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High pressure nucleophilic fluoride-ion substitution reactions: formation of fluoroalkylbenzenes

John M. Gerdes [a,*], Robert N. Keil [b], Alexander T. Shulgin [c], Chester A. Mathis [a]

[a] *PET Facility, Department of Radiology, University of Pittsburgh, 200 Lothrop Street, Pittsburgh, PA 15213-2582, USA*

[b] *PET Center, Department of Radiology, Emory University Hospital, 1364 Clifton Road NE, Atlanta, GA 30322, USA*

[c] *1483 Shulgin Road, Lafayette, CA 94549, USA*

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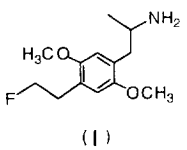
Abstract

A series of 1-phenyl-2-tosyloxy- and 1-phenyl-3-tosyloxyalkanes was synthesized and then subjected to tetrabutylammonium fluoride in THF under 15 kbar (1.5 GPa), 8 kbar or 1 bar pressures. The resultant substitution and elimination reaction product distributions were analyzed. The application of pressure enhanced the progress of the fluoride-ion substitution reactions. The degree of selectivity of the one reaction over the other was found to be a function of tosylate substrate structure and the amount of pressure applied. The exclusive formation of fluoroalkanes from 1-phenyl-2-tosyloxyalkane substrates under 15 kbar pressure demonstrated the potential of the pressure method for prospective use in fluorine-18 radiolabelling applications.

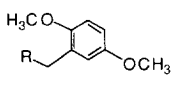
Keywords: High-pressure reactions; Nucleophilic substitution; Fluoroalkylbenzenes; NMR spectroscopy; IR spectroscopy

1. Introduction

The incorporation of fluorine atoms at selective molecular sites of central nervous system (CNS) pharmaceuticals can provide agents with potent biological activities [1]. Analogs radiolabelled with fluorine-18 (^{18}F, $t_{1/2} = 110$ min) can serve as useful ligands for imaging in vivo biological processes employing positron emission tomography (PET) [2,3]. High specific activity ^{18}F-labelled agents are required to quantify CNS ligand–receptor complexes with PET [2–4]. Radiosyntheses utilize no-carrier-added (NCA) conditions in which substrates are labelled by nucleophilic fluoride ion ([^{18}F]KF, Kryptofix®-222, K_2CO_3) substitution reactions under basic buffered conditions [4]. Elevated temperatures (≥ 40 °C) are employed to expedite the incorporation of the short-lived isotope. During non-radioactive (cold) nucleophilic fluorination reaction [5–7] studies with substrate **2** (Scheme 1) aimed at the eventual synthesis of the serotonergic PET ligand [^{18}F]**1** [8,9] (Chart 1),



(**1**)



(**5**) R = CH_2OTs
(**6**) R = $CH(OTs)CH_3$
(**7**) R = CH_2CH_2OTs
(**8**) R = $CH_2CH(OTs)CH_3$

we observed the formation of the fluoroalkyl adduct **3** (55%) and styrene **4** (18%) [8]. The formation of **3** and **4** may be rationalized by competition between fluoride-anion substitution (Sn2) and elimination (E2) reaction processes [5,10]. Similar competitive synthetic difficulties were experienced during the syntheses of fluoroalkylbenzene ligands for the dopamine system [11].

The product distribution (**3** and **4**) is not surprising since the fluoride-ion is able to function as both a nucleophile [5–7,10] and a base [10,12], and 1-phenyl-2-tosyloxyethanes have a propensity to undergo elimination reactions [11,13,14]. Profiles of competitive Sn2 and E2 reactions are known to be influenced by a host of variables [10,13,14] encompassing reaction temperatures, medium effects, nucleofuge types, fluoride counterion variability and substrate reactivities such as steric hindrance at the reacting center, effects of neighboring group phenyl rings and acidities

* Corresponding author. Present address: Department of Chemistry, Central Washington University, 400 E. 8th Avenue, Ellensburg, WA 98926-7539, USA.

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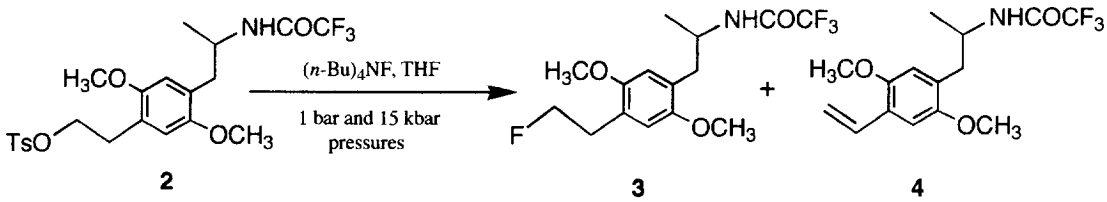

2 3 4

Scheme 1. Synthesis of the amphetamine precursor 3.

of nearby protons. While increased fluoroalkyl/alkene product ratios can be achieved by modulating a number of these reaction variables [4,10,11], the formation of unwanted alkene products can be problematic [4,10]. In an effort to overcome this limitation we considered varying the pressure [15–17] on the nucleophilic fluoride-ion substitution processes.

The influence of pressure on reaction rate constants (k) follows the relationship described in Eq. (1) [17], where $\Delta V^{\ddagger}$ ($cm^3\ mol^{-1}$) is the reaction volume of activation defined as the volume difference between the transition state and reactants. Reactions characterized with negative $\Delta V^{\ddagger}$ values are accelerated under pressure [15–18]. Activation volume is defined [Eq. (2)] as the sum of the van der Waals volumes of the reactants ($\Delta V_1^{\ddagger}$) and solvation ($\Delta V_2^{\ddagger}$) terms [17]. The $\Delta V_1^{\ddagger}$ term is the difference between the total partial molar volumes of all reactants participating in bond-making or -breaking processes and the reaction transition state. The $\Delta V_2^{\ddagger}$ parameter accounts for changes in the degree of solvent ordering and charge dispersion through the medium, otherwise known as electrostriction. The literature is devoid of $\Delta V^{\ddagger}$ values for fluoride-ion-induced Sn2 and E2 reactions. However, activation volumes for analogous reactions are known [15–19]. For Sn2 processes in which no charges are created or destroyed by neutral substrates undergoing displacements with anions, $\Delta V^{\ddagger}$ values range between -5 and $-15\ cm^3\ mol^{-1}$ [17–19]. For E2 reactions, volumes of activation range between -1 and $-12\ cm^3\ mol^{-1}$ [17,18]. These analogies suggested that both Sn2 and E2 fluoride-ion-induced reactions should be accelerated with pressure[1].

