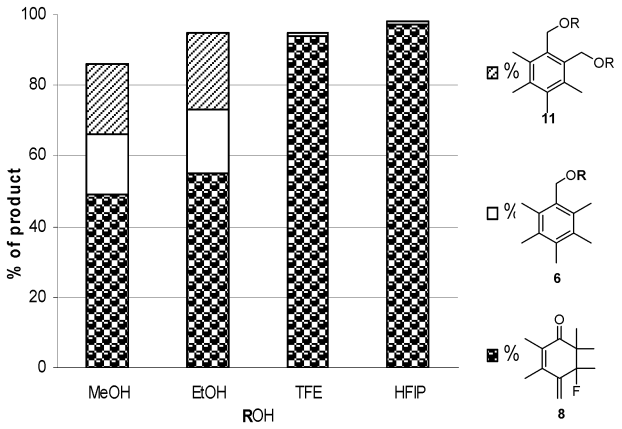
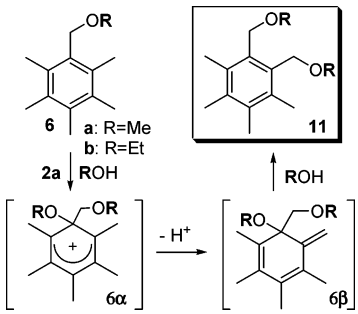


FIGURE 2. Selectivity of fluorination of HMB (**1**) with F-TEDA-BF_4 (**2a**) in MeCN in the presence of water and alcohols (**4a**−**d**). Reagents and conditions: 1 mmol of HMB (1), 2 mmol of **2a**, 10 mL of acetonitrile, 10 mmol of water, 10 mmol of alcohol (**4a**−**d**), $T = 55$ °C, reaction time 1−2 h.

SCHEME 3



stimulated us to study the selectivity of transformation in an acetonitrile mixture of water and alcohols. As evident from Figure 2, the structure of the alcohol plays an important role in the reaction pathway in the functionalization of HMB. When fluorination was performed in the presence of 10 mmol of water, 10 mmol of methanol, and 2 mmol of **2a** in 10 mL of acetonitrile, three products were formed: 49% of fluoro-substituted product **8**, 18% of ether **6a**, and 19% of 1,2-disubstituted ether **11a**, and 14% of HMB remained unreacted. Fluorination became a little more pronounced (55% of **8**) in the presence of ethanol (19% **4b**, 21% **11b**), while the side chain process was completely eliminated when 2,2,2-trifluoroethanol (TFE) or HFIP was present and fluorination became the exclusive process. To study the effect of HFIP as a potent stabilizer of cation-radicals on the selectivity of functionalization of HMB with F-TEDA-BF_4, we performed an experiment in which 10 mmol of methanol, 10 mmol of water, and 10 mmol of HFIP were present in the MeCN reaction media during the transformation of HMB with 2 mmol of **2a**, establishing that in this case the ratio between side chain functionalization (**6a**, **11a**) and ring attack (**8**) changed from 1:1.3 (Figure 2) to 1.2:1.

We also established that the presence of nitrobenzene (0.1−1.0 mmol) as a radical scavenger had no effect on the type or the effectiveness of the functionalization of HMB with **2a** in MeCN, since no significant reduction in the formation of products in the case of fluorination in the presence of water, or of side chain methoxylation in the presence of methanol, or of side chain amidation in the presence of TFA was observed.

Further we studied the effect of the structure of the N−F (**2b**−**d**) reagent on the functionalization of HMB. NFTh (**2b**),

TABLE 1. Effect of the Structure of Methyl-Substituted Benzene Derivatives and Reaction Conditions on the Rate Constants and Activation Parameters for Functionalizations with F-TEDA-BF_4 (2a)

