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Diisopropylethylamine mono(hydrogen fluoride) for nucleophilic fluorination of sensitive substrates: synthesis of sevoflurane

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Abstract

Diisopropylethylamine mono(hydrogen fluoride) (**8**), which can be prepared by addition of two equivalents of diisopropylethylamine to the complex diisopropylethylamine tris(hydrogen fluoride) (**7**), is shown to be an effective and selective nucleophilic fluorinating reagent when applied to halogen-exchange reactions of chloromethyl ethers, in particular the conversion of 1,1,1,3,3,3-hexafluoroisopropyl chloromethyl ether (**3**) to the volatile anesthetic sevoflurane (1,1,1,3,3,3-hexafluoroisopropyl fluoromethyl ether). The amine portion of the reagent does not react with the starting material to give a troublesome quaternary ammonium salt, as is the case for the species formed by addition of two equivalents of triethylamine to triethylamine tris(hydrogen fluoride). These particular chloromethyl ether substrates require a 1:1 stoichiometry of diisopropylethylamine to hydrogen fluoride to give useful rates of reaction and yields when solventless conditions are desired. Two other complexes, diisopropylethylamine bis(hydrogen fluoride) and **7**, are ineffective for conversion of **3** to sevoflurane.
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1. Introduction

Sevoflurane (1,1,1,3,3,3-hexafluoroisopropyl fluoromethyl ether) is a recently introduced inhaled anesthetic. It is now one of the most widely used anesthetics because, unlike other fluorinated inhaled anesthetics, it lacks a pungent odor, and thus, can be used for induction of anesthesia. We report herein a high-yielding and industrially practical synthesis of sevoflurane which showcases diisopropylethylamine mono(hydrogen fluoride) as a halogen-exchange (halex) reagent. This reagent not only gives an excellent yield of sevoflurane, but when applied to the synthesis of other fluoromethyl ethers, gives higher yields when compared with the more commonly used triethylamine–hydrogen fluoride complex.

The shortest syntheses of sevoflurane start from 1,1,1,3,3,3-hexafluoroisopropyl alcohol (**1**), which is treated with either bis(fluoromethyl) ether, or a hydrogen halide and formaldehyde, or aluminum trichloride and a formaldehyde equivalent, to give sevoflurane directly [1–5] or in two steps [6–8]. These are very practical routes, despite low

conversions and use of excess reagents that result in large amounts of chemical waste. Other methods employ 1,1,1,3,3,3-hexafluoroisopropyl methyl ether (**2**), conveniently prepared by methylation of alcohol **1** [9]. Direct monofluorination of the methyl group of methyl ether **2** is possible using either fluorine or bromine triflouride [1,2,10,11], but these methods aren't practical on a large scale due to the expense of and hazards associated with the reagents. A practical way to convert methyl ether **2** to sevoflurane proceeds through 1,1,1,3,3,3-hexafluoroisopropyl chloromethyl ether (**3**). The problem then becomes selection of an inexpensive and efficient nucleophilic fluorinating reagent for the final halex reaction. Bromine trifluoride has been used [1,2], but is not a viable reagent due its aforementioned limitations. Alkali metal fluoride salts can be used, either in a high-boiling solvent or neat [1,7,8,12]. The high temperatures and pressures involved and/or use of large amounts of solvent limit the usefulness of these methods. Finally, while this work, which has culminated in a practical industrial-scale synthesis of sevoflurane [13], was in progress, a method independently appeared employing various amine–hydrogen fluoride complexes to convert chloromethyl ether **3** to sevoflurane [14]. However,

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in the latter case, the percent conversions were in general poor, and the yields were less than ideal.

