and it is very difficult to make a clear-cut distinction among them. Nevertheless, the total difference among the reactivities of $CsSO_4F$ and other fluorinating agents with methyl-substituted benzene derivatives has been demonstrated, with $CsSO_4F$ as a unique reagent for the direct fluorosubstitution of benzylic hydrogen showing reasonable to excellent selectivity and yield.

Experimental Section

^1H and ^{19}F NMR spectra were recorded at 60 and 56.45 MHz, respectively. Chemical shifts are expressed in ppm from Me_4Si or CCl_3F as internal standards. TLC was carried out on Merck PCS-Fertigplatten Silicagel F-254. Alkyl aromatics from commercial sources were used, and $CsSO_4F$ was prepared according to the literature[12,20] and handled and stored in compliance with applicable instructions[20].

Fluorination of Alkyl-Substituted Aromatics with $CsSO_4F$. General Procedure. A solution of 1 mmol of alkyl-substituted aromatic substrate in 2 mL of freshly distilled and dry CH_3CN was degassed with dry oxygen-free N_2. Then 400 mg (1.6 mmol) of $CsSO_4F$ was introduced, and the reaction mixture was stirred under N_2 at 35–40 °C for 1 h and diluted with 20 mL of CH_2Cl_2. The insoluble residue was filtered off. The filtrate was washed with 20 mL of water, dried (Na_2SO_4), and evaporated under reduced pressure. The crude reaction mixtures were analyzed by GLC and ^1H and ^{19}F NMR spectroscopy. The amounts of the fluorinated products formed were determined from ^{19}F NMR spectra of the crude reaction mixtures using octafluoronaphthalene as internal standard. Products were isolated by preparative GLC (DNP 10%, Chromosorb W A/W 80/100) or TLC and identified on the basis of the spectroscopical data and comparison with literature and in some cases also by conversion to known compounds.

Benzyl fluoride[25] **(2a)**: 70%, liquid. **1-Fluoro-1-phenylethane**[26] **(2b)**: 73%, converted to styrene. **2-Fluoro-2-phenylpropane**[26] **(2c)**: 70.5%, converted to α-methylstyrene. **Fluorodiphenylmethane**[26] **(2d)**: TLC, 54%, oily. **Fluorotriphenylmethane**[26] **(2e)**: TLC, 55.3%, mp 102–103 °C, mp[27] 103–104 °C. **2-Methylbenzyl fluoride**[28] **(5a)**: GLC, 36%, liquid. **3-Methylbenzyl fluoride**[25] **(5b)**: GLC, 24%, liquid. **4-Methylbenzyl fluoride**[25] **(5c)**: TLC, 66%, liquid. **1-(Fluoromethyl)naphthalene**:[29] TLC, 35%, oily. **2-(Fluoromethyl)naphthalene**:[29] TLC, 22%, mp 52–53 °C. **1-Fluoro-2-methylnaphthalene**:[30] TLC, 45.5%, oily.

3,5-Dimethylbenzyl fluoride (5f): GLC, 18%, liquid; NMR (CCl_4) δ_F −210.3 (t, J = 47 Hz), δ_H 2.3 (s, 6 H), δ_H 5.2 (d, J = 47 Hz, 2 H), δ_H 7.0 (m, 3 H); HRMS calcd for $C_9H_{11}F$ m/z 138.0844, found m/z 138.0845; MS m/z 138 (M, 100), 137 (20), 123 (95), 105 (25), 91 (10).

2,3-Dimethylbenzyl fluoride and 2,6-dimethylbenzyl fluoride[31] **(5d, 2:1 mixture)**: TLC, 54%, liquid; NMR (CCl_4) δ_F −210.0 (t, $^2J_{FH}$ = 47 Hz), δ_H 2.2–2.4 (m, 6 H), δ_H 5.3 (d, J = 47 Hz, 2 H), δ_H 7.1 (m, 3 H), and δ_F −211.5 (t, $^2J_{FH}$ = 47 Hz), δ_H 2.2–2.4 (m, 6 H), δ_H 5.4 (d, J = 47 Hz, 2 H), δ_H 7.0 (m, 3 H); HRMS calcd for $C_9H_{11}F$ m/z 138.0844, found m/z 138.0850; MS m/z 138 (M^+, 90), 137 (25), 123 (100), 105 (80), 91 (20), 77 (20). **3,4-Dimethylbenzyl fluoride,**[25] **2,4-dimethylbenzyl fluoride,**[25] **and 2,5-dimethylbenzyl fluoride**[25] **(6e, 1:0.5:1 mixture)**: TLC, 51%, liquid; NMR (CCl_4) δ_F −204.0, 206.5, and 209.3 (t, J_{FH} = 47 Hz); MS m/z 138 (M^+, 75), 137 (25), 123 (100), 105 (75), 91 (20), 77 (20).

Fluorination of Alkyl-Substituted Aromatics with $CsSO_4F$ in the Presence of Oxygen. A solution of 1 mmol of alkyl-substituted aromatic substrate in 2 mL of dry CH_3CN was saturated with dry oxygen. $CsSO_4F$ (400 mg, 1.6 mmol) was added, and the reaction mixture was stirred under O_2 at 35–45 °C for 1 h. After the usual workup procedure, the crude reaction mixtures were analyzed by ^{19}F NMR. The distributions of the products are presented in Table II.