$$\frac{\partial \ln k}{\partial P} = \frac{-\Delta V^{\ddagger}}{RT} \quad (1)$$

$$\Delta V^{\ddagger} = \Delta V_1^{\ddagger} + \Delta V_2^{\ddagger} \quad (2)$$

Selective rate enhancement of one reaction over another is possible if differences between respective $\Delta V^{\ddagger}$ values exist [15–17]. Furthermore, reaction solvent choice is critical since altered electrostriction profiles ($\Delta V_2^{\ddagger}$) can greatly influence the overall reaction $\Delta V^{\ddagger}$ value for either process [15–17]. In addition, $\Delta V^{\ddagger}$ values may themselves be pressure-dependent under high-pressure conditions [17]. With these criteria in mind, we examined the effects of high pressure on competitive nucleophilic fluoride-ion substitution and elimination reaction processes in order to assess the potential of using pressure to enhance the formation of [^{18}F]fluoroalkyls.

[1] Fluoride ion functions as a base under pressure [20].

The study encompassed subjecting phenylalkyl tosylates **5–8** (Chart 1) to cold fluoride anion in tetrahydrofuran (THF) under 15 kbar (1.5 GPa) and 8 kbar pressures and measuring the resultant reaction product distributions. Substrates **5–8** were selected based on their similarity to the amphetamine analog **1** and structural variability such as neighboring group phenyl rings and α-branching near the reacting centers. Tetrabutylammonium fluoride (TBAF) and THF were chosen as fluoride-ion source [10,20–22] and solvent in order to enhance solubilities at elevated pressures [15,17]. Additionally, the effect of pressure on the ionization of TBAF was thought to be favorable since the related tetraethylammonium iodide possesses a negative $\Delta V^{\ddagger}$ of dissociation ($-17\ cm^3\ mol^{-1}$) [18]. For the reaction processes, the modest polarity of THF was thought to offer favorable electrostriction profiles [15].

2. Results and discussion[2]

The syntheses of tosylate substrates **5–8** required the preparation of the corresponding alcohols **9–12** shown in Table 1. The alcohols were synthesized from the known starting materials **13–16**. Borohydride reduction of acid chloride **13**[3] provided 2-arylethyl alcohol **9**. Formation of the lithium anion [24] of 2,5-dimethoxybenzene[3] and subsequent anion quench with propylene oxide [25] yielded the 2-propanol **10**. The 1-propanol **11** was synthesized by hydride reduction of methyl cinnamate **15** [26]. The 3-butanol **12** was prepared by a two-step procedure [27]. Condensation of 2,5-dimethoxybenzaldehyde (**16**)[3] with acetone provided the corresponding 1-phenyl-1-buten-3-one adduct (53% yield, structure not shown) which was subsequently reduced with hydride to yield **12** (70%). Tosylates **5–8** were generated from the alcohols **9–12** utilizing p-toluenesulfonyl chloride and pyridine [28] followed by column chromatographic purifications (**5**, 74%; **6**, 82%; **7**, 79%; and **8**, 50%).

The reaction product distributions, resulting from treating substrates **5–8** to fluoride-ion in THF under several pressures, are summarized in Table 2. For all reactions, pure tosylates (0.10 mmol) were allowed to react with a slight excess of dry [10] TBAF (0.11 mmol) in anhydrous THF (1 ml). The room-temperature 15 kbar (16 h) and 8 kbar (8 h) high-

[2] During the course of our studies, a new and completely anhydrous tetraalkylammonium fluoride reagent was described [23].

[3] Commercially available from Aldrich Chemical Co., Milwaukee, WI, USA.

Table 1
Syntheses of the phenylalkanols **9–12**

Phenylalkanol [a]	Reaction conditions (yield) [b]	Starting material [c]
$ArCH_2CH_2OH$ (**9**)	$NaBH_4$, THF (74%)	$ArCH_2COCl$ (**13**)
$ArCH_2CH(OH)CH_3$ (**10**)	(a) BuLi, THF (b) propylene oxide (63%)	ArH (**14**)
$ArCH_2CH_2CH_2OH$ (**11**)	$LiAlH_4$, Et_2O (82%)	$ArCH=CHCO_2CH_3$ (**15**)
$ArCH_2CH_2CH(OH)CH_3$ (**12**)	(a) Acetone, NaOH (b) $LiAlH_4$, Et_2O (37%) [d]	ArCHO (**16**)

[a] Ar = 2,5-dimethoxyphenyl.
[b] Yields are isolated and unoptimized.
[c] See text for starting material sources.
[d] Combined two-step yield.

pressure runs were accomplished with the technology described previously [29][4]. The elevated pressure reaction times were chosen based on pressure apparatus availability[5]. Atmospheric 1 bar control reactions were performed under an argon atmosphere at both 20 °C (168 h) and 40 °C (24 h). The extended duration (168 h) 1 bar pressure, 20 °C reactions were employed in an attempt to optimize the progress of the substitution reaction. All resultant product mixtures were separated and purified by high-performance liquid chromatography (HPLC) and the yields reported are based on the weights of isolated products. The alkenes **23** (entry No. 4) were inseparable by HPLC (normal or reverse phase) and preparative gas chromatography (GC). The alkene mixtures were characterized by analytical GC mass spectrometry (MS) and proton NMR spectroscopy. Their combined yields are reported as single values.

Distinct product distributions were obtained for the reaction of the 1-phenyl-2-tosyloxyethane **5** (entry No. 1) with fluoride ion at various pressures. At all pressures, the starting

[4] Commercial high-pressure equipment is available from several sources. Semi-preparative and preparative high-pressure apparatuses which operate between 5–10 kbar pressures are available from Harwood Engineering Co. Inc., South St., Walpole MA 02081, USA and Tem-Press Division, Leco Corporation, Bellefonte, PA 16823, USA.

[5] The 8 kbar reactions were performed under the auspices of Mr. J. Holthuis, MCS Division, Lawrence Berkeley Laboratory, Berkeley, CA. The 15 kbar reactions were accomplished with the equipment of Prof. William G. Dauben, Department of Chemistry, University of California, Berkeley, CA.