2. Results and discussion

Our initial attempts at a sevoflurane synthesis involved treatment of the intermediate chloromethyl ether **3** with one equivalent of the complex prepared from one-third of an equivalent of triethylamine tris(hydrogen fluoride) (**4**) [15] and two-thirds of an equivalent of triethylamine, which presumably forms one equivalent of triethylamine mono(-hydrogen fluoride) (**5**)[1] in situ (Scheme 1). The added amine was not only necessary for neutralization of the hydrogen chloride by-product, but also enhanced the reactivity of the reagent; see below for further discussion of the latter aspect. This particular reagent combination has been used previously for halex reactions of some fluorinated chloromethyl ethers [16]. We expected that this reagent combination would have the advantage of generating only a small amount of chemical waste because the amine is in principle recyclable after reaction of the by-product hydrochloride salt with base.

After heating at reflux overnight, sevoflurane was distilled from the reaction mixture and isolated in 79% yield, which is in the range of typical yields found by Terrell [14]. While this yield is good, it was not clear what was happening to the rest of the product, for all of the starting material was being consumed. A careful check of the reaction mixture revealed the presence of quaternary ammonium salt **6**, which we were unable to convert to sevoflurane. This suggested that the reagent formed by addition of triethylamine to complex **4** was not simply an amine salt, but contained free amine as well; this free amine was perhaps the culprit which caused quaternization (Scheme 2). We hypothesized that the free amine was in equilibrium with triethylamine mono(hydrogen fluoride) (**5**), which suggested that use of a more sterically hindered amine would cause complete suppression of by-product salt **6** and allow a high-yielding practical synthesis of sevoflurane.

Diisopropylethylamine, a much-used sterically hindered amine, appeared to be a good candidate for replacement of triethylamine. The complex diisopropylethylamine tris(hydrogen fluoride) (**7**) has been prepared by treatment of diisopropylethylamine with three equivalents of either liquid hydrogen fluoride [17,18] or hydrogen fluoride in the form
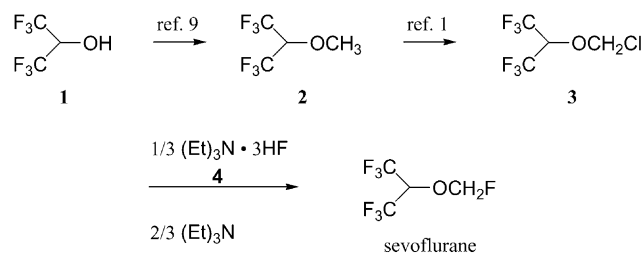
Scheme 1. Synthesis of sevoflurane.
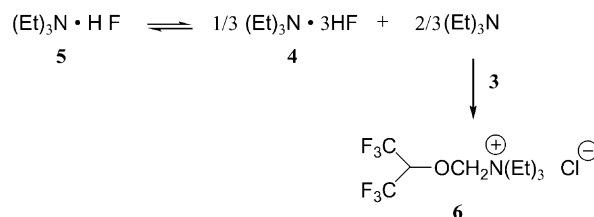
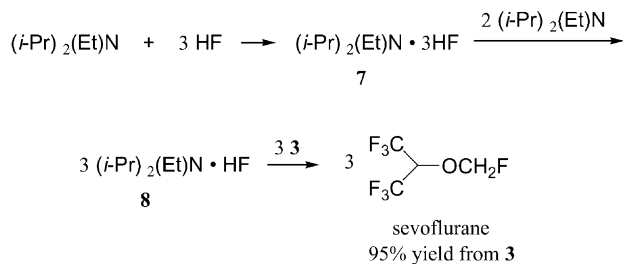Scheme 2. Proposed equilibrium and by-product formation.

of concentrated hydrofluoric acid [19]. We have used the former procedure in this work, and have found that no purification is necessary. The presumed fluorinating reagent, diisopropylethylamine mono(hydrogen fluoride) (**8**), was generated by addition of two equivalents of diisopropylethylamine to tris complex **7** in situ. Alternatively, mono complex **8** can be prepared directly by using a 1:1 molar ratio of hydrogen fluoride and amine. Data which we will present later will show that mono complex **8** is an ephemeral species, making tris complex **7**/two equivalents amine the reagent of choice for work in the laboratory; this reagent combination has been used as a source of nucleophilic fluoride in the opening of epoxides [18,19]. On the other hand, for preparation of multi-kilogram quantities of sevoflurane, we simply adjusted the molar ratio of amine to hydrogen fluoride to 1:1 in situ.