E	Substrate	Solvent : nucleophile[a]	k_2[b,c] at 20 °C (L/mols)	$\Delta H^{\#}$[a] (kJ/mol)	$\Delta S^{\#}$[a] (J/molK)	$\Delta G^{\#}$[a] (kJ/mol) at 25 °C
1		MeCN : TFA	$11.21*10^{-2}$	74.7	-8.30	**77.1**
2		MeCN : MeOH	$4.95*10^{-2}$	76.0	-10.50	**79.0**
3		MeCN : H_2O	$9.54*10^{-2}$	80.0	9.10	**77.0**
4		MeCN	$9.83*10^{-2}$	77.0	-1.60	**77.0**
5		MeCN : H_2O	$7.11*10^{-4}$	89.6	0.50	**89.5**
6		MeCN	$7.40*10^{-4}$	90.0	0.60	**89.0**
7		MeCN : H_2O	$8.20*10^{-4}$	87.6	-5.20	**89.1**
8		MeCN	$9.53*10^{-4}$	83.0	-19.40	**89.0**
9		MeCN : H_2O	$1.61*10^{-3}$	82.7	-16.20	**88.0**
10		MeCN	$1.45*10^{-3}$	84.8	-9.90	**87.7**
11		MeCN : H_2O	$1.74*10^{-4}$	85.0	-26.70	**93.0**
12		MeCN	$1.68*10^{-4}$	88.9	-13.80	**93.0**
13		MeCN : H_2O	$7.76*10^{-5}$	92.4	-8.40	**95.0**
14		MeCN	$9.69*10^{-5}$	88.0	-20.00	**94.0**

[a] 55 mL of an acetonitrile−nucleophile mixture (ratio: MeCN:TFA and MeCN H_2O = 54:1; MeCN:MeOH = 50:5), 2 mmol of methyl-substituted benzene, 1 mmol of **2a**. [b] Relative errors: k_2 ±2%, $\Delta H^{\#}$ ±0.2 and max value 3%, $\Delta S^{\#}$ ±0.01 and max value 1%, $\Delta G^{\#}$ ±0.5 and max value 3%. [c] k_2 values are extrapolated to a temperature of 20 °C.

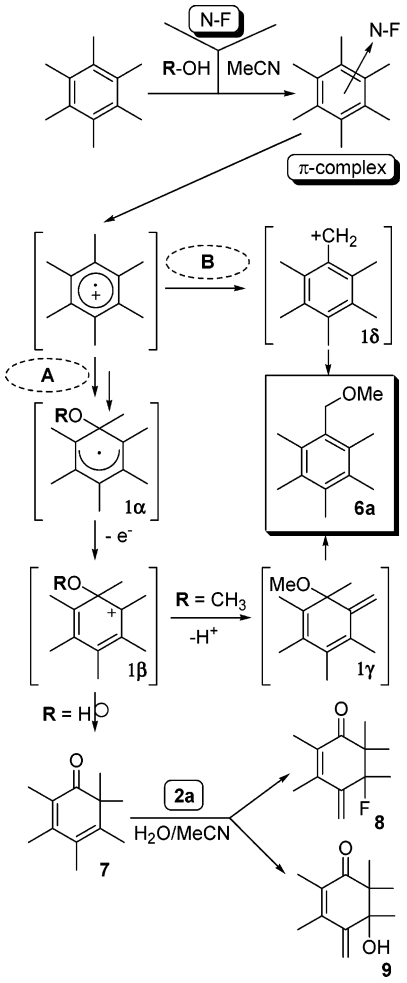
which is a structural analogue of F-TEDA-BF_4, gave fluoro-substituted product **8** as the sole product, but conversion was found to be mutch lower (68%), while NFSi (**2c**) and FP-B800 (**2d**) did not react at all under the similar conditions (10 mL of MeCN, 10 mmol of H_2O, 2 mmol of N−F, 1.5 h, 55 °C). However, side chain methoxylation was achieved with all three fluorinating reagents. The reactivity of **2b** and **2c** was comparable, while the pyridinium salt **2d** was much less effective (36%). (For additional information concerning the structure of the N−F reagents see the Supporting Information.) From the data it is evident that the structure of the N−F reagents does not change the reaction route, but their relative reactivity is strongly influenced by the solvent and nucleophile used.