Table 2
Fluoride-ion substitution and elimination reactions of phenylalkyltosylates **5–8** under high and 1 bar pressures [a]

Entry No.	Tosylate starting material [b]	Reaction products [b]	High-pressure yields (%) [c]		1 bar Control yields (%) [c]	
			15 kbar, 20 °C, 16 h	8 kbar, 20 °C, 8 h	20 °C, 168 h	40 °C, 24 h
1	$ArCH_2CH_2OTs$ (**5**)	$ArCH_2CH_2F$ (**17**)	69	36	38	42
		$ArCH=CH_2$ (**18**)	0	45	26	45
		recovered (**5**)	0	0	0	0
2	$ArCH_2CH(OTs)CH_3$ (**6**)	$ArCH_2CH(F)CH_3$ (**19**)	34	15	9	6
		(*E*)-$ArCH=CHCH_3$ (**20**)	59	47	34	38
		recovered (**6**)	0	17	33	28
3	$ArCH_2CH_2CH_2OTs$ (**7**)	$ArCH_2CH_2CH_2F$ (**21**)	89	92	84	90
		recovered (**7**)	0	0	0	0
4	$ArCH_2CH_2CH(OTs)CH_3$ (**8**)	$ArCH_2CH_2CH(F)CH_3$ (**22**)	63	60	32	51
		$ArCH_2CH_2CH=CH_2$ (**23a**)	25 [d]	21 [d]	0	13 [d]
		(*E* and *Z*)-$ArCH_2CH=CHCH_3$ (**23b, 23c**)				
		recovered (**8**)	0	16	58	30

[a] Reactions were carried out using a 0.10 mmol:0.11 mmol:1.0 ml ratio of tosylate **5–8**/$^nBu_4NF$/THF.
[b] Ar = 2,5-dimethoxyphenyl.
[c] Yields are based on the weights of isolated products and are unoptimized.
[d] Combined yield of alkenes **23a–c**.

material **5** proved reactive (and/or labile) in that the starting material was not recovered. At the 8 kbar and 1 bar pressures, the desired fluoroalkyl **17** and undesired styrene **18** [30] were obtained. Overall reaction progress (combined yields of fluoroalkyl + alkene) fell within a similar range at 8 kbar (81%) and 1 bar (20 °C, 64% and 40 °C, 87%) pressures. A comparison of the relative ratios of **17/18** revealed modest selective formations of one product over the other at these pressures (8 kbar, 1:1.3; 1 bar 20 °C, 1.5:1 and 1 bar 40 °C, 1:1.1). The formation of a greater amount of the alkene **18** at 1 bar pressure and 40 °C relative to 20 °C is in accord with the observations that increased temperatures enhance E2 elimination processes [13]. When the reaction was subjected to 15 kbar pressure, only the desired fluoroalkyl product **17** was obtained (69%)[6]. The difference between the substitution and elimination reaction $\Delta V^{\ddagger}$ values at 15 kbar pressure may be greater than the difference between these volumes of activation at 8 kbar pressure. A large difference of activation volume values at the higher pressure (15 kbar) may be indicative that either or both of the substitution and elimination $\Delta V^{\ddagger}$ values are pressure-dependent.

The addition of an α-methyl group to the substrate reacting center, as in tosylate **6** (entry No. 2), resulted in different substitution/elimination product distributions as compared to those in entry No. 1. At all pressures, the more encumbered **6** afforded both fluoroalkane **19** and alkene **20** [31] products. Only the 15 kbar experiment resulted in the complete consumption of tosylate **6**. The reactions under high pressure (15 kbar, 93% and 8 kbar, 62%) progressed further than those reactions at atmospheric pressure (20 °C, 43% and 40 °C, 44%). A comparison of the fluoroalkyl/alkene (**19/20**) product distributions at 15 kbar (1:1.7), 8 kbar (1:3.1) and 1 bar (20 °C, 1:3.8 and 40 °C, 1:6.3) demonstrates pressure-enhanced formation of product **19** even though elimination product formation predominates. The different product selectivities obtained under 15 kbar pressure for entry Nos. 1 and 2 reflect the effect of the addition of an α-methyl group to the reacting center. The lack of selectivity for substitution product formation (entry No. 2, 15 kbar) is thought to be a result of increased steric hindrance at the substitution reacting center [13] and possibly similar substitution and elimination $\Delta V^{\ddagger}$ values for substrate **6**.

As shown in entry No. 3, the exclusive formation of the 1-phenyl-3-fluoropropane **21** (entry No. 3) from tosylate **7** at all pressures and temperatures [6] demonstrates the benefit of moving the aromatic ring one carbon further away from the reacting center as compared to substrate **5** (entry No. 1). The dramatically different reactivities observed between the 1-phenyl-2-tosyloxy- and 1-phenyl-3-tosyloxyalkanes (**5** and **7**) to fluoride ion have also been noted in other syntheses [11]. The results support the notion that the ease with which the 1-phenyl-3-fluoropropane motif (**21**) is generated by nucleophilic fluoride-ion substitution makes this a favored moiety for PET [^{18}F]fluoropropyl-substituted ligands [11]. Addition of an α-methyl group to the substrate, as in the tosylate **8** (entry No. 4), results in loss of exclusive substitution reaction. At 8 kbar and 1 bar pressures, tosylate **8** failed to react completely and provided the fluoroalkyl **22** and alkenes **23**. The characteristic analytical GC elution profiles and integrations for **23** (2.0:1.5:1.0) revealed virtually no changes in the relative ratios of the alkene products at the various pressures.

The reaction progress of **8** (entry No. 4) was extensive at 15 kbar (88%), 8 kbar (81%) and 1 bar, 40 °C (64%) pressures. Similar substitution/elimination (**22/23**) product selectivities favoring substitution were observed under pressure (15 kbar, 2.5:1 and 8 kbar, 2.9:1). Under atmospheric pressure conditions, selectivities were different from one another in that at 20 °C only the fluoroalkane **22** was produced while at 40 °C a mixture of **22/23** (3.9:1) was obtained. A comparison of the substitution/elimination product distributions at 15 and 8 kbar pressures in entry No. 4 to those obtained in entry No. 2 reveals the positional effect that the neighboring aromatic ring has on these α-methyl branched substrates. Under pressure, when the ring is two carbons away from the reacting center (entry No. 4) substitution is favored over elimination, whereas when the ring is distal by one carbon (entry No. 2) elimination reaction predominates. The propensity for the formation of only a conjugated alkene in entry No. 2 (**20**) compared to the multitude of unconjugated alkenes produced in entry No. 4 (**23**) is noteworthy. These limited comparative observations indicate that α-branched substrates which fail to afford conjugated alkenes also demonstrate greater selectivity for fluoride-ion substitution reaction.