The reaction of chloroether **3** with mono complex **8** gave a 95% yield of sevoflurane after 16 h at reflux (Scheme 3); none of the quaternary salt analogous to salt **6** or any by-products other than the expected diisopropylethylamine hydrochloride were detected. The reaction can be run with no solvent present, which allows simple distillation of the product from the reaction mixture. And very little waste is generated because we have been able to recover the amine by treatment of the by-product hydrochloride salt with aqueous base followed by phase separation.

The following observations support our contention that mono complex **8** is not a hydrofluoride salt, but is possibly a weakly coordinated complex[2] as depicted: first, we have

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[1] We prefer this formulation rather than that of a salt. Picq and coworkers [20] has shown that addition of two equivalents of triethylamine to tris complex **4** does not give a hydrofluoride salt, but instead gives triethylamine bis(hydrogen fluoride), which can be isolated as a solid in the presence of the excess amine. Based on this fact and some data we will present pertaining to the closely related diisopropylethylamine–hydrogen fluoride complexes, we view the 1:1 complex in solution of either of these two amines and hydrogen fluoride as $R_3N \cdot HF$ in equilibrium with other complexes and free amine, with the possibility that a small amount of the ionic hydrofluoride salt is present.

[2] All the data we present here are also consistent with the notion that mono complex **8** is actually a mixture of species, including a hydrofluoride salt, free amine, and bis and tris complexes, in equilibrium with each other. In this case, it may be that the fluoride ion of the hydrofluoride salt is acting as the nucleophile.

$$(i\text{-Pr})_2(\text{Et})\text{N} \ + \ 3\ \text{HF} \ \longrightarrow \ (i\text{-Pr})_2(\text{Et})\text{N} \cdot 3\text{HF} \ \xrightarrow{2\ (i\text{-Pr})_2(\text{Et})\text{N}}$$

7

$$3\ (i\text{-Pr})_2(\text{Et})\text{N} \cdot \text{HF} \ \xrightarrow{3\ \mathbf{3}} \ 3 \ \underset{F_3C}{\overset{F_3C}{>}}\!\!\!-\text{OCH}_2\text{F}$$

8

sevoflurane
95% yield from **3**

Scheme 3. Synthesis of sevoflurane using mono complex **8**.

treated tris complex **7** with two equivalents of diisopropylethylamine in an attempt to prepare a salt, but have failed under a variety of conditions. Mixing the two in ether/methylene chloride to form a homogeneous solution at room temperature for 1 h and removal of the solvent in vacuo resulted in isolation of a bi-phasic mixture of the two unchanged reactants. Similar results were obtained at elevated temperature, either in acetonitrile at 82°C or neat at 95°C. Not even the bis complex, diisopropylethylamine bis(hydrogen fluoride) was isolated. In contrast, triethylamine bis(hydrogen fluoride) is an isolable solid [20]. Second, when tris complex **7** was dissolved in chloroform-*d* and portions of diisopropylethylamine were added up to two equivalents of amine, the chemical shifts of the methylene and methine protons in the nuclear magnetic resonance (NMR) spectrum of the amine–hydrogen fluoride complex gradually moved upfield several tenths of a ppm, indicating that these protons were becoming more shielded as amine was added. The opposite trend would be expected if the amine became a true salt (i.e. the nitrogen atom acquired a full positive charge) at the end of the addition of amine when the stoichiometry was 1:1.