Registry No. **1a**, 108-88-3; **1b**, 100-41-4; **1c**, 98-82-8; **1d**, 101-81-5; **1e**, 519-73-3; **2a**, 350-50-5; **2b**, 7100-97-2; **2c**, 74185-81-2; **2d**, 579-55-5; **2e**, 427-36-1; **4a**, 95-47-6; **4b**, 108-38-3; **4c**, 106-42-3; **4d**, 526-73-8; **4e**, 95-63-6; **4f**, 108-67-8; **5a**, 62037-88-1; **5b**, 456-44-0; **5c**, 459-50-7; **5f**, 136822-77-0; **6e**, 52547-99-6; **6f**, 392-69-8; $CsSO_4F$, 70806-67-6; 2,3-dimethylbenzyl fluoride, 117455-55-7; 2,6-dimethylbenzyl fluoride, 62037-90-5; 3,4-dimethylbenzyl fluoride, 75787-75-6; 2,4-dimethylbenzyl fluoride, 75787-74-5; 2,5-dimethylbenzyl fluoride, 136822-78-1; 2-(fluoromethyl)naphthalene, 55831-11-3; 1-fluoro-2-methylnaphthalene, 573-99-9; 1-(fluoromethyl)naphthalene, 55831-10-2; 3-fluoro-1,2-dimethylbenzene, 443-82-3; 4-fluoro-1,2-dimethylbenzene, 452-64-2; 2-fluoro-1,3-dimethylbenzene, 443-88-9; 4-fluoro-1,3-dimethylbenzene, 452-65-3; 2-fluoro-1,4-dimethylbenzene, 696-01-5; 3-fluoro-1,2,4-trimethylbenzene, 26630-72-8; 5-fluoro-1,2,4-trimethylbenzene, 400-01-1.

Supplementary Material Available: ^1H and ^{19}F NMR spectra of compound **5f** (2 pages). Ordering information is given on any current masthead page.

(25) Bensadat, A.; Bodennec, G.; Laurent, E.; Tardivel, R. *Nouv. J. Chim.* **1980**, *4*, 453.
(26) Weigert, F. J. *J. Org. Chem.* **1980**, *45*, 3476.
(27) Coverdale, A. K.; Kohnstam, G. *J. Chem. Soc.* **1960**, 3806.
(28) Beguin, C.; Gout-Mallaret, E. *J. Fluorine Chem.* **1976**, *8*, 279.
(29) (a) Adcock, W.; Dewar, M. J. S.; Golden, R.; Zeb, M. A. *J. Am. Chem. Soc.* **1975**, *97*, 2198. (b) Dixon, E. A.; Fischer, A.; Robinson, F. P. *Can. J. Chem.* **1981**, *59*, 2642.
(30) Newman, M. S.; Dhawan, B.; Kumar, S. *J. Org. Chem.* **1978**, *43*, 524.
(31) Adcock, W.; Abeywickrema, A. N. *Aust. J. Chem.* **1980**, *33*, 181.

Nucleophilic Aromatic Substitution by Hydroxide Ion under Phase-Transfer Catalysis Conditions: Fluorine Displacement in Polyfluorobenzene Derivatives

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Nucleophilic aromatic substitution reactions can be conveniently performed under phase-transfer catalysis conditions (PTC).[2] A few examples for the generality of this technique are the formation of aryl sulfides in activated aromatic rings by catalysis of ammonium and phosphonium salts,[3,4] aryl alkyl ethers by catalysis of poly(ethylene glycols),[5] and phenylalkyl nitriles by catalysis of ammonium salts.[6] The application of alkylpyridinium salts as phase-transfer catalysts affords aromatic nucleophilic substitution reactions at high temperatures[7] while activation by complexes of transition metals affords a high yield even at low temperatures.[8] The role of the base in these reactions is to form the active nucleophile, e.g., alkoxide, thiolate, etc. However, there are no examples of direct nucleophilic aromatic substitutions with hydroxide ion under PTC conditions. This can be rationalized by the expectation that the hydration sphere that surrounds the hydroxide ion would cause a decrease in the hydroxide's nucleophilicity.[9] In recent years a growing number

(1) For a preliminary report of some of our results see: Feldman, D.; Rabinovitz, M. *Tetrahedron Lett.* **1989**, *30*, 6091.
(2) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*, 2nd ed.; Verlag Chemie: Weinheim, 1983; p 199.
(3) Reeves, W. P.; Bothwell, T. C.; Rudis, J. A.; McClusky, J. V. *Synth. Commun.* **1982**, *12*, 1071.
(4) Brunelle, D. J. *J. Org. Chem.* **1984**, *49*, 1039.
(5) Neumann, R.; Sasson, Y. *Tetrahedron* **1983**, *39*, 3437.
(6) Makosza, M.; Jaqusztyn-Grochowska, M.; Ludwickow, M.; Jawdosink, M. *Tetrahedron* **1974**, *30*, 3723.
(7) Brunelle, D. J.; Singleton, D. A. *Tetrahedron Lett.* **1984**, *25*, 3383.
(8) Alemagna, A.; Baldoli, L.; Del Buttero, P.; Licanddro, E.; Mairorana, S. *Gazz. Chim. Ital.* **1985**, *115*, 555.