We started to investigate the kinetics of the reaction of hexamethylbenzene (**1**) with F-TEDA-BF_4 (**2a**) via reactions in acetonitrile in the presence of methanol or TFA where side chain methoxylation or acetamidation seems to be a clean reaction route. The process was monitored by iodometric titration and we found that the rates of functionalization obey the following simple rate equation: $v = d[N-F]/dt = k_2[N-F][C_6Me_6]$. As evident from Table 1 the structure of the nucleophile (TFA, MeOH, H_2O) not only plays an important role in the type of transformation, but also significantly influenced its rate. Fluorination in the presence of water is a little bit slower than acetamidation ($k_2^{WATER}/k_2^{TFA} = 0.9$; entries 1 and 3), while side chain methoxylation became significantly slower ($k_2^{TFA}/k_2^{MeOH} = 2.3$; entries 1 and 2). As mentioned before, functionalization of HMB in acetonitrile without the presence of a nucleophile gave a complex reaction mixture, but transformation monitored by iodometric titration revealed a clear second-order process with a rate constant very similar to that observed in the presence of water (entry 4). This indicated that the rate determining step in all processes must be very similar, while in the later stage the important role of the structure of the nucleophile present becomes crucial for the reaction pathway. Similar behavior has already been observed in the case of reactions of F-TEDA-BF_4 with substituted styrenes, where Hammet correlation analysis gave similar values for reaction constants for fluorination under different reaction conditions:[32] in acetonitrile *fluoro-amidation* took place and $\rho^+ = -1.48$ was established, in the presence of water *fluoro-hydroxylation* gave $\rho^+ = -1.52$, and in the presence of methanol *fluoro-methoxylation* gave $\rho^+ = -1.80$. Measurement of the activation parameters for the transformations of HMB with F-TEDA-BF_4 gave us further valuable information about the course of these functionalizations. As is evident from Table 1, the highest activation enthalpy of 80 kJ/mol is required for the transformation in the presence of water (entry 3), while side chain methoxylation or acetamidation had lower barriers (entries 1 and 2). However, the most important difference was evident in the values of the activation entropies, being positive for reaction in the presence of water (9.1 J/(mol K), entry 3), while the analoguous value for methoxylation (−10.5 J/(mol K), entry 2) suggests that in this case a more ordered transition state is involved. These results demonstrate the important role of the reaction conditions on the type of transformation of HMB, while the most evident difference lies between water on one hand and methanol and acids on the other. In Scheme 4 different pathways leading to side chain or ring functionalization caused by the presence of water or methanol as the external nucleophile are presented. In the first step the formation of a π-complex between electron-rich HMB and the electron-deficient N−F reagent is suggested, which following electron transfer results in the formation of a pair of ion-radicals. Further transformation of the HMB cation-radical could proceed in two ways. Path A includes ipso attack by the nucleophile thus giving a radical intermediate **1**α, which is further converted by one electron transfer to cationic intermediate **1**β. In the case of methanol as nucleophile, deprotonation of the methyl group should be the dominant process resulting in **1**γ, while further addition of methanol gives methoxy derivative **6a**. On the other hand, in the presence of water intermediate **1**β undergoes ionic rearrangement of the methyl group and deprotonation of the hydroxyl group, thus forming cyclohexadienone product **7**, which is more reactive than **HMB** and quickly transforms further to **8** or **9**. Functionalization of cyclohexadienone product **7** depends on the amount of water present (Figure 1). Both these products are probably formed through cation radicals which are trapped either with fluorine or with water. Side chain methoxylation, similar to our results, was already observed by Rozen and co-workers.[18]

They observed ortho regioselectivity of methoxylation of methyl pentamethylbenzyl ether **6a** with MeOF in MeOH leading to exclusive formation of 1,2-bismethoxymethyl-3,4,5,6-tetramethylbenzene (**11a**) suggesting carbonium ion **1**β and its deprotonated analogue **1**γ as the key intermediates. An analogous explanation for the formation of **11a,** as well as **11b** in the case of the ethanol-mediated reaction, is presented on Scheme 3. Alkyl pentamethylbenzyl ether **6** is transformed after formation of a cation-radical, nucleophilic attack of methanol, and a second electron transfer to cationic intermediate **6**α, while further deprotonation of the neighboring methyl group gave **6**β,

(32) (a) Stavber, S.; Sotler-Peèan, T.; Zupan, M. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1141−1145. (b) Stavber, S.; Sotler-Peèan, T.; Zupan, M. *Tetrahedron* **2000**, *56*, 1929−1936.