The exclusive formation of substitution product **17** at 15 kbar pressure (entry No. 1) prompted us to evaluate the production of the amphetamine precursor **3** (Scheme 1) under 15 kbar pressure for a short time akin to the duration utilized in radiofluorination. Treatment of **2** with dry TBAF (110 mol%) in THF at 15 kbar pressure for 1 h afforded the desired substitution product **3** (75%) and recovered starting material **2** (10%). Formation of the styrene **4** was not observed under pressure[6] but was obtained in the 1 bar control reactions. The reaction performed under 1 bar pressure at 40 °C [8] resulted in complete consumption of the starting material **2** and afforded both fluoroalkyl **3** (55%) and styrene **4** (18%). When the control reaction was carried out at 20 °C (168 h), **3** (43%) and **4** (23%) were obtained (recovered **2** was not observed). It appears that the 1-phenyl-2-tosyloxyethane substrates (**5** and **2**) are sufficiently reactive (and/or labile) not to be observed in the respective reaction product mixtures. However with high pressure at short duration (1 h), a small amount of the normally reactive substrate **2** is recovered.

Extension of these high-pressure findings conducted at 0.1 mmol concentrations to radiofluorinations conducted at nanomol concentrations of [^{18}F]fluoride requires consideration of experimental aspects which are unique to NCA

[6] The corresponding alkene was not detected by ^{1}H NMR spectroscopy or HPLC analysis.

radiolabelling reactions [4]. In the NCA case, the tosylate is present in more than 1000-fold excess over [^{18}F]fluoride and the reactions are performed under basic buffered conditions (Kryptofix®-222, K_2CO_3). If the elimination reaction rate constant is relatively large, macroscopic quantities of the alkene can be formed regardless of whether fluoride ion or the basic buffer assists the NCA elimination reaction. While the alkene does not contain an ^{18}F radiolabel, it may well compete with the radiofluorinated compound for the binding site in vivo. The presence of a potent, competitive ligand in the final product leads to a decrease in the *effective* specific activity of the radiopharmaceutical [4]. Hence, the alkene must be removed prior to radiotracer administration. Semi-preparative HPLC is often used to effect the separation and removal of reaction precursors and side-products. In practice, it is sometimes difficult to separate compounds quantitatively with relatively small lipophilicity differences such as alkenes and [^{18}F]fluoroalkyl ligands; more so when ligand molecular weights exceeds 300. The high-pressure reaction cylinders used in this work could easily be adapted to fit within the confines of a radiolabelling hot cell[4,5] whereby the reactions could be remotely conducted.

In summary, the series of tosylates **5–8** were easily generated from the available starting materials **13–16**. For substrates **5–8**, the use of high pressure imparts favorable effects on the competition between substitution (S_N2) and elimination (E2) reaction processes by enhancing the fluoride-ion substitution reaction. The observed pressure reaction selectivities appear to be a function of substrate structure, including neighboring group phenyl rings and α-branching near the reacting centers, and the amount of pressure applied. The optimal substrate for fluoride-ion substitution reaction was **7** which underwent substitution reaction exclusively at all pressures (1 bar–15 kbar) to afford only the desired fluoropropane **21**. The ease with which the 1-phenyl-3-fluoropropane moiety is generated with fluoride ion makes this structural motif an excellent choice for [^{18}F]fluoroalkyl-substituted PET ligands. For other substrates which have a propensity to undergo elimination, including the 1-phenyl-2-tosyloxyethanes (**5** and **2**) and the α-branched 1-phenyl-3-tosyloxybutane **8**, the application of pressure resulted in enhanced substitution product formation concurrent with undesired alkene production. The exclusive formation of the 1-phenyl-2-fluoroethane moiety (**17**) under 15 kbar pressure exemplified the large effect pressure can have on the competitive S_N2 and E2 reaction pathways. Substrates such as **6**, which are both α-branched at the reacting center and have an aromatic ring one carbon away from the reacting center, afford significantly reduced amounts of desired substitution product making the 1-phenyl-2-fluoropropane moiety less attractive for use in fluoroalkylated PET ligands.

The application of high pressure to high specific activity radiofluorination protocols may prove useful for some cases of [^{18}F]fluoroalkyl-substituted PET ligands. The 1 h, 15 kbar pressure conversion of the tosylate **2** to the fluoroethane **3**, occurring without competitive alkene **4** formation, serves as an example of the potential utility of pressure for rapid and exclusive nucleophilic fluoride-ion substitution reaction. Additional efforts are required to assess the effects of pressure on other fluoride-ion substitution reaction variables, including the presence of the NCA potassium carbonate buffer, before attempts are made to apply pressure to radiofluorination reactions.

3. Experimental details

Dichloromethane (CH_2Cl_2) and hexane were distilled from CaH_2 immediately prior to use. Pyridine was distilled from CaH_2 and stored over 4 Å molecular sieves. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from lithium aluminum hydride. Commercially available tetrabutylammonium fluoride (TBAF) trihydrate (Fluka Chemical Co.) was processed according to literature protocol [10] to afford dry TBAF which was used in freshly distilled THF. Other reagents and starting materials were purchased from commercial suppliers as noted and were used as received with the exception of *p*-toluenesulfonyl chloride (TsCl) which was purified by recrystallization from chloroform and petroleum ether [28]. All non-aqueous atmospheric-pressure reactions were carried out under an argon atmosphere unless otherwise noted. Column chromatography purifications were performed using EM silica gel (70–230 mesh). High-performance liquid chromatography (HPLC) purifications were effected with a Waters Associates M45 pumping system and R401 differential refractometer, Rheodyne injector and Whatman M9-Partisil (silica) column for normal phase, and a Whatman M9-ODS 18 for reverse phase. The column chromatography and HPLC solvents employed (hexane, ethyl acetate, Et_2O and CH_2Cl_2) were glass-distilled. The chromatographic solvent mixtures are reported as volume/volume ratios.

