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# A convenient and practical method for the selective preparation of deuterofluorocarbons



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#### ABSTRACT

A detailed study of the development of efficient and practical conditions for the selective synthesis of 1-deuterononafluorobutane from 1-iodononafluorobutane is reported. The optimal conditions involve treatment of the iodo-precursor in  $D_2O$  at ~170 °C in the presence of metallic zinc in a sealed Schlenk tube to give a 59% yield of 1-deutero-1,1,2,2,3,3,4,4-nonafluorobutane. The same method was applied successfully to two higher homologues to produce 1-deutero-1,1,2,2,3,3,4,4,5,5,5-undecafluoropentane and 1-deutero-1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexane in yields of 64% and 56%, respectively. Surprisingly, even the non-perfluorinated product 6-deutero-1,1,2,2,3,3,4,4-nonafluorohexane could be synthesized in 69% yield with this method.

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#### 1. Introduction

As part of a research program directed at the study of vibrational overtone dynamics in polyfluorinated hydrocarbons [1], we required a source of highly isotopically enriched monodeuterofluorocarbons (DFCs). These compounds are generally not commercially available and literature reports of their synthesis, and of their hydroisotopomers, are limited. For example, Hudlicky et al. reported in 1992, in a study of potentially anesthetic monoand di-hydrofluorocarbons (HFCs), that 1,1,1,2,2,3,3,4,4-nona-fluorobutane **1** ("4H-nFB") could be prepared by addition of 4-iodononafluorobutane **2** ("4I-nFB") to a warm mixture of zinc metal, catalytic zinc chloride, and methanol, followed by reflux (Scheme 1) [2]. This approach was based on seminal studies of the preparation and reactivity of perflouoroorganozinc iodides by Miller et al. [3] and by Haszeldine [4,5].

In related subsequent work, Howell et al. reported that primary iodoperfluoroalkanes also can be converted efficiently to the corresponding primary hydroperfluoroalkanes by treatment with sodium methoxide in methanol [6]. Howell, et al. conducted mechanistic studies (including deuterium transfer experiments proceeds through either an anion-mediated mechanism (high temperature, methanol solution, no radical initiators present; Scheme 2) or a radical-mediated mechanism (low temperature, methanol solution, elemental iodine present as radical initiator; Scheme 3). We reasoned that simple extension of Hudlicky et al.'s method

with CH<sub>3</sub>OD, CD<sub>3</sub>OH, or CD<sub>3</sub>OD) that demonstrated this conversion

for zinc-mediated transformation of iodofluorocarbons to include a suitable deuterium source would provide access to our desired mono-deuterofluorocarbons, and might also provide a general route to selectively deuterated synthetic targets. Selective deuterium incorporation plays a critical role in a broad range of experimental applications, from mechanistic studies employing kinetic isotope effects to spectroscopic work in which deuterium substitution provides easier spectral analysis and peak assignment. Moreover, recent pharmaceutical research has focused on the preparation and study of selectively deuterated drugs in order to increase overall drug efficacy by decreasing toxicity and slowing excretion rates, and to accomplish patent lifetime stretching [7]. Examples include deuterium-enriched *N*-pyrrolidinyl arylamides for treatment of urinary stress incontinence [8] and deuteriumenriched montelukast for treatment of asthma and allergies [9]. Deuterated organic compounds are also useful in the construction of light-emitting devices and photodiodes [10]. The research described herein details our attempts to maximize the efficiency of

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Scheme 1. Zinc-mediated synthesis of 4H-nonafluorobutane 1.



**Scheme 2.** Proposed [6] anion-mediated mechanism for transformation of primary iodoperfluoroalkanes.



Scheme 3. Proposed [6] radical-mediated mechanism for transformation of primary iodoperfluoroalkanes.

the synthesis of singly deuterated fluorocarbons by the simplest, mildest, and cheapest method possible through the use of  $D_2O$  as deuterium source.

#### 2. Results and discussion

#### 2.1. General aims and preliminary results

Our primary goal was to develop a convenient, efficient and economical method to synthesize 1-deutero-1,1,2,2,3,3,4,4,nonafluorobutane **3** (1-deuterononafluorobutane, "1D-nFB"). Hudlicky et al.'s preparation of the hydroisotopomer of **3** (**1**, Scheme 1) from **2** demonstrated that a readily protonated reactive intermediate was accessible from primary iodoperfluoroalkanes under very mild conditions (Zn°/catalytic ZnCl<sub>2</sub>/refluxing methanol). On the downside, isolating the highly volatile **1** (b.p. = 14 °C) in reasonable yield (72%) using this approach required conducting the reaction on large scale (100 g), the use of a dry ice trap and product purification by spinning-band distillation. Hence, our initial aims were to demonstrate that the Hudlicky et al. approach could be extended to produce **3** using a suitably deuterated form of methanol as solvent, and to develop a method that could conveniently provide highly pure product on a relatively modest scale (1-20 g).