SCHEME 4

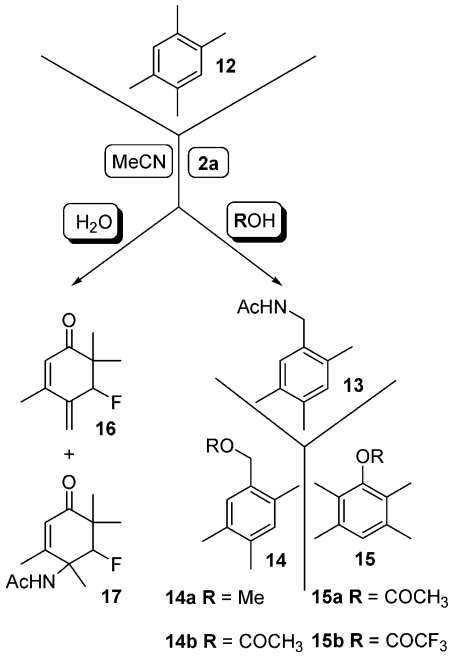


which following further attack of methanol gave the ortho dimethoxy derivative **11a**. Similar ipso attack of water or alcohols has already been observed in F-TEDA-BF_4-mediated functionalizations of sterically hindered phenols, but deprotonation of the hydroxyl group was the dominant process there, and dienone derivatives were thus formed.[33] However, side chain functionalized products could also be formed by a second route (Scheme 4, path **B**), where deprotonation of cation-radical is followed by one-electron transfer thus giving the cationic intermediate **1***δ*, which could further collapse with methanol resulting in the formation of **6a** or **6e**, **6f**, or **5** if acetic acid, trifluoroacetic acid or acetonitrile were the source of the nucleophile, respectively.

We decided to take 1,2,4,5-tetramethylbenzene (**12**, DUR) as another probe in our further study since this molecule, besides two potentially active sites on the side chain, also has two different sites (ipso and H) on the aromatic ring, so that formation of different types of products could be expected from its reactions with N−F reagents (Scheme 5). We established that, as in the fluorination of HMB in acetonitrile, DUR with F-TEDA-BF_4 at 55 °C after 160 min gave an even more complex reaction mixture with up to 10 products. Among them the following monosubstituted products were confirmed: *N*-(2,4,5-trimethylbenzyl)acetamide, 1-fluoromethyl-2,4,5-trimethyl-

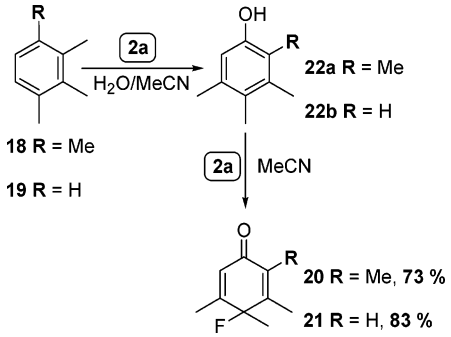
(33) (a) Stavber, S.; Jereb, M.; Zupan, M. *Arkivoc* **2001**, 98−107. (b) Stavber, S.; Jereb, M.; Zupan, M. *J. Phys. Org. Chem.* **2002**, *15*, 56−61.

SCHEME 5



benzene, 3-fluoro-1,2,4,5-tetramethylbenzene, and 1,4-difluoro-2,3,5,6-tetramethylbenzene, while other products corresponded to dimeric and trimeric fluoro-substituted compounds. On the other hand, DUR remained unreacted when water was used as a reaction medium, while in other protic solvents the site of functionalization depended on the structure of the solvent. In methanol only side chain functionalization took place and 1-methoxymethyl-2,4,5-trimethylbenzene (**14a**, Scheme 5) was formed, while a much longer time (18 h, 65 °C, 93%) was required for high yield conversion than in the case of HMB (1 h, 55 °C, 90%). In acetic acid DUR is even less reactive (17 h, 120 °C), but regioselectivity significantly changed, and besides the side chain product acetic acid 2,4,5-trimethylbenzyl ester (**14b**), predominant ring acetoxylation took place and acetic acid 2,3,5,6-tetramethylphenyl ester (**15a**) was formed as the major product (**14b**:**15a** = 29:71). DUR became much more reactive in trifluoroacetic acid, and exclusive ring functionalization was observed and trifluoroacetic acid 2,3,5,6-tetramethylphenyl ester (**15b**) was formed in an excellent yield. However, TFA as a catalyst in acetonitrile solution (MeCN/TFA = 9:1) plays a completely different role: a shorter reaction time was required for conversion of the starting material and side chain functionalization took place exclusively forming *N*-(2,4,5-trimethylbenzyl)acetamide (**13**). It is evident that under these reaction conditions acetonitrile became a better nucleophile than TFA and Ritter-type amidation became the dominant process. Complete loss of regioselectivity was observed when acetic acid was used as catalyst and ring acetoxylation to acetate took place as the predominant functionalization (**13**:**14**:**15** = 27:21:52). Reactions in aqueous MeCN again completely changed the course of functionalization since with 2 mmol of F-TEDA-BF_4, two products were formed in equimolar amounts and identified as 5-fluoro-3,6,6-trimethyl-4-methylenecyclohex-2-enone (**16**), and *N*-(6-fluoro-1,2,5,5-tetramethyl-4-oxo-cyclohex-2-enyl)acetamide (**17**). The reaction course could be explained by a very similar process as in the case of HMB. The formation of 3,4,6,6-tetramethylcyclohexa-2,4-dienone is suggested as the first step of the reaction, while further fluorination differs from that observed in the case of HMB, and besides fluorination followed