0022-3263/91/1956-7350$02.50/0

Table I. The Influence of the Temperature and the Phase-Transfer Catalyst Concentration on the Conversion of Hexafluorobenzene (1)

	catalyst, M%[a]			
	20	50	100	50 °C[b]
% convn after 2 h	27	43	64	91

[a] Standard conditions: 2 mmol of HFB, 0.8 g of 50% NaOH, 5 mL of cyclohexane, 25 ± 0.5 °C. [b] In the presence of 2 mmol of $(Bu)_4N^+HSO_4^-$.

Table II. The Influence of the Phase-Transfer Catalyst Choice on the Conversion of Hexafluorobenzene (1)[a]

PTC catalyst	% convn after 2 h
$(Bu)_4N^+HSO_4^-$	64
$Me(Bu)_3N^+HSO_4^-$	20
$(Bu)_4N^+Br^-$	2
$(Oct)_4N^+Br^-$	2
$(Et)_4N^+HSO_4^-$	5

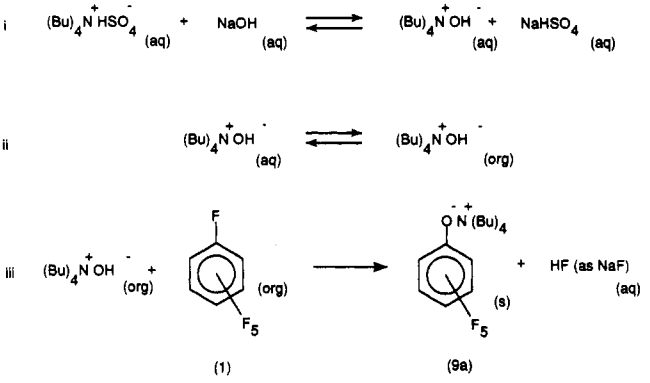
[a] Standard conditions: 2 mmol of HFB, 2 mmol of PTC catalyst, 0.8 g of 50% NaOH, 5 mL of cyclohexane, 25 ± 0.5 °C.

of reports have appeared in which synthetic achievements were attributed to OH^- extraction. It seems that hydroxide extraction into a nonpolar organic medium can be achieved under a proper choice of PTC conditions.[10] Under these conditions, the hydroxide ion is extracted into the organic phase with a limited number of water molecules in its hydration sphere and proved to be a very strong base indeed.[11] This enhanced basicity has been applied for oxidation,[12] isomerization,[13] and H/D exchange of carbon acids as weak as those with pK_a values of 38.[12]

We have previously reported that under extraction conditions (organophilic catalyst, hydrophilic counterion, and high OH^- concentration) the hydroxide ion can react in a direct nucleophilic aromatic substitution with 1,2,3,4-tetrafluorobenzene (2).[1] Under these conditions we examined the competition reaction between H/D exchange and nucleophilic aromatic substitution and showed that the tendency of the OH^- anion to behave as a base is greater than its ability to act as a nucleophile. Nevertheless, this first example of a direct nucleophilic aromatic substitution by OH^- under PTC conditions affords a very convenient method for the formation of a series of polyfluorophenols.

The traditional synthetic methods for polyfluorophenols include multistage reactions which require the use of dangerous reactants and inconvenient reaction conditions.[14-17] A direct nucleophilic aromatic substitution requires solvents such as liquid ammonia,[18] dry pyridine,[19] or *tert*-butyl alcohol[20] under reflux or high pressure and temperature.[21] The use of ethanolic potassium hydroxide

Scheme I. Nucleophilic Aromatic Substitution by Hydroxide Ion on Hexafluorobenzene (1) under Phase-Transfer Catalysis Conditions



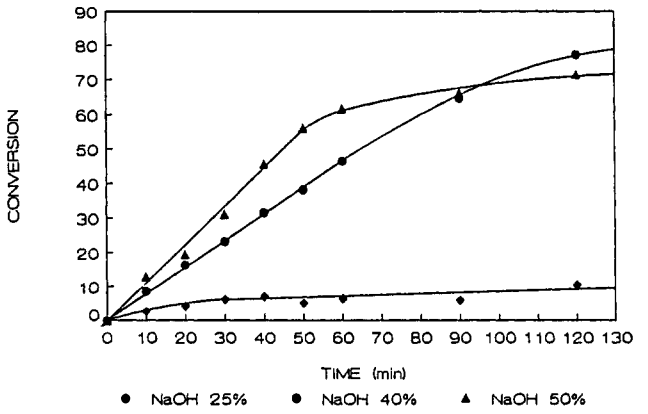


Figure 1. The influence of the base concentration on the conversion of hexafluorobenzene (1).

affords a mixture of phenolic derivatives and ethers.[19,20]

Results and Discussion

The nucleophilic aromatic substitution of fluorine atom in hexafluorobenzene (1) by hydroxide ion under extractive PTC conditions was chosen as a model reaction for this novel process (Scheme I). The influence of the catalyst concentration, the temperature, and the choice of phase-transfer catalyst are presented in Tables I and II. The sensitivity of the reaction to the catalyst concentration is rationalized by assuming formation of ammonium phenolate which precipitates from the organic solvent. Increase of the catalyst concentration causes an increase in the conversion of the starting material as a result of the greater concentration of the hydroxide ion in the organic phase. This increase of the above mentioned conversion is not directly proportional to the catalyst concentration as a competing reaction that causes a decomposition of the ammonium catalyst under these strong basic conditions also occur.[22] The effect of different catalysts on the conversion of the starting material (Table II) supports an extraction mechanism. A prerequisite for such a phase-transfer process is the presence of an hydrophilic counterion, e.g. HSO_4^-. By changing the counterion from HSO_4^- to Br^-, the hexafluorobenzene conversion drops from 64% to 2% as the presence of the lipophilic bromide ion poisons the catalyst and avoids OH^- extraction. The presence of HSO_4^- as a counterion is not a sufficient condition for effective catalysis, thus the alkyl chains of the ammonium