The 1:1 stoichiometry of amine to hydrogen fluoride is important for the reaction to proceed. The results of Picq and coworkers [20] indicated that a molar ratio of 2:1 of hydrogen fluoride:amine was most effective for nucleophilic displacement reactions when triethylamine was used and the reaction was run in acetonitrile as solvent, while the complex of 1:1 stoichiometry (i.e. mono complex **5**) was least effective, as judged by the rate of the reaction. In contrast, we have tested

2:1 and 3:1 ratios of hydrogen fluoride to diisopropylethylamine against the 1:1 ratio (i.e. mono complex **8**) and have found that mono complex **8** and the 2:1 complex have approximately the same rate of reaction in acetonitrile: when chloroether **3** was treated with three equivalents of either complex, each resulted in >90% conversion to sevoflurane after 4 h at reflux, while three equivalents of complex **7** itself gave <20% completion after the same time period. We have also tested the 2:1 and 3:1 complexes versus mono complex **8** in the absence of solvent, and have found that mono complex **8** gives by far a faster rate: after 2 h at reflux, the reaction using three equivalents of mono complex **8** was 79% complete, while the reaction using the 2:1 complex was only 22% complete and had appeared to stop converting chloroether **3**. Complex **7** was the least efficacious in the absence of solvent: after 2 h, <10% conversion to sevoflurane was observed, and the reaction had appeared to stop. Whether neat or in acetonitrile, the 2:1 complex and tris complex **7** both etch glassware during the reaction, while mono complex **8** does not. So from a practical standpoint, mono complex **8** is the preferred reagent for this particular reaction.

In an attempt to gain some insight into the reactivity of mono complex **8** with fluorinated chloromethyl ethers, we have studied the kinetics of the reaction of the complex with chloroether **3**. Values of the rate constant *k* were calculated, assuming either first- or second-order kinetics [21], for the reaction of mono complex **8** with chloroether **3** at 88°C (Table 1). The homogeneous reaction mixture at various times was monitored directly by ^{1}H NMR analysis, using the integration values of the $-\text{OCH}_2\text{Cl}$ singlet versus the $-\text{OCH}_2\text{F}$ doublet to calculate the rate of disappearance of chloromethyl ether **3** over time. Making the assumption that the reaction can be only first- or second-order overall, the second-order *k* values were reasonably constant, indicating an SN2 mechanism. Because the reaction is bimolecular in nature, a classical SN1 mechanism, where a free carbocation forms in a slow first step can be ruled out. The powerfully electron-withdrawing trifluoromethyl groups of chloroether **3** apparently do not allow the stabilization of a carbocation by the neighboring oxygen atom. However, the reaction is accelerated by presence of the oxygen atom: for example, a

Table 1

First- and second-order rate constants for reaction of mono complex **8** with chloromethyl ether **3** at 88°C

Time (min)[a]	Percent completion (%)	$k \times 10^{-4}$ (s^{-1}) (first-order)[b]	$k \times 10^{-4}$ (l mol s^{-1}) (second-order)[c]
10	24	3.0	1.2
20	35	2.9	1.2
30	42	2.6	1.1
40	49	2.5	1.1
50	53	2.2	1.0
60	58	2.2	1.1
115	72	1.7	1.1

[a] The 0 time point was when the mixture had reached 88°C; $[\mathbf{3}]_o$ was calculated at this point.
[b] The formula $k = (2.303/t)\,(\log([\mathbf{3}]_o/[\mathbf{3}]_t))$ was used.
[c] The formula $k = (1/[\mathbf{3}]_t - 1/[\mathbf{3}]_o)/t$ was used, where *t* is the time in seconds, $[\mathbf{3}]_o$ the original concentration of **3**, and $[\mathbf{3}]_t$ the concentration of **3** at time *t*.

simple primary alkyl mesylate does not react to a significant extent with complex **5** [20]. It is most likely that the reaction of mono complex **8** with chloroether **3** occurs in one step via a simple nucleophilic substitution reaction, with the oxygen atom of chloroether **3** exerting an accelerating influence. But formation of a carbocation in a reversible fast first step, followed by rate-determining capture by fluoride ion cannot be ruled out. It appears that even though the acid–base interaction of diisopropylethylamine and hydrogen fluoride in mono complex **8** is relatively weak, it is strong enough to allow the fluorine atom to behave as a nucleophile, bearing enough of a negative charge to displace chloride in this specially activated substrate.