SCHEME 6



by elimination process thus giving **16**, the intermediate fluoro carbonium ion could also be competitively trapped by acetonitrile, this Ritter-type fluoroamidation process resulting in **17**.

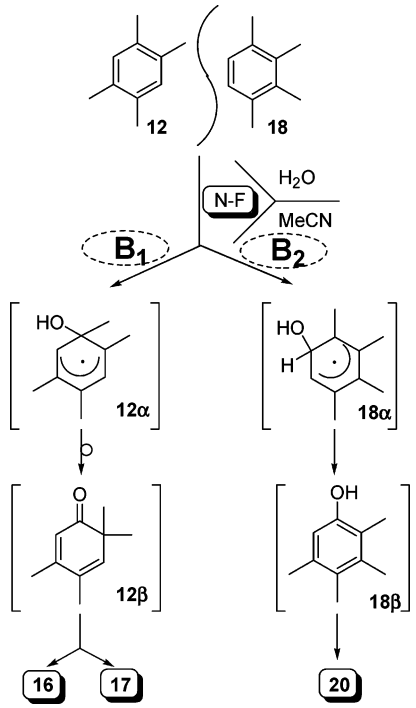
A different course of functionalization during the reaction of F-TEDA-BF_4 in MeCN/H_2O as solvent was observed when we took the isomeric tetramethyl benzene derivative 1,2,3,4-tetramethylbenzene (**18**, Scheme 6) as the substrate. The reaction resulted in high yield formation of 4-fluoro-2,3,4,5-tetramethylcyclohexa-2,5-dienone (**20**). It is evident that in this case attack of water no longer occurred at the ipso position as in the case of HMB or DUR, but at position 1 and 2,3,4,5-tetramethylphenol (**22a**) was formed in the first step.

This product was more reactive than starting material **18** and was quickly further transformed to cyclohexadienone derivative **20**. The last transformation is a well-known and documented process observed during the reactions of N−F reagents with methyl-substituted phenols.[35] The third tetramethyl-substituted benzene isomer 1,2,3,5-tetramethylbenzene (**23**) was found to be less reactive in acetonitrile and an acetonitrile−water solution of **2a** than isomers **12** and **18**, but under both conditions very complex reaction mixtures were formed.

Finally, we studied the fluorination of mesitylene (**24**) in acetonitrile and in the presence of water, but in both cases complex reaction mixtures were formed. 1,2,3-Trimethylbenzene (**19**) in acetonitrile also gave a complex reaction mixture, while in the presence of water it was regioselectively transformed to 4-fluoro-3,4,5-trimethylcyclohexa-2,5-dienone (**21**) in high yield (Scheme 6). Also in this case the assumption that 3,4,5-trimethylphenol **22b** was formed in the first step was confirmed by the independent fluorination of **22b**.

Kinetic evaluations of the reactions of tetramethyl- and trimethyl-substituted benzene derivatives with F-TEDA-BF_4 are collected in Table 1. The fact that the reactions of trimethyl- and tetramethyl-substituted benzene derivatives with **2a** in acetonitrile gave complex reaction mixtures did not interfere with the very clear second-order kinetics of these reactions. As is evident, tetramethyl-substituted benzenes (entries 6, 8, and 10) were less reactive than HMB (entry 4), while their relative reactivities in MeCN followed the sequence **23** > **18** > **12**. The presence of water had no significant effect on the rate constants (entries 5, 7, and 9). Trimethyl-substituted benzenes were less reactive than their tetramethyl analogues, in pure or aqueous MeCN (entries 11−14). In this pair **24** was more reactive than **19**, but in the latter case water had a certain diminishing effect on the value of the rate constant. The most

SCHEME 7



pronounced differences in the activation parameters were evident in the values of the activation entropies, being positive in cases where methyl group migration followed the ipso attack of water.