(9) Landini, D.; Maia, A. *J. Chem. Soc., Chem. Commun.* **1984**, 1041.
(10) Rabinovitz, M.; Cohen, Y.; Halpern, M. *Angew. Chem., int. Ed. Engl.* **1986**, *25*, 960.
(11) Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem.* **1986**, *51*, 5475.
(12) Feldman, D.; Rabinovitz, M. *J. Org. Chem.* **1988**, *53*, 3779.
(13) Halpern, M.; Sasson, Y.; Rabinovitz, M. *J. Org. Chem.* **1983**, *48*, 1022.
(14) Forbes, E. J.; Richardson, R. D.; Stacey, M.; Tatlow, J. C. *J. Chem. Soc.* **1959**, 2019.
(15) Brooke, G. M.; Forbes, E. J.; Richardson, R. D.; Stacey, M.; Tatlow, J. C. *J. Chem. Soc.* **1965**, 2088.
(16) Brooke, G. M.; Furniss, B. S. *J. Chem. Soc. C* **1967**, 869.
(17) Bogachev, A. A.; Kobrina, L. S.; Yakobson, G. G. *Zh. Org. Khim.* **1986**, *22*, 2578; Engl. translation 2313.
(18) Shtark, A. A.; Kizner, T. A.; Shteingarts, V. D. *Zh. Org. Khin.* **1982**, *18*, 2321; Engl. translation 2051.
(19) Pummer, W. J.; Wall, L. A. *Science* **1958**, *127*, 643.
(20) Birchall, J. M.; Haszeldine, R. N. *J. Chem. Soc.* **1959**, 13.
(21) Wall, L. A.; Pummer, W. J.; Fearn, J. E.; Antonucci, J. M. *J. Res. Nat. Bur. Stand.* **1963**, *67A*, 481.
(22) (a) Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem.* **1986**, *51*, 3189. (b) De la Zerda, J.; Neumann, R.; Sasson, Y. *J. Chem. Soc., Perkin Trans. 2* **1986**, 823.

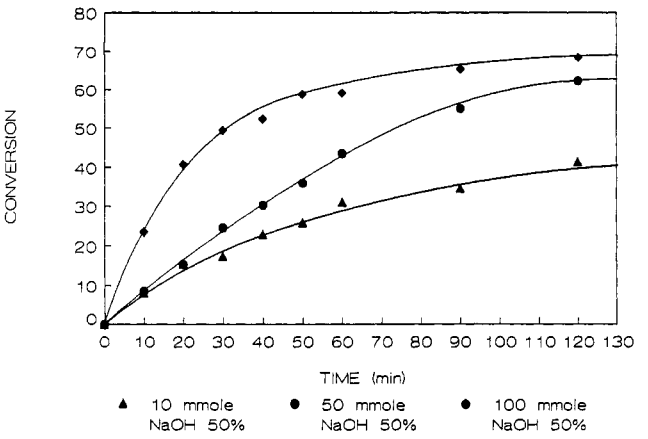


Figure 2. The influence of the base excess on the conversion of hexafluorobenzene (1).

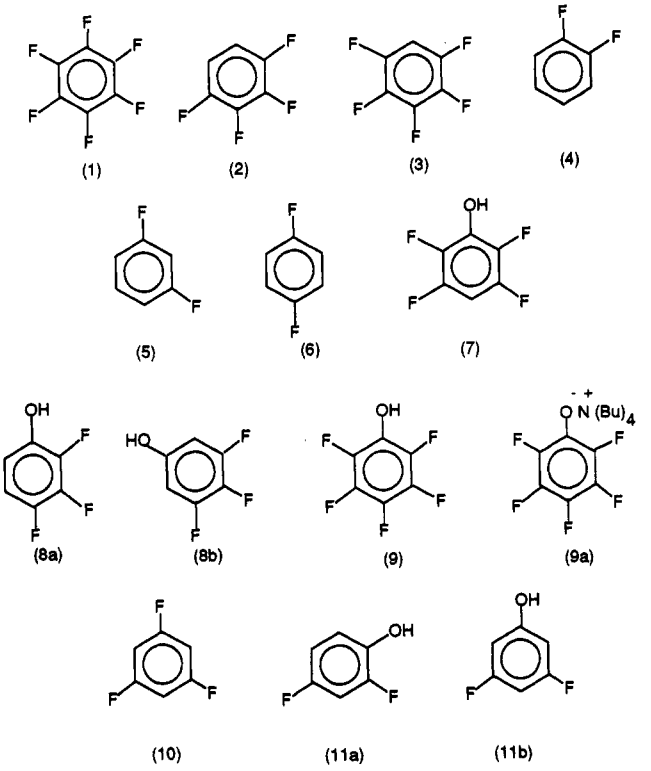
ion must be lipophilic enough to enable extraction of the ammonium salt. Therefore, $Bu_4N^+HSO_4^-$ is an efficient catalyst while $Et_4N^+HSO_4^-$ shows very little activity. The catalyst $(Oct)_4N^+Br^-$, with a lipophilic ammonium ion but a lipophilic counterion, is a very poor catalyst. Shortening of one of the butyl chains in $(Bu)_4N^+HSO_4^-$ to methyl causes a 30% decrease in the reaction conversion, probably due to the enhanced sensitivity of this ammonium ion to Hoffmann degradation.