When applied to other chloromethyl ethers, mono complex **8** gives superior yields when compared to mono complex **5** (Table 2, entries 1–6). In all cases, the cause of the lower yield when mono complex **5** was used was traced to quaternization. This suggests that quaternization of highly reactive chloromethyl ethers may be a general phenomenon when triethylamine is used as base in this type of halex reaction. All reactions employed one equivalent of mono complex **8** and used no solvent; thus, the products could be distilled directly from the reaction mixture with only small amounts of starting material as contaminant in some cases. Reaction times at reflux were an overnight period or less, except in the case of entry 9, where 35 h were required for a reasonable level of completion. Entries 5 and 6 were performed at room temperature and went to completion almost instantaneously. Mono complex **8** shows some selectivity: no exchange of the other chlorine atoms was seen in entries 7, 8, and 10. This new method complements antimony pentachloride-catalyzed halex reactions, which are only suitable in general for ethers more highly halogenated than the ones shown in Table 2, due to the instability of ethers containing a halomethyl group [22–24].

An unexpected by-product was seen in the reaction mixture of entry 7, Table 2. The product of both halogen-exchange and reduction, $CHClFCF_2OCH_2F$, was obtained in 6% yield. This reduction process also occurred when the substrate $CHClFCF_2OCCl_3$ was treated with complex **8** at reflux: the result of mono-reduction, $CHClFCF_2OCHCl_2$, formed in 13% yield, was the predominant product. While starting material made up most of this reaction mixture, also seen was a 3% yield of the halogen-exchange product $CHClFCF_2OCFCl_2$. It is likely that the reduction is occurring via a radical-mediated process with the amine as reductant. Possible initiating species include either adventitious metal ions [25] or oxygen, which could convert a small amount of the amine into a radical-producing impurity. It has been shown that mono-reductions of this type are possible with alcohols or ethers as reductants [26,27], and in some cases the reductions are thermally initiated [27]. In support of the hypothesis of a radical-mediated process, we have found that irradiation with UV light (254 nm high-pressure Hg lamp shined through pyrex glass) of a solution of $CF_3CCl_2OCHF_2$ in excess complex **8** plus a trace of acetone gives the product of mono-reduction, $CF_3CHClOCHF_2$, in about 10% yield; no other products were seen. This same conversion was obtained when diisopropylethylamine was substituted for complex **8**. But on the other hand, no reaction of any kind was seen when $CF_3CCl_2OCHF_2$ was treated with complex **8** at reflux in the dark; in this case, the reflux temperature of the reaction mixture was much lower than in the other cases, making a thermally initiated free-radical reduction less likely. These observations lead us to infer that diisopropylethylamine was acting as the reductant in a free-radical reaction, with the source of hydrogen being the C–H bond alpha to the nitrogen atom. It has been shown [28] that amines can undergo scission of this C–H bond to give a free radical, formation of which is among the early steps in reductions of this type [27].

Although the exact nature of the species formed by addition of a two-fold excess of amine to a tertiary amine tris(hydrogen fluoride) complex is far from being understood, this study shows that the mono complex can be a selective source of fluoride for bimolecular substitution reactions. Further clarification of the structure and reactivity

Table 2
Preparation of fluoromethyl ethers[a]

Entry	Reagent	Starting material		Product		Yield (%)
		Formula	Compound	Formula	Compound	
1	**8**	$CF_3CHFOCH_2Cl$	**9**	$CF_3CHFOCH_2F$	**10**	78
2	**5**	$CF_3CHFOCH_2Cl$	**9**	$CF_3CHFOCH_2F$	**10**	52
3	**8**	$CF_3CHFCF_2OCH_2Cl$	**11**	$CF_3CHFCF_2OCH_2F$	**12**	81
4	**5**	$CF_3CHFCF_2OCH_2Cl$	**11**	$CF_3CHFCF_2OCH_2F$	**12**	35
5	**8**	$CH_3CH_2OCH_2Cl$	**13**	$CH_3CH_2OCH_2F$	**14**	65
6	**5**	$CH_3CH_2OCH_2Cl$	**13**	$CH_3CH_2OCH_2F$	**14**	Trace[b]
7	**8**	$CCl_2FCF_2OCH_2Cl$	**15**	$CCl_2FCF_2OCH_2F$	**16**	65
8	**8**	$CHClFCF_2OCH_2Cl$	**17**	$CHClFCF_2OCH_2F$	**18**	66
9	**8**	$(CF_3)_2CHOCHClF$	**19**	$(CF_3)_2CHOCHF_2$	**20**	66
10	**8**	$CF_3CHClOCHClF$	**21**	$CF_3CHClOCHF_2$	**22**	67