In Scheme 7 an explanation of the differences in the functionalizations of DUR (**12**) and 1,2,3,4-tetramethylbenzene (**18**) is proposed. As in the case of HMB (Scheme 4), in the first step the formation of a π-complex is suggested, which after electron transfer transforms further to a pair of ion-radicals, while the tetramethylbenzene cation-radical is attacked by water at the ipso (B_1 route) or ring (B_2 route) position. Route B_1 proceeds thereafter by another electron transfer from the thus formed intermediate **12**α, methyl group migration, and side chain proton release from the cationic intermediate. This results in the formation cyclohexadienone derivative **12***β*, which is more reactive than starting compound **12**, and reacts further with F-TEDA-BF_4 to the products **16** and **17**. In the presence of water this part of the process differs from that observed with HMB, where besides fluorination hydroxylation also took place. This difference, however, could be expected in view of the results of earlier investigations of the reactions of alkenes with F-TEDA-BF_4 in MeCN,[36] which revealed that very reactive alkenes gave fluorinated alkenes after an addition−elimination process, while less reactive alkenes gave vicinal fluoroamides after Ritter-type collapse of MeCN with a fluorocarbonium intermediate species. Route B_2, however, follows regioselective water attack at the unsubstituted position of the tetramethybenzene cation-radical in the case of reaction of 1,2,3,4-tetramethylbenzene (**18**), thus giving intermediate **18**α. After electron transfer and ring proton release this intermediate transforms to tetramethyl-substituted phenol derivative **18***β*, which is more reactive than the starting substrate and is further fluorinated to fluorocyclohexadienone derivative **20**. The reaction pathway proposed in Scheme 7 also supports the results of the reaction

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(35) (a) Stavber, S.; Jereb, M.; Zupan, M. *Synlett* **1999**, *9*, 1375−1378. (b) Jereb, M.; Zupan, M.; Stavber, S. *Arkivoc* **2003**, 187−197.

(36) (a) Stavber, S.; Sotler-Peèan, T.; Papež, M.; Zupan, M. *Chem. Commun.* **1996**, 2247−2248. (b) Zupan, M.; Škulj, P.; Stavber, S. *Tetrahedron* **2001**, *57*, 10027−10031.

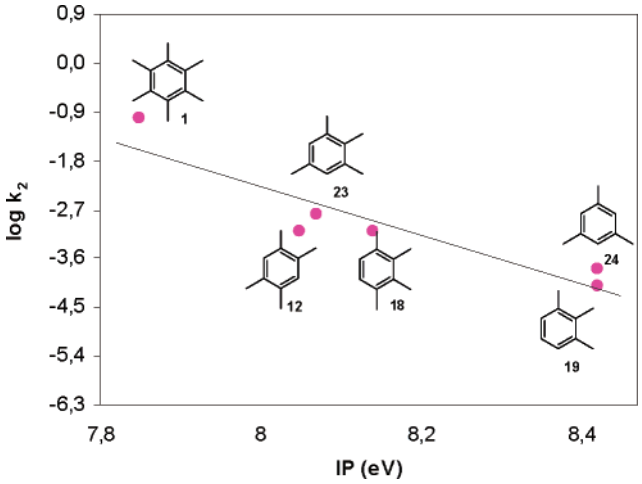

FIGURE 3. The correlation of ionization potentials (IP, eV) for methyl-substituted benzene derivates[37] and the second order rate constant for their functionalization with **2a** in aqueous MeCN.

TABLE 2. Effect of the Structure of the Reagent on the Type of Functionalization of Mesitylene (24) and Durene (12): σ-Complex versus Cation−Radical Reaction Pathway

reagent/solvent	reactivity ratios k_{MES}/k_{DUR}	ref
Br_2/AcOH	66	38
I_2/F-TEDA-BF_4/MeCN	61	39
ICl/MeCN	46	40
acylation	28.6	38
Cl_2/AcOH	18.8	38
$Hg(OAc)_2$/TFA	7.3	38
F-TEDA/MeCN/H_2O	2.4×10^{-1}	
ICl/HFIP	2.3×10^{-1}	40
$CeNH_4NO_3$/AcOH	5×10^{-3}	38

of 1,2,3-trimethylbenzene with **2a** in aqueous MeCN, which follows route B_2 with regioselective ring attack of water at the 5 position, thus forming phenol **22b**, and its further fluorination to **21**.