The NMR spectra were recorded with an IBM-Bruker AF-300 spectrometer. Proton (^{1}H) signals were obtained at 300 MHz, tetramethylsilane as internal standard and $CDCl_3$ as solvent. The following notation has been utilized for proton spectra interpretations: s, singlet; d, doublet; t, triplet; q, quintet; m, multiplet. Coupling constants (J) are noted in Hz. The fluorine (^{19}F) NMR spectra were proton-decoupled and recorded at 282 MHz, $CFCl_3$ as an internal standard and $CDCl_3$ as solvent. Infrared (IR) spectra were obtained using a Perkin-Elmer model 1310 spectrometer as thin films either neat or mineral oil mulls on NaCl plates. Melting points reported are uncorrected and were obtained with a Mel-Temp melting point apparatus. Kugelrohr distillation temperatures refer to the oven temperature range during which distillate was collected and may not represent precise boiling points. Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley. High-resolution mass spectra (HR MS) were obtained using a Kratos MS-50 high-resolution mass spectrometer, electron impact mode, operated by the

College of Chemistry, University of California, Berkeley. Low-resolution mass spectra (GC–MS) were obtained with a Hewlett Packard HP-5890 gas chromatograph in series with an HP-5970B quadrupole mass selective detector, utilizing a 12 m×0.2 mm fused silica capillary column coated with cross-linked 5% phenylmethyl silicone and helium carrier gas.

3.1. Preparation of 2-(2,5-dimethoxyphenyl)ethanol (9)

A solution of sodium borohydride (5.30 g, 139.5 mmol) in THF (50 ml) was cooled (0 °C) and then 2,5-dimethoxyphenylacetyl chloride (**13**, 15.0 g, 69.76 mmol)[3] in THF (10 ml) added (dropwise). The resulting pink suspension was stirred at 0 °C (30 min), then warmed to reflux and stirred for 2 h. The solution was cooled (0 °C) and the reaction mixture was quenched with acetone (10 ml) and then water (30 ml). The solution was filtered and the solvent removed under reduced pressure to yield a crude gold oil. Kugelrohr distillation of the crude oil afforded the alcohol **9** (9.36 g, 74%) as a clear oil, b.p. 105–107 °C/0.5 mmHg. ^{1}H NMR δ: 2.25 (s, 1H, OH); 2.86 (t, 2H, J=6.4 Hz); 3.74 (s, 3H); 3.76 (s, 3H); 3.79 (t, 2H, J=6.4 Hz); 6.70–6.79 (m, 3H) ppm. IR (neat) (cm^{-1}): 3400. Analysis: $C_{10}H_{14}O_3$ requires: C, 65.9; H, 7.7%. Found: C, 65.5; H, 7.6%.

3.2. Preparation of (±)-1-(2,5-dimethoxyphenyl)-2-propanol (10)

1,4-Dimethoxybenzene (**14**, 15.0 g, 138 mmol)[3] was dissolved in THF (40 ml) and cooled to 0 °C and n-butyllithium (11.38 ml, 7.65 g, 119.6 mmol, 10.5 M in hexanes) added (slow stream). After addition was complete, the mixture was warmed to reflux and stirred for 48 h. The tan, opaque anion solution was cooled to 0 °C and propylene oxide (8.4 ml, 6.94 g, 58 mmol) in THF (10 ml) added (slow stream). The resultant yellow mixture was stirred at 0 °C (1 h), then at 20 °C (50 min) followed by heating at reflux for 2.5 h. The reaction mixture was cooled to room temperature and quenched with water (25 ml) to afford a white suspension which was diluted with THF (50 ml) and then water (100 ml). The THF was removed under reduced pressure and the resulting aqueous portion was extracted with CH_2Cl_2 (300 ml). The organic portion was washed with brine (50 ml) then dried ($MgSO_4$), filtered and the solvent removed in vacuo to provide a crude gold oil. The oil was purified by column chromatography (ethyl acetate/hexane, 1:5) and the isolated residue was Kugelrohr-distilled to yield the alcohol **10** (13.32 g, 63%) as a clear viscous oil, b.p. 118–120 °C/0.7 mmHg. ^{1}H NMR δ: 1.20 (d, 3H, J=6.24 Hz); 2.38 (s, 1H); 2.67–2.81 (m, 2H); 3.75 (s, 3H); 4.03 (s, 3H); 6.70–6.78 (m, 3H) ppm. IR (neat) (cm^{-1}): 3400. Analysis: $C_{11}H_{16}O_3$ requires: C, 67.3; H, 8.2%. Found: C, 67.0; H, 8.2%.

3.3. Preparation of 3-(2,5-dimethoxyphenyl)propanol (11)

A suspension of lithium aluminum hydride (1.80 g, 47.3 mmol) in Et_2O (80 ml) was cooled (0 °C) and stirred while a solution of 3-(2,5-dimethoxyphenyl)-2-propenoate, methyl ester (**15**, 10.0 g, 45.0 mmol) [26] in Et_2O (80 ml) was added over a period of 15 min. After addition was complete, the reaction mixture was gradually warmed to room temperature and then heated at reflux for 30 min. The resultant gray solution was cooled (0 °C), quenched with water (5 ml) and then 10% H_2SO_4 (80 ml) was added. The mixture was extracted with Et_2O (100 ml) and the organic portion washed with sat. $NaHCO_3$, dried ($MgSO_4$), filtered and the solvent then removed under reduced pressure to yield a pale yellow oil. Kugelrohr distillation of the oil (110–112 °C/2.2 mmHg) afforded the alcohol **11** (7.25 g, 82%) as a clear liquid. ^{1}H NMR δ: 1.78–1.88 (m, 2H); 2.69 (t, 2H, J=7.3 Hz); 3.58 (t, 3H, J=6.2 Hz); 3.75 (s, 3H); 3.78 (s, 3H); 6.67–6.81 (m, 3H) ppm. IR (neat) (cm^{-1}): 3400. Analysis: $C_{11}H_{16}O_3$ requires: C, 67.3; H, 8.2%. Found: C, 67.7; H, 8.1%.