The system is heterogenic as the phase-transfer catalyst appears to be sparingly soluble in the organic phase as well as in the aqueous phase and is present as a suspension. Nevertheless, it is essential for the reaction progress. Without the ammonium ion there is no reaction at all even at elevated temperatures and excess of alkali base. The influence of the concentration and the excess of the base is shown in Figures 1 and 2. An increase of the base concentration in the aqueous phase (Figure 1) involves a large increase of the reaction rate, probably as an outcome of an enhanced extraction of hydroxide ion into the organic phase (equilibrium II is shifted to the right, Scheme I). When a high base concentration is present, the effect of its stoichiometry on the reaction rate is moderate due to the concomitant enhancement of the decomposition of the ammonium ion (a phenomenon that can be seen in other PTC OH^- reactions as well[12]). An increase of the volume of the 50% NaOH solution increases the reaction rate (Figure 2). This rate enhancement can be rationlized by an increase of the effective OH^- concentration in the organic phase.

The nucleophilic aromatic substitution reaction is applicable to a variety of polyfluoro aromatic derivatives (Figure 3, Scheme II). The reaction was followed by UV spectroscopy, using the decrease in the absorption band of the starting material to follow the reaction progress. Under these basic conditions, the product, i.e., the fluorophenolate salt, precipitates from the organic phase (cyclohexane) and therefore cannot be detected by UV spectroscopy; only the net nucleophilic displacement could be followed, i.e., the consumed starting material.

Attempts to follow the phenolate concentration in the aqueous phase failed because the absorptions were inconsistant due to the presence of the phase-transfer catalyst. We studied the reactions of 1,2,3,4-tetrafluorobenzene (2), pentafluorobenzene (3), and hexafluorobenzene (1) in preparative scales as well. The expected phenols were isolated and identified by IR, ^1H NMR, ^{19}F NMR, and GC/MS. The products gave a purple color with 5% ferric chloride solution and released CO_2 from a saturated solution of sodium bicarbonate. It can be seen that

Scheme II. Starting Materials and Products of the Nucleophilic Aromatic Substitution of Fluorine on Polyfluorobenzene Derivatives



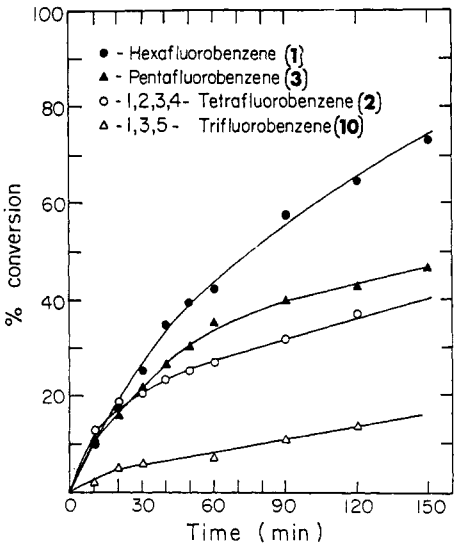


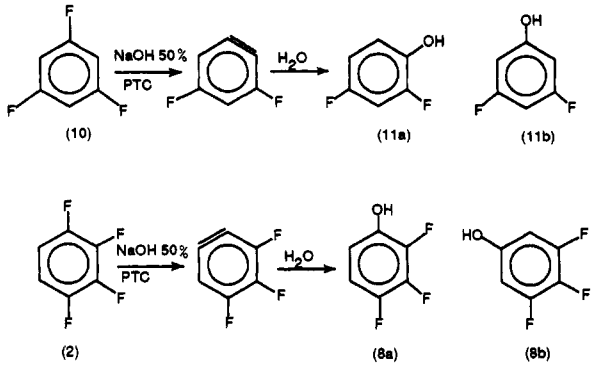
Figure 3. Nucleophilic aromatic substitution of fluorine by hydroxide ion in polyfluorobenzene derivatives.

a decrease in the number of the fluoro substituents causes a decrease in the conversion. Therefore, 1,2-difluorobenzene (4), 1,3-difluorobenzene (5), and 1,4-difluorobenzene (6) afford only a conversion of 10% while fluorobenzene does not react at all. The presence of the phenol in reactions with low conversion was identified by GC/MS only.

From ^{19}F NMR and GC/MS measurements it can be seen that only one product was obtained under the phase-transfer catalysis conditions—the product of a single nucleophilic aromatic substitution. A second nucleophilic substitution would involve a reaction with the resulting ammonium phenoxide which is negatively charged.

The ^{19}F NMR spectrum of the product of pentafluorobenzene (3), i.e. 2,3,5,6-tetrafluorophenol (7), indicates that

Scheme III. Nucleophilic Aromatic Substitution by Hydroxide Ion in an Elimination–Addition Mechanism



the nucleophilic substitution occurs only at the position para to the hydrogen atom. It may be rationalized by the ability of the fluorine atom to release electrons.[23-25] Thus, the reaction occurs at the position of lowest negative charge density, i.e. para to the hydrogen atom.[23] As other parameters may also play a role in the orientation of the attacking nucleophile, the identified product of 1,2,3,4-tetrafluorobenzene (**2**) was 2,3,4-trifluorophenol (**8a**) (^{19}F NMR).