Some further support for single-electron transfer (SET) as the key process suggested for the functionalization of methyl-substituted benzene derivatives with F-TEDA-BF_4 in the presence of water could also be obtained from the correlation between the second-order rate constants and the ionization potentials, presented in Figure 3. A similar correlation between oxidation potentials for methyl-substituted benzene derivatives in TFA and ionization potentials has already been confirmed.[37] In view of the suggestion that in reactions where MES is more reactive than DUR the formation of a σ complex is the dominant process, while when DUR expresses higher reactivity SET is the rate determining step, we compared the relative reactivity of the two compounds in various other functionalizations, as shown in the collected data in Table 2 [39]. It is evident that the nature of the electrophilic species has an important effect on the relative reactivity of transformations of MES and DUR. The lower reactivity of MES observed in functionalizations with F-TEDA-BF_4 in acetonitrile or acetonitrile−water mixtures supports the presumption that single-electron transfer is the dominant process in the studied functionalizations of methyl-substituted benzene derivatives with F-TEDA-BF_4.

In conclusion, we can claim that, following the example of methyl-substituted benzene derivatives, the present study demonstrated that even a small variation in the structure of the organic molecule from a class of analoguous compounds has an important effect on the transformation of these compounds with N−F reagents. Reaction conditions are crucial for the type and efficiency of these transformations, while the remarkable effect of water on these processes should especially be stressed, since it enables some mechanistic insight into the reactions of N−F reagents with organic compounds in general.

Experimental Section

Reaction of Methyl-Substituted Benzene Derivatives with F-TEDA-BF_4 in Acetonitrile in the Presence of a Nucleophile. To a solution of substrate (**1**, **12**, **18**, and **19**, 1 mmol) in 10 mL of MeCN was added 10 mmol of selected nucleophile (CH_3OH, CH_3CH_2OH, CF_3CH_2OH, CH_3COOH, CF_3COOH, or H_2O) and 1 mmol of F-TEDA-BF_4 (**2a**) (2 mmol for reactions in the presence of water) and the reaction mixture was stirred at 55−75 °C for various times (1−23 h). The progress of the transformation was monitored by TLC or by KI/starch paper, checking the oxidation properties of the reaction mixture. The workup procedure depended on the nucleophile used. In the case of CH_3OH, CH_3CH_2OH, CF_3CH_2OH, and H_2O the solvent was evaporated under reduced pressure, methylene chloride (20 mL) was added to the crude residue, insoluble material was filtered off, the solution was washed with water (2 × 25 mL) and dried over anhydrous sodium sulfate, and methylene chloride was evaporated under reduced pressure. In the case of CH_3COOH or CF_3COOH as nucleophile, methylene chloride was added to the crude residue, insoluble material was filtered off, and the solution was washed with 1% aqueous KOH (2 × 25 mL) and further treated as mentioned above. The crude reaction mixtures were analyzed by TLC and ^1H and ^{19}F NMR spectroscopy and pure compounds were isolated either by TLC, CC or GLC and identified on the basis of their spectroscopic data and elemental combustion analysis or high-resolution MS spectroscopy, while in the case of known compounds through comparison of their spectroscopic data with the literature.

5-Fluoro-2,3,5,6,6-pentamethyl-4-methylene-cyclohex-2-enone (8). **1** was transformed (conditions: 2 mmol of F-TEDA-BF_4, CH_3CN, 10 mmol of H_2O, 55 °C, 1.5 h) to 226 mg of crude reaction mixture. TLC (SiO_2, CH_2Cl_2) gave 157 mg (80%) of pure highly hygroscopic oily product. ^1H NMR: δ H 1.09 (s, 3H), 1.18 (s, 3H), 1.38 (d, J = 22.1 Hz, 3H), 1.88 (s, 3H), 2.10 (s, 3H), 5.50 (d, J = 4.4 Hz, 1H), 5.58 (s, 1H); ^{19}F NMR δ F −155.68 (qd, J = 22.1 Hz, J = 4.4 Hz, 1F); ^{13}C NMR δ C 12.34 (s), 16.43 (d, J = 2.5 Hz), 17.59 (s), 21.63 (d, J = 5.1 Hz), 23.19 (d, J = 28.3 Hz), 50.66 (d, J = 19.6 Hz), 98.31 (d, J = 187.5), 113.00 (d, J = 12.2 Hz), 130.10 (s), 144.98 (d, J = 4.9 Hz), 147.80 (d, J = 17.5 Hz), 201.70 (d, J = 7.4 Hz); MS m/z 196 (M^+, 52%), 181 (42), 153 (100), 136 (83), 133 (76), 121 (62), 91 (32); high-resolution MS, m/z 196.1269 (calcd for $C_{12}H_{17}OF$ m/z 196.1263); IR ν [cm^{-1}] 2985, 1670, 1375, 1135, 1072, 920; elemental analysis calcd for $C_{12}H_{17}OF \cdot {}^1/_5H_2O$ C 72.11, H 8.78, found C 72.01, H 8.75.