3.4. Preparation of (E)-1-(2,5-dimethoxyphenyl)-1-buten-3-one and (±)-1-(2,5-dimethoxyphenyl)butan-3-oil (12)

A solution of 2,5-dimethoxybenzaldehyde (**16**, 10.0 g, 60.0 mmol)[3] in acetone (30 ml) was treated with 5% NaOH (wt./wt., 3 ml) then stirred at 20 °C (30 min) [27]. The reaction mixture was acidified with 1 N HCl (25 ml) and then the acetone was removed under reduced pressure. The aqueous portion was extracted with CH_2Cl_2 and the organic layer was dried (Na_2SO_4) and then concentrated in vacuo to yield a viscous brown oil. Purification of the oil by column chromatography (Et_2O/hexane, 1:3) afforded (*E*)-1-(2,5-dimethoxyphenyl)-1-buten-3-one (6.55 g, 53%, structure not shown) as a pale yellow solid, m.p. 43–44 °C. ^{1}H NMR δ: 2.33 (s, 3H); 3.74 (s, 3H); 3.81 (s, 3H); 6.67 (d, 1H, J=16.5 Hz); 6.81 (d, 1H, J=8.91 Hz); 6.88 (dd, 1H, J=8.91, 2.80 Hz); 7.03 (d, 1H, J=2.80 Hz); 7.80 (d, 1H, J=16.5 Hz) ppm. IR (mull) (cm^{-1}): 1650. Analysis: $C_{12}H_{14}O_3$ requires: C, 69.9; H, 6.8%. Found: C, 69.9; H, 6.9%.

A suspension of lithium aluminum hydride (396 mg, 10.4 mmol) in Et_2O (20 ml) was cooled to 0 °C and then the above (*E*)-1-(2,5-dimethoxyphenyl)-1-buten-3-one (1.09 g, 5.3 mmol) in Et_2O (20 ml) was added (dropwise). After the addition was complete, the reaction mixture was stirred at 0 °C (10 min), then warmed to room temperature followed by heating at reflux (30 min). The reaction mixture was cooled (0 °C), quenched with 1 N HCl (15 ml) and diluted with water (10 ml). The Et_2O portion was separated, then washed successively with water (30 ml), sat. $NaHCO_3$ (30 ml) and brine. The organic portion was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to afford a crude yellow oil. Purification of the crude oil by column chromatography (Et_2O/hexane, 1:2) yielded the

alcohol **12** (1.38 g, 76%) as a clear oil. ^{1}H NMR δ: 1.15 (d, 3H, J=6.05 Hz); 1.63–1.71 (m, 2H); 1.97 (s, 1H); 2.57–2.74 (m, 2H); 3.72 (s, 3H); 3.76 (s, 3H); 6.66 (dd, 1H, J=8.65, 2.52 Hz); 6.70 (d, 1H, J=2.52 Hz); 6.74 (d, 1H, J=8.66 Hz) ppm. IR (neat) (cm^{-1}): 3360. Analysis: $C_{12}H_{18}O_3$ requires: C, 68.5; H, 8.6%. Found: C, 68.2; H, 8.6%.

3.5. Preparation of the tosylates 5–8

3.5.1. 1-(2,5-Dimethoxyphenyl)-2-tosyloxyethane (5)

A mixture of the alcohol **9** (2.26 g, 12.4 mmol) and pyridine (980 mg, 12.4 mmol) in CH_2Cl_2 (20 ml) was cooled to 0 °C and treated with TsCl (2.37 g, 12.4 mmol). The mixture was stirred at 0 °C for 2 h, then stored at 5 °C (22 h). The mixture was poured into ice water (100 ml) and extracted with CH_2Cl_2. The organic portion was washed successively with cold (4 °C) 1 N HCl, sat. $NaHCO_3$ and then brine. The organic layer was dried (Na_2SO_4), filtered and the solvent removed under reduced pressure (20 °C) to provide a gold oil. Purification of the oil by column chromatography (Et_2O/hexane, 1:4) afforded the tosylate **5** (3.08 g, 74%) as a clear oil. ^{1}H NMR δ: 2.39 (s, 3H); 2.88 (t, 2H, J=6.9 Hz); 3.63 (s, 3H); 3.69 (s, 3H); 4.17 (t, 2H, J=6.9 Hz); 6.59–6.69 (m, 3H); 7.23 (d, 2H, J=7.7 Hz); 7.64 (d, 2H, J=7.7 Hz) ppm. IR (neat) (cm^{-1}): 1350; 1170. Analysis: $C_{17}H_{20}O_5S$ requires: C, 60.7; H, 6.0%. Found: C, 60.3; H, 5.6%. The tosylates described below were prepared in an analogous fashion.

(±)-1-(2,5-Dimethoxyphenyl)-2-tosyloxypropane (**6**): The tosylate **6** was obtained (82%) after HPLC purification (CH_2Cl_2) as a white solid, m.p. 63–65 °C. ^{1}H NMR δ: 1.31 (d, 3H, J=6.4 Hz); 2.36 (s, 3H); 2.76 (d, 2H, J=5.9 Hz); 3.61 (s, 3H); 3.66 (s, 3H); 4.81 (m, 1H); 6.52–6.65 (m, 3H); 7.13 (d, 2H, J=8.0 Hz); 7.53 (d, 2H, J=8.0 Hz) ppm. IR (mull) (cm^{-1}): 1330; 1160. Analysis: $C_{18}H_{22}O_5S$ requires: C, 61.6; H, 6.3%. Found: C, 61.3; H, 6.5%.

1-(2,5-Dimethoxyphenyl)-3-tosyloxypropane (**7**): The tosylate **7** was isolated (79%) after column chromatography (Et_2O/hexane, 1:1) as a clear oil. ^{1}H NMR δ: 1.94 (m, 2H); 2.47 (s, 3H); 2.63 (t, 3H, J=7.4 Hz); 3.76 (s, 6H); 4.06 (t, 2H, J=6.3 Hz); 6.62–6.76 (m, 3H); 7.35 (d, 2H, J=8.1 Hz); 7.81 (d, 2H, J=8.1 Hz) ppm. IR (cm^{-1}): 1360; 1175. Analysis: $C_{18}H_{22}O_5S$ requires: C, 61.6; H, 6.3%. Found: C, 61.6; H, 6.3%.