Polyfluoro- and perfluorophenoxides can also react with fluoro aromatics to obtain the ether derivatives.[26-28] However, these reactions which are performed in the presence of aprotic polar solvents, high temperatures, or reflux conditions do not occur under PTC conditions. The pentafluorophenoxide (**9a**) is a weak nucleophile and under the basic reaction conditions is obtained as a salt which precipitates from the organic medium. The Hoffman degradation of the ammonium catalyst affords tributylamine which under high temperature and pressure may further react with fluorobenzene.[21] We find that this reaction does not occur under mild PTC conditions.

Two possible mechanisms can be suggested for the nucleophilic aromatic substitution under these strong basic conditions: (a) bimolecular displacement, S_NAr, and (b) Elimination–addition (benzyne) mechanism.

The observation that fluoro derivatives react better than the chloro derivatives points to a bimolecular displacement. Hexafluorobenzene (**1**) cannot react in an elimination–addition mechanism. In the case of the tri- and tetrafluorobenzene derivatives, i.e. **10** and **2**, respectively, only one product was obtained instead of the two expected products from the elimination–addition mechanism (^{1}H NMR, ^{19}F NMR, GC) (Scheme III).

Conclusion

The extraction of hydroxide ion under phase-transfer catalysis conditions affords an extremely strong nucleophile. This enhanced nucleophilicity was applied for fluorine displacement in nucleophilic aromatic substitution of polyfluorobenzene derivatives. These observations are the first demonstration of a direct nucleophilic aromatic substitution by OH^- under PTC conditions and suggest a convenient method for the synthesis of polyfluorophenol derivatives under mild conditions.

Experimental Section

Materials and Spectroscopy. The polyfluorobenzenes and catalysts are commercially available and of a high degree of purity. They were applied without further purification.

NMR spectra were recorded with the aid of a Bruker WH-300 specterometer operating at 300.133 MHz for protons and 282.200 MHz for fluorine. $SiMe_4$ served as a standard for proton absorptions and hexafluorobenzene for fluorine absorptions.

(a) Standard Procedure: Nucleophilic Aromatic Substitution. Into a 25-mL flask were placed 2 mmol of the fluoroaromatic substrate, 680 mg (2 mmol) of $Bu_4N^+HSO_4^-$, 800 mg (10 mmol) of 50% NaOH solution, and 5 mL of cyclohexane (spectroscopic grade). The 50% NaOH solution was introduced immediately after the first sample (t = 0) was taken. The reactions were carried out in a thermostated bath (25 ± 1 °C) with strong magnetic stirring. The flask was equipped with a reflux condenser to prevent substrate and solvent evaporation. The reaction progress was followed by UV spectroscopy. Samples of 40 μL were taken from the organic phase in constant time intervals and diluted to 10 mL with cyclohexane. The decrease of the absorption of the substrate was determined.

A calibration curve was prepared for each of the substrates to assure linearity during all the measured concentration range. The UV measurements were taken in the following wavelengths: hexafluorobenzene (**1**) at 229 nm; pentafluorobenzene (**3**) at 259 nm; 1,2,3,4-tetrafluorobenzene (**2**) at 259 nm; 1,3,5-triflurobenzene (**10**) at 251 nm; 1,2-difluorobenzene (**4**) at 265 nm; 1,3-difluorobenzene (**5**) at 264 nm; and 1,4-difluorobenzene (**6**) at 272 nm.

The reaction products were identified by ^{1}H and ^{19}F NMR, IR, and GC/MS after acidification with concentrated HCl, extraction with diethyl ether, and evaporation of the solvent.

(b) Kinetic Studies. The effect of the catalyst concentration on the reaction of hexafluorobenzene (**1**) was examined after 2 h with 0.4, 1, and 2 mmol of $(Bu)_4N^+HSO_4^-$. The effect of the temperature was studied in a thermostated bath (±0.5 °C) at 25 °C and 50 °C. The influence of the nature of the phase-transfer catalyst was studied by the comparison of the conversion of hexafluorobenzene (**1**) after 2 h in the presence of 2 mmol of one of the following phase-transfer catalysts: $(Bu)_4N^+HSO_4^-$, $Me(Bu)_3N^+HSO_4^-$, $(Et)_4N^+HSO_4^-$, $(Bu)_4N^+Br^-$, and $(Oct)_4N^+Br^-$.

The effect of the concentration of the base was studied by the addition of 5 mL of 25, 40, and 50% (w/w) NaOH solution in a series of experiments at the standard reaction conditions. The effect of the base was studied by addition of an excess of 10, 50, and 100 mmol of 50% NaOH solution in each experiment.

(c) Preparative-Scale Experiments. Reaction conditions: 20 mmol of substrate, 6.8 g (20 mmol) of $(Bu)_4N^+HSO_4^-$, 8 g (100 mmol) of 50% w/w NaOH solution, and 50 mL of cyclohexane as solvent.