We found that conducting the reaction in a 50 mL Schlenk tube was the easiest way to decrease its scale. Subsequent transfer to a second Schlenk tube, using standard vacuum line transfer techniques, then accomplished product isolation. In a preliminary trial, we found that simply shaking **2** in a sealed Schlenk tube containing zinc dust (1.4 eq.), a catalytic amount of anhydrous ZnCl<sub>2</sub> and CH<sub>3</sub>OD ([2] ~0.8 M) gave an exothermic reaction and produced a mixture of 3 (1D-nFB) contaminated with unreacted 2, the hydroisotopomer 1 (4H-nFB), perfluorooctane 6 ("dimer"), and traces of methanol, following product isolation and <sup>19</sup>F NMR analysis (Scheme 4,  $R = CH_3$ ) [11]. Because reaction was so spontaneous and vigorous under these conditions, we took pains to temporarily isolate the ZnCl<sub>2</sub> catalyst by placing it in a small test tube that was carefully positioned in the bottom of the Schlenk tube. After being sealed, the Schlenk tube was carefully tipped, allowing the reaction solvent to enter the test tube. Gentle shaking then allowed the catalyst to mix with the other reactants leading to vigorous bubbling and heat release.

We observed low levels of the dimeric side product **6** throughout our studies of zinc-mediated transformation of **2**. <sup>19</sup>F NMR and GC–MS data analyses of product mixtures were consistent with a molecular formula of  $C_8F_{18}$  for **6**, clearly suggesting that two nonafluorobutane fragments combined during its formation. Howell et al.'s work [6] indicated that either anionic (**4**, Scheme 2) or radical (**5**, Scheme 3) intermediates can be produced during transformation of primary iodoperfluoroalkanes. Hence, formation of **6** in our experiments could result from  $S_N2$  reaction between an anionic intermediate (**2i**) and a molecule of **2**, or from coupling of a pair of radical intermediates (**2r**), as shown in Scheme 5.

Our initial study sought to maximize conversion to and yield of 1D-nFB 3 while minimizing contamination with unreacted 2, isotopomer 1, "dimer" 6, and solvent. Parameters varied included reaction time, reaction temperature, concentration, and deuterium source (i.e. CH<sub>3</sub>OD and CD<sub>3</sub>OD). Results for these experiments are summarized in Table 1. In this Table, and all that follow, we include data that we measured in an effort to determine both the conversion of starting iodide to the desired deuterated product and the isolated yield of the product. Due to the extremely volatile nature of the deuterated products, and the necessarily small reaction scales involved, however, it was only possible in our experiments to estimate conversion and yield based on NMR analysis of products that could be only incompletely purified by a single stage of low-temperature/low-pressure bulb-to-bulb distillation. Thus, Trials 1-3 explored the use of CH<sub>3</sub>OD as deuterium source (Scheme 4,  $R = CH_3$ ). Trial 1 examined the effect of conducting the reaction at an elevated temperature: the reactants were mixed briefly at room temperature and then the Schlenk tube was immediately placed in a heating bath (60 °C). Under these conditions, crude yield of **3** appeared moderate (43%) and the very low level (<1%) of unreacted 2 contaminating the isolated product indicated conversion was high. However, contamination with the undesired hydroisotopomer 1 (7%) and reaction solvent ( $\sim$ 45%) were far from ideal. Contamination with solvent was essentially



Scheme 4. Zinc-mediated synthesis of 1D-nonafluorobutane 3.



Scheme 5. Possible competing dimerization pathways in zinc-mediated synthesis of 1D-nFB 3.

Table 1
Zinc-mediated preparation of 1D-nFB (3) from 4I-nFB (2) in CH <sub>3</sub> OD or CD <sub>3</sub> OD.

Trial	Solvent	Scale (g <b>2</b> )	Reactant ratios (mmol reactant/ mmol <b>2</b> ) <sup>a</sup>		ratios T (°C) <sup>b</sup> Rxn tim actant/ a		Relativ	ve product	ion (%) <sup>c</sup>	Crude yield (%) <sup>d</sup>	
			Solvent	Zn°			3	2	1	6	
1	CH₃OD	2.7	31.8	1.4	60	0.5	45	<1	7	2	43
2	CH₃OD	2.7	31.8	1.4	0, 22, 60	0.5 at each T	89	<1	9	<1	39
3	CH₃OD	2.1	8.0	1.4	22	0.5	84	<1	16	<1	30
4	CD <sub>3</sub> OD	15.8	6.1	1.4	22	0.5	99	<1	<1	<1	46

 $^a\,$  All reactions included a catalytic amount of ZnCl\_2: Trials 1–3:  ${\sim}10\,mg;$  Trial 4:  ${\sim}60\,mg.$ 

<sup>b</sup> Temperature of external heating/cooling bath.

<sup>c</sup> Relative composition was determined by integration of appropriate <sup>19</sup>F NMR signals in the product mixture following bulb-to-bulb transfer from the reaction flask. Percentages listed as <1% indicate that a trace of the specific product could be detected but not accurately integrated.

<sup>d</sup> Crude (e.g. uncorrected) yield based on total mass of product mixture collected relative to theoretical yield of **3** after bulb-to-bulb transfer from the reaction flask. Thus, these numbers are only roughly indicative of the actual yield of **3**.

eliminated in subsequent trials (Trials 2–4) by passing the volatilized product