(±)-1-(2,5-Dimethoxyphenyl)-3-tosyloxybutane (**8**): The tosylate **8** was isolated (50%) after HPLC purification (EtOAc/hexane, 1:9) as a clear oil. ^{1}H NMR δ: 1.30 (d, 3H, J=6.0 Hz); 1.78–1.87 (m, 2H); 2.45 (s, 3H); 2.52–2.59 (m, 2H); 3.73 (s, 3H); 3.75 (s, 3H); 4.62–4.66 (m, 1H); 6.61–6.75 (m, 3H); 7.31 (d, 2H, J=8.2 Hz); 7.78 (d, 2H, J=8.2 Hz) ppm. IR (neat) (cm^{-1}): 1350; 1170. Analysis: $C_{19}H_{24}O_5S$ requires: C, 62.6; H, 6.6%. Found: C, 62.2; H, 6.7%.

3.6. High- and ambient-pressure fluoride reactions of 5–8 (Table 2)

A solution of dry TBAF (110 mol%), phenylalkyltosylate (**5–8**, 0.1 mmol) and anhydrous THF (1.0 ml) in a dry round-bottomed flask was transferred under argon to a Teflon tube which was clamped at both ends. The tube was subjected to 15 kbar (1.5 GPa) pressure for 16 h or 8 kbar pressure for 8 h at 20 °C (see Table 2)[4,5]. The reaction systems were depressurized and concentrated in vacuo (20 °C). The resulting residues were washed successively with four generous portions of Et_2O which were combined and the solvent was removed under reduced pressure (20 °C) to afford crude product mixtures. The reaction mixtures were separated by HPLC. The atmospheric (1 bar) pressure control runs were performed in a similar way to the high-pressure runs employing an identical ratio of reagents. The atmospheric pressure reactions were performed under argon at the temperatures and times noted in Table 2. The reactions were processed as described above and the following compounds were obtained.

1-(2,5-Dimethoxyphenyl)-2-fluoroethane (**17**) and 2,5-dimethoxyphenylethene (**18**): Purification of the crude reaction mixture by HPLC (EtOAc/hexane, 1:4) afforded the more polar ethyl fluoride **17** as a clear oil, b.p. 90–93 °C/0.4 mmHg. ^{1}H NMR δ: 2.98 (dt, 2H, J=21.5, 6.73 Hz); 3.72 (s, 3H); 3.75 (s, 3H); 4.57 (dt, 2H, J=4.73, 6.66 Hz); 6.69–ie6.77 (m, 3H) ppm. ^{19}F NMR δ: −214.2 ppm. IR (neat) (cm^{-1}): 1225. Analysis: $C_{10}H_{13}FO_2$ requires: C, 65.2; H, 7.1%. Found: C, 64.9; H, 7.2%. The less polar styrene **18** was obtained in the 8 kbar and 1 bar pressure runs and possessed spectroscopic qualities and physical properties identical to those described previously [30].

(±)-1-(2,5-Dimethoxyphenyl)-2-fluoropropane (**19**) and (*E*)-1-(2,5-Dimethoxyphenyl)-1-propene (**20**): Purification of the crude reaction mixture by HPLC revealed only two components (EtOAc/hexane, 1:9) and afforded the more polar fluoropropane **19** as a clear oil, b.p. 80–82 °C/0.3 mmHg. ^{1}H NMR δ: 1.29 (dd, 3H, J=23.71, 6.11 Hz); 2.79–2.94 (m, 2H); 3.72 (s, 3H); 3.74 (s, 3H); 4.86 (m, 1H); 6.69–6.76 (m, 3H) ppm. ^{19}F NMR δ: −169.5 ppm. IR (neat) (cm^{-1}): 1220 (C–F). Analysis: $C_{11}H_{15}O_2F$ requires: C, 66.7; H, 7.6%. Found: C, 66.4; H, 7.6%.

The less polar alkene **20** was isolated as a clear oil. ^{1}H NMR δ: 1.90 (d, 3H, J=7.37 Hz); 3.78 (s, 3H); 3.80 (s, 3H); 6.22 (dq, 1H, J=15.65, 6.84 Hz); 6.62–6.80 (m, 3H); 6.96 (d, 1H, J=2.86 Hz) ppm. The large coupling constant (15.65 Hz) observed for one of the non-aromatic alkene proton resonances was considered a result of (*E*)-double-bond geometry. The resonance for the other (*E*)-vinyl proton was overlapped and obscured by two of the aromatic signals (δ 6.62–6.80 ppm). IR (neat) (cm^{-1}): 1600; 1575. Analysis: $C_{11}H_{14}O_2$ requires: C, 74.1; H, 8.0%. Found: C, 73.7; H, 7.9%.

1-(2,5-Dimethoxyphenyl)-3-fluoropropane (**21**): Purification of the crude reaction mixture by HPLC (CH_2Cl_2) afforded the propyl fluoride **21** as a clear oil. ^{1}H NMR δ: 2.00

(dtt, 2H, J=27.0, 7.60, 6.0 Hz); 2.74 (t, 2H, J=7.6 Hz); 3.72 (s, 3H); 3.74 (s, 3H); 4.48 (dt, 2H, J=47.2, 6.0 Hz); 6.71–6.81 (m, 3H) ppm. ^{19}F NMR δ: −218.3 ppm. IR (neat) (cm^{-1}) 1220. Analysis: $C_{11}H_{15}FO_2$ requires: C, 66.7; H, 7.6%. Found: C, 66.5; H, 7.8%. The corresponding 1-propene side-product was not observed by ^{1}H NMR, HPLC and analytical GC–MS analyses in the runs under high and atmospheric pressures.