[a] Detailed preparations for sevoflurane, **10**, and **12** can be found in [13].
[b] Quaternization of the starting material by the amine was the major outcome.

of these complexes may allow prediction of which kind and what proportion of amine would work best for a particular class of substrates.

3. Experimental

3.1. General methods and starting materials

^{1}H NMR spectra were recorded in $CDCl_3$ solvent at either 300 MHz with a Bruker WH-300 instrument, or, for routine analyses, at 60 MHz with a Hitachi R-1200 instrument; chemical shifts (δ) are reported in ppm downfield from the standard tetramethylsilane, $\delta = 0$. ^{19}F NMR spectra were recorded in $CDCl_3$ solvent at 282 MHz with a Bruker WH-300 instrument; chemical shifts are reported in ppm upfield from the standard fluorotrichloromethane, $\delta = 0$. Gas chromatographic analyses were performed on a Hewlett-Packard 5890 gas chromatograph fitted with a packed Supelco 10% igepalco-880/50% lb-550X on 80/60 Chromasorb PAW column with TCD detection.

Detailed preparations for sevoflurane, 1,2,2,2-tetrafluoroethyl fluoromethyl ether (10) [16], and 1,1,2,3,3,3-hexafluoropropyl fluoromethyl ether (12) [16] can be found in [13]. The starting materials 1,2,2,2-tetrafluoroethyl chloromethyl ether (9) [16], 1,1,2,3,3,3-hexafluoropropyl chloromethyl ether (11) [16], 2,2-dichloro-1,1,2-trifluoroethyl chloromethyl ether (15) [29], 2-chloro-1,1,2-trifluoroethyl chloromethyl ether (17) [29], 1,1,1,3,3,3-hexafluoroisopropyl chlorofluoromethyl ether (19) [30], and 1-chloro-2,2,2-trifluoroethyl chlorofluoromethyl ether (21) [31] were prepared as previously reported. Chloromethyl ethyl ether (13), diisopropylethylamine, triethylamine, triethylamine trihydrofluoride (triethylamine tris(hydrogen fluoride), 4) were purchased from Aldrich Chemical Co.

3.2. Fluoromethyl ethyl ether (14) [32]

Diisopropylethylamine (6.63 ml, 38.1 mmol) was added to complex 7 under nitrogen, giving a biphasic mixture. With rapid stirring, chloroether 13 (5.32 ml, 57.3 mmol) was added in one portion, giving a mild exotherm. Upon cooling, the mixture solidified. Simple distillation under nitrogen gave 2.9 g (65% yield) 14 as a colorless liquid, bp 36°C. ^{1}H NMR δ 5.27 (d, 2H, $J = 57$ Hz), 3.79 (qd, 2H, $J = 7.2$ and 1.2 Hz), 1.29 (t, 3H $J = 7.2$ Hz) [**WARNING**: Compound 14 is highly unstable to moisture. Upon exposure to the atmosphere, it decomposes rapidly, producing HF fumes].

3.3. 2,2-Dichloro-1,1,2-trifluoroethyl fluoromethyl ether (16) [33]

A mixture of complex 7 (2.79 g, 14.7 mmol), diisopropylethylamine (4.07 g, 31.5 mmol), and chloroether 15 (10.15 g, 46.69 mmol) was heated at reflux under nitrogen for 16 h. After cooling to RT, the volatile component was

removed under vacuum into a dry ice-cooled trap, giving 7.55 g of liquid. GC analysis indicated that this liquid was 28.5% 15 and 64.0% 16, equivalent to 4.83 g 16 (65% yield based on consumed starting material). ^{1}H NMR δ 5.63 (d, $J = 51.3$ Hz). ^{19}F NMR (H-coupled) δ −75.9 (t, 1F, $J = 8.2$ Hz), −88.3 (t, 2F, $J = 8.2$ Hz), −154.8 (tt, 1F, $J = 51.2, 8.2$ Hz).