Durene (**12**) was transformed (conditions: 2 mmol of F-TEDA-BF_4, CH_3CN, 10 mmol of H_2O, 55 °C, 4.5 h) to 253 mg of crude reaction mixture containing 84 mg of **16** and 113 mg of **17**.

5-Fluoro-3,6,6-trimethyl-4-methylenecyclohex-2-enone (16). TLC (SiO_2, CH_2Cl_2) gave 66 mg (39%) of pure highly hygroscopic oily product. ^1H NMR δ H 1.15 (s, 3H), 1.16 (s, 3H), 2.11 (s, 3H), 4.90 (d, J = 49.5 Hz, 1H), 5.66 (s, 1H), 5.69 (d, J = 8.9 Hz, 1H), 5.87 (broad s, 1H); ^{19}F NMR δ F −188.00 (d, J = 49.5 Hz, 1F); ^{13}C NMR δ C 18.90 (d, J = 4.9 Hz), 19.41 (s), 21.67 (d, J = 3.9 Hz), 47.58 (d, J = 19.9 Hz), 97.36 (d, J = 181.8 Hz), 118.83 (d,

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(40) Fabbrini, M.; Galli, C.; Gentili, P.; Macchitella, D.; Petride, H. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1516−1521.

J = 9.8), 125.72 (d, J = 1.3 Hz), 140.71 (d, J = 16.8 Hz), 149.77 (d, J = 3.4 Hz), 201.23 (d, J = 5.2 Hz); MS m/z 168 (M^+, 67%), 153 (55), 125 (81), 121 (100), 105 (67), 91 (22); high-resolution M, m/z 168.0957 (calcd for $C_{10}H_{13}OF$ m/z 168.0950); IR ν[cm^{-1}] 2988, 1680, 1400, 1175, 1120, 935; elemental analysis calcd for $C_{10}H_{13}OF\cdot{}^1/_6H_2O$ C 70.15, H 7.85, found C 70.48, H 7.95.

***N*-(6-Fluoro-1,2,5,5-tetramethyl-4-oxo-cyclohex-2-enyl)acetamide (17).** TLC (SiO_2, $CH_2Cl_2/CH_3CH_2OCOCH_3$) gave 79 mg (35%) of pure hygroscopic solid product, mp 110.5−112 °C. ^{1}H NMR δ H 1.15 (s, 3H), 1.29 (s, 3H), 1.46 (d, J = 1.4 Hz, 3H), 1.94 (q, J = 1.2 Hz, 3H), 2.00 (s, 3H), 5.20 (d, J = 48.2 Hz, 1H), 5.87 (d, J = 1.2 Hz, 1H), 6.10 (broad s, 1H); ^{19}F NMR δ F −203.33 (d, J = 48.2 Hz); ^{13}C NMR δ C 18.36 (d, J = 3.3 Hz), 20.62 (s), 20.71 (broad s), 23.40 (s), 24.05 (s), 46.46 (d, J = 18.1 Hz, C5), 58.60 (d, J = 20.3 Hz, C1), 94.85 (d, J = 187.9 Hz, C6), 125.37 (s, C3), 161.02 (d, J = 5.5 Hz, C2), 169.47 (s, COMe), 200.22 (d, J = 8.8 Hz, C4); MS m/z 227 (M^+, 9%), 191 (6), 168 (20), 111 (100), 84 (41); high-resolution MS, m/z 227.1325 (calcd for $C_{12}H_{18}NO_2F$ m/z 227.1322); IR ν [cm^{-1}] 3220, 2990, 1730, 1550, 1450, 1380, 1290, 1180, 1120, 1040, 935.

Acknowledgment. We thank the Slovenian Research Agency for financial support.

Supporting Information Available: Experimental data concerning reaction protocols and kinetic measurements, and the spectroscopic characteristics of isolated products. This material is available free of charge via the Internet at http://pubs.acs.org.

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