(±)-1-(2,5-Dimethoxyphenyl)-3-fluorobutane (**22**) and 1-(2,5-dimethoxyphenyl)butene mixture (**23a**, **23b** and **23c**): Purification of the crude reaction mixture by HPLC (EtOAc/hexane, 1:9) yielded the more polar fluorobutane **22** as a clear oil, b.p. 95–96 °C/0.6 mmHg. ^{1}H NMR δ: 1.33 (dd, 3H, J=24.17, 6.16 Hz); 2.77–2.98 (m, 4H); 3.76 (s, 3H); 3.77 (s, 3H); 4.91 (m, 1H); 6.75–6.80 (m, 3H) ppm. ^{19}F NMR δ: −174.6 ppm. IR (neat) (cm^{-1}): 1220. Analysis: $C_{12}H_{17}FO_2$ requires: C, 67.9; H, 8.1%. Found: C, 67.8; H, 8.0%. The less polar fraction contained a three-component mixture of the 2- and 3-butenes **23**. Attempted separation of the mixture by HPLC (normal and reverse phases) and preparative gas chromatography was not effective. Analysis by GC–MS revealed only three peaks, eluting at 7.87, 8.08 and 8.19 min with the respective relative areas of 2.0:1.5:1.0. Similar relative ratios of the three components were observed for the 15 kbar, 8 kbar and 1 bar 40 °C. Each of the components of the mixture had identical parent ions (M^+) of m/z 192. Characterization of the mixture by high-resolution MS, m/z: calc. for $C_{12}H_{16}O_2$: 192.1151. Found: 192.1145 (M^+, base). The ^{1}H NMR spectra of the three-component mixture was complex; however several distinct resonances were observed which were neither overlapped nor obscured by other signals. Methyl resonances were found at δ 1.68 (d, J=5.58 Hz); 1.70 (d, J=5.65 Hz) ppm which were indicative of the geometric 2-butene isomers; vinyl proton signals for these isomers were obscured by other resonances. The unique signal splitting at δ 5.0–5.83 (ABX) ppm was indicative of the terminal 3-butene vinyl protons.

(±)-1-[2,5-Dimethoxy-4-(2-tosyloxyethyl)phenyl]-2-trifluoroacetamidopropane (**2**): A solution of (±)-1-[2,5-dimethoxy-4-(2-hydroxyethyl)phenyl]-2-trifluoroacetamidopropane [8] (901 mg, 2.92 mmol) and pyridine (300 mg, 3.80 mmol) in CH_2Cl_2 was cooled (0 °C) then treated with TsCl (726 mg, 3.80 mmol). The mixture was stirred at 0 °C for 1 h then stored at 5 °C for 16 h. The solvent was removed under reduced pressure (20 °C) and the residue was suspended in Et_2O and washed successively with 6 N HCl (0 °C), water and then brine. The organic portion was dried (anhydrous K_2CO_3), filtered and concentrated in vacuo to afford a golden solid. Purification of the solid by column chromatography (CH_2Cl_2) afforded the tosylate **2** (1.37 g, 96%) as a white solid, m.p. 132–134 °C (dec.). ^{1}H NMR δ: 1.25 (d, 3H, J=6.5 Hz); 2.42 (s, 3H); 2.72–2.85 (m, 2H); 2.93 (t, 2H, J=7.0 Hz); 3.66 (s, 3H); 3.78 (s, 3H); 4.09 (m, 1H); 4.21 (t, 2H, J=7.0 Hz); 6.54 (s, 1H); 6.55 (s, 1H); 7.27 (d, 2H, J=8.0 Hz); 7.44 (m, 1H); 7.69 (d, 2H, J=8.0 Hz) ppm. IR (mull) (cm^{-1}): 1682; 1170. Analysis: $C_{22}H_{26}F_3NO_6S$ requires: C, 54.0; H, 5.4%. Found: C, 54.2; H, 5.4%.

(±)-1-[2,5-Dimethoxy-4-(2-fluoroethyl)phenyl]-2-trifluoroacetamidopropane (**3**): The fluoride-ion substitution reaction of tosylate **2** (0.10 mmol) was performed utilizing the general procedure described above for the substrates listed in Table 2. The mixture was pressurized at 15 kbar for 1 h (20 °C) and the reaction processed as per the general procedure noted above. Purification of the crude reaction mixture by HPLC (CH_2Cl_2) provided the less polar fluoroethane **3** (75%) as a white solid, m.p. 136–137 °C. ^{1}H NMR δ: 1.27 (d, 3H, J=6.4 Hz); 2.80–2.85 (m, 2H); 3.01 (dt, 2H, J=20.0, 6.8 Hz); 3.78 (s, 3H); 3.82 (s, 3H); 4.1 (m, 1H); 4.61 (dt, 2H, J=47, 6.8 Hz); 6.63 (s, 1H); 6.76 (s, 1H); 7.47 (s, 1H) ppm. ^{19}F NMR δ: −214.4 ppm. IR (mull) (cm^{-1}): 3310; 1690. Analysis: $C_{15}H_{19}F_4NO_3$ requires: C, 53.4; H, 5.7%. Found: C, 53.7; H, 5.9%.

The more polar component of the crude reaction mixture was recovered tosylate **2** (10%). The styrene **4** was not observed by HPLC and ^{1}H NMR spectroscopic analyses of the crude high-pressure reaction mixture.

3.7. Atmospheric 1 bar pressure control reactions of 2.

3.7.1. Preparation of (±)-1-[2,5-dimethoxy-4-(ethen)phenyl]-2-trifluoroacetamidopropane (4)

The atmospheric (1 bar) pressure control reactions were performed by treating two different solutions of the tosylate **2** (200 mg, 0.43 mmol) in THF (4 ml) with TBAF (124 mg, 0.47 mmol). In the first case the mixture was heated at 40 °C for 1 h and in the second case the reaction was stirred at 20 °C for 168 h. The solvent was removed under reduced pressure (20 °C), and the resultant residues for each run were washed with several portions of Et_2O. The organic portions were combined and the solvent removed in vacuo (20 °C). The residues were purified by HPLC (CH_2Cl_2). The 40 °C control reaction failed to provide recovered starting material **2** and afforded the more polar fluoroethane **3** (74 mg, 51%) along with the less polar styrene **4** (18 mg, 18%). Compound **4** was obtained as a white solid, m.p. 132–133 °C. ^{1}H NMR δ: 1.27 (d, 3H, J=6.4 Hz); 2.80–2.85 (m, 2H); 3.79 (s, 3H); 3.83 (s, 3H); 4.11 (m, 1H); 5.27 (d, 1H, J=11.8 Hz); 5.72 (d, 1H, J=17.6 Hz); 6.65 (s, 1H); 7.0 (s, 1H); 7.03 (ABX, 1H); 7.43 (s, 1H) ppm. IR (mull) (cm^{-1}): 1690, 1560. Analysis: $C_{15}H_{18}F_3NO_3$ requires: C, 56.8; H, 5.7%. Found: C, 56.6; H, 5.67%.

The 20 °C control reaction yielded only fluoroalkyl **3** (62 mg, 43%) and styrene **4** (23 mg, 23%).

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