3.4. 2-Chloro-1,1,2-trifluoroethyl fluoromethyl ether (18) [33]

A mixture of complex 7 (17.2 g, 91 mmol), diisopropylethylamine (23.5 g, 182 mmol), and chloroether 17 (50.0 g, 273 mmol) was heated at reflux under nitrogen for 18 h. The volatile components were transferred in vacuo to a dry-ice-cooled receiver, giving 46.4 g liquid. This was washed with 10% aqueous HCl and water to remove traces of diisopropylethylamine. Drying over $CaCl_2$ gave 39.8 g liquid which showed by GC analysis a 2.0:1.0 mixture of 18 and 17. Fractional distillation using a $2\,\text{ft} \times 1/2\,\text{in.}$ vacuum-jacketed column packed with glass beads gave 21.7 g 18 (66% yield based on consumed starting material), bp = 82°C (lit. = 83.5°C [33]). ^{1}H NMR δ 6.14 (dt, 1H $J = 48.0, 4.28$ Hz), 5.62 (dt, 1H, $J = 54.2, 3.33$ Hz). ^{19}F NMR (H-decoupled) δ −82 (m, 2F), −154.5 (t, 1F, $J = 9.0$ Hz), −154.8 (br t, 1F, $J = 11.6$ Hz).

3.5. 1,1,1,3,3,3-Hexafluoroisopropyl difluoromethyl ether (20) [30]

A mixture of complex 7 (3.1 ml, 16 mmol), diisopropylethylamine (5.7 ml, 33 mmol), and chloroether 19 (10.8 g, 46.0 mmol) was heated at reflux under nitrogen for 35 h. Periodic monitoring by ^{1}H NMR of aliquots dissolved in $CDCl_3$ indicated the reaction was 77% complete after this time. Simple distillation gave 7.27 g distillate, bp 52–56°C (lit. bp of pure 20 = 41.5°C [30]). ^{1}H NMR analysis indicated that the distillate was composed of 91% ether 20, 6.5% starting ether 19, and 2.5% diisopropylethylamine, equivalent to 6.6 g (66% yield) of 20. ^{1}H NMR δ 6.44 (t, 1H $J = 70.5$ Hz), 4.84 (sept, 1H, $J = 5.66$ Hz). ^{19}F NMR (H-decoupled) δ −74.6 (t, 6F, $J = 4.40$ Hz), −85.6 (sept, 2F, $J = 4.40$ Hz).

3.6. 1-Chloro-2,2,2-trifluoroethyl difluoromethyl ether (isoflurane, 22) [29]

A mixture of complex 7 (7.00 ml, 36.8 mmol), diisopropylethylamine (12.8 ml, 73.4 mmol), and chloroether 21 (20.0 g, 99.6 mmol) was heated at reflux under nitrogen for 21 h. Periodic monitoring by ^{1}H NMR of aliquots dissolved in $CDCl_3$ indicated the reaction was 77% complete after 4 h. Simple distillation gave 16.4 g distillate, bp 55–87°C (lit. bp of pure 22 = 48.5°C [29]). ^{1}H NMR analysis indicated that the distillate was composed of 86% ether 22, and 14% diisopropylethylamine, equivalent to 16.4 g (77%)

of product **22**. The diisopropylethylamine was removed by washing with cold 1 M aqueous HCl. Drying over $CaCl_2$ gave 12.3 g (67% yield) pure product **22**. ^{1}H NMR δ 6.43 (dd, 1H $J = 72.0$, 69.9 Hz), 6.04 (q, 1H, $J = 4.05$ Hz). ^{19}F NMR (H-decoupled) δ −80.8 (s, 3F), −87.6 (d, 1F, $J = 161$ Hz), −88.6 (d, 1F, $J = 161$ Hz).

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