The reactions were carried out in 100-mL round-bottomed flasks with vigorous magnetic stirring at 50 °C (in a thermostated bath). The workup was performed by the addition of 50 mL of diethyl ether and 50 mL of water. Three layers were obtained: an ether layer (top), an aqueous layer (bottom), and an oily layer in between. The ethereal phase was washed with water and separated. The aqueous phase together with the oil layer were acidified with concd HCl and extracted with diethyl ether (3 × 50 mL). In some cases additional diethyl ether was needed to dissolve all the oily residue. The organic layer was separated, dried over magnesium sulfate, and filtered. The solvent was evaporated under vacuum. The product (yellow oil) was distilled under reduced pressure at 50–90 °C.

Reaction of Hexafluorobenzene (1). A total of 2.6 g (71%) of white crystals was obtained. The product was identified as pentafluorophenol (**9**) (^{19}F NMR, GC/MS, and IR). ^{19}F NMR ($CDCl_3$): δ 7.47 (tt, $J_{3,4}$ = 21.8 Hz, $J_{2,4}$ = 5.7 Hz, 1 F), 2.46 (dd, $J_{3,4}$ = 21.8 Hz, $J_{2,3}$ = 21.7 Hz, 2 F), 1.15 (dd, $J_{2,3}$ = 21.7 Hz, $J_{2,4}$ = 5.7 Hz, 2 F). IR (CCl_4): ν_{max} (cm^{-1}) 3645, 3560, 3270 (broad) (OH), 1520 (C–F), 1010, 995, 950 (C–F). GC/MS:[29] m/e 184 (M), 155 (M–COH), 136, 117.

(23) Tatlow, J. C. *Endeavour* **1963**, *22*, 89.
(24) Yakobson, G. G.; Vlasov, V. M. *Synthesis* **1976**, 652.
(25) Brooke, G. M.; Furniss, B. S.; Musgrave, W. K. R.; Quasem, Md. A. *Tetrahedron Lett.* **1965**, 2991.
(26) Buxton, M. W.; Mobbs, R. H.; Wotton, D. E. M. *J. Fluorine Chem.* **1972/73**, *2*, 387.
(27) De Pasquale, R. J.; Tamborski, C. *J. Org. Chem.* **1967**, *32*, 3163.
(28) Pummer, W. J.; Wall, L. A. *J. Res. Nat. Bur. Stand.* **1964**, *68A*, 277.
(29) Heller, S. R.; Milne, G. W. A. EPA/NIH Mass Spectral Data Base, U.S. Dept. of Commerce, N.B.S., p 960.

Reaction of Pentafluorobenzene (3). A total of 2.3 g (68%) of white solid was obtained. The product was identified as 2,3,5,6-tetrafluorophenol (7) (^{1}H NMR, ^{19}F NMR, GC/MS, and IR). ^{19}F NMR ($CDCl_3$): δ 1.34 (m, 2 F), -21.31 (m, 2 F). ^{1}H NMR ($CDCl_3$): δ 6.62 (m, 1 H), 5.5 (broad s, 1 H). IR (CCl_4): ν_{max} (cm^{-1}) 3670, 3560, 3200 (broad) (OH), 1640, 1560, 1500 (C-F), 1085, 935 (C-F). GC/MS: *m/e* 166 (M), 137 (M - COH), 118, 99, 68.

Reaction of 1,2,3,4-Tetrafluorobenzene (2). After 3.5 h, standard workup, and distillation, 1.3 g of 2,3,4-trifluorophenol (**8a**) was obtained (44% yield). ^{19}F NMR ($CDCl_3$): δ -4.64 (dd, $J_{2,3}$ = 20.4 Hz, $J_{2,4}$ = 6.75 Hz, 1 F), -20.5 (dd, $J_{2,3}$ = 20.4 Hz, $J_{3,4}$ = 13 Hz, 1 F), -21.27 (dd, $J_{3,4}$ = 13 Hz, $J_{2,4}$ = 6.75 Hz, 1 F). Decoupling of the protons afforded only ortho-coupled fluorine atoms. ^{1}H NMR ($CDCl_3$): δ 6.82 (m, 1 H), 6.66 (m, 1 H), 5.7 (broad s). IR (CCl_4): ν_{max} (cm^{-1}) 3640, 3570, 3270 (broad) (OH), 1630, 1505 (C-F), 980, 969 (C-F). GC/MS: *m/e* 148 (M), 128 (M - HF), 119, 100, 81.

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Registry No. 1, 392-56-3; 2, 551-62-2; 3, 363-72-4; 4, 367-11-3; 5, 372-18-9; 6, 540-36-3; 7, 769-39-1; 8a, 2822-41-5; 8b, 99627-05-1; 9, 771-61-9; 10, 372-38-3; 11a, 367-27-1; 11b, 2713-34-0; tetrabutylammonium hydrogen sulfate, 32503-27-8; tributylmethylammonium hydrogen sulfate, 79494-37-4; tetrabutylammonium bromide, 1643-19-2; tetraoctylammonium bromide, 14866-33-2; tetraethylammonium hydrogen sulfate, 16873-13-5.

Supplementary Material Available: ^{19}F NMR, IR, and mass spectra of compounds 7, 8, and 9 (9 pages). Ordering information is given on any current masthead page.

A New Abietane Diterpene from *Salvia wiedemannii* Boiss

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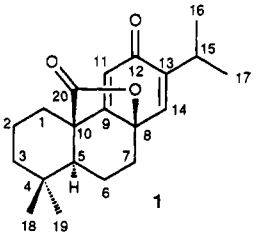
Species of *Salvia* (Labiatae) are prominent members of the pharmacopia of numerous countries throughout the world.[1] Perhaps the best known example is *S. miltiorrhiza*, Chinese sage, from the roots of which numerous abietanoid diterpenes have been isolated which are thought to be the active components of the medicine prepared from this species.[2] *Salvia* species are also commonly employed as traditional medicines in Turkey, where 87 different species are found, 44 of which are endemic to Turkey.[3] One of these latter species is *S. wiedemannii*, which has also yielded abietanoid diterpenes from the extract of the aerial parts of the plant.[4] Further examination of this extract has led to the isolation of a new abietane diterpene **1** which bears the intriguing cross-conjugated dienone functionality.



1

The appearance of 20 carbons in the ^{13}C NMR spectra[5] and the high-resolution mass spectrum, which showed a molecular ion *m/z* 314.1854 requiring a molecular formula of $C_{20}H_{26}O_3$ and therefore eight units of unsaturation, suggested a diterpene with two trisubstituted double bonds (δ 115.5, d, and 165.9, s; 148.0, s, and 135.2 d), a lactone group (^{13}C NMR δ 175.5; IR 1785 cm^{-1}), and a conjugated ketone (^{13}C NMR δ 184.4; IR 1640 cm^{-1}). The appearance of an isopropyl group as one of the double-bond substituents as suggested by the downfield shift of the methine proton (^{1}H NMR δ 1.03 and 1.07, both d, J = 6.8 Hz; δ 2.97, sept, J = 6.8; ^{13}C NMR δ 21.4 and 21.8, both q; δ 26.5, d) was highly reminescent of an abietane skeleton. The COSY (homonuclear correlation) and HETCOR (one-bond ^{1}H/^{13}C heteronuclear correlation) spectra enabled the two isolated spin systems of C-1 through C-3 (three sequential methylene groups), and C-5 through C-7 (a methine and two methylenes in sequence) to be delineated. A FLOCK spectrum[6] (for long-range ^{1}H/^{13}C heteronuclear scalar correlation) which showed three-bond coupling from H-18 to C-19, and from H-19 to C-18 confirmed the geminal nature of the methyl singlets in the ^{1}H NMR spectrum (the one-bond couplings were originally assigned from the HETCOR spectrum). Long-range heteronuclear couplings also apparent in this spectrum indicated that the *gem*-dimethyl group connected the two spin systems (C-1 through C-3 and C-5 through C-7) by couplings between both H-18 and H-19 with C-3, C-4, and C-5.

These observations indicated the typical abietane nature of the A and B rings, with the angular C-20 oxidized to a lactone carbonyl (δ 175.5), similar to that found in carnosol,[7] with the remaining units of unsaturation (two double bonds and the ketone) located in the C ring. The coupling between H-5 and the H-6 protons ($J_{5,6\beta}$ = 12.2 Hz, $J_{5,6\alpha}$ = 5.1 Hz, Table I) confirmed the axial orientation of H-5 (relative to the B ring) and hence the trans stereochemistry of the A,B ring fusion, as expected. The location of the lactone carbonyl at C-20 was supported by long-range heteronuclear couplings to this carbonyl carbon (δ 175.5) from H-1α and H-5 observed in the cross-section at the C20 resonance frequency of the FLOCK spectrum.

(1) (a) Grieve, M. In *A Modern Herbal*; Dover: New York, 1971; Vol. II, pp 700-707. (b) Morton, J. F. In *Atlas of Medicinal Plants of Middle America*; Charles C. Thomas, Publisher: Springfield, IL, 1981; pp 780-784. (c) Duke, J. A. In *Handbook of Medicinal Herbs*; CRC Press, Inc.: Boca Raton, FL, 1985; pp 118, 419-422. (d) In *Pharmacology and Applications of Chinese Materia Medica*; Chang, H. M., But, P. P. H., Eds.; World Scientific: Singapore, 1986; Vol. 1, pp 255-268.

(2) See: Chang, H. M.; Cheng, K. P.; Choang, T. F.; Chow, H. F.; Chui, K. Y.; Hon, P. M.; Tan, F. W. L.; Yang, Y.; Zhong, Z. P.; Lee, C. M.; Sham, H. L.; Chan, C. F.; Cui, Y. X.; Wong, H. N. C. *J. Org. Chem.* **1990**, *55*, 3537 and references therein.

(3) Davis, P. H. In *Flora of Turkey and East Aegean Islands*; Edinburgh University Press: Edinburgh, 1982; Vol. 7, pp 400-459.

(4) (a) Topcu, G.; Ulubelen, A. *Phytochemistry* **1990**, *29*, 2346. (b) Topcu, G.; Ulubelen, A. *Phytochemistry* **1991**, *30*, 2412.

(5) Only eighteen signals appeared in the ^{13}C NMR spectrum due to the overlap of two signals at δ 20.1 and at 26.4. Since the overlapped signals were of different multiplicity in each case, both the APT and the DEPT spectra revealed the resonances for the carbons which appeared at each of these chemical shifts. (See Table I for complete assignments.)

(6) Reynolds, W. F.; McLean, S.; Perpick-Dumont, M.; Enriquez, R. G. *Magn. Reson. Chem.* **1989**, *27*, 162.

(7) Brieskorn, C. H.; Fuchs, A.; Bredenberg, J. B.; McChesney, J. D.; Wenkert, E. *J. Org. Chem.* **1964**, *29*, 2293.

0022-3263/91/1956-7354$02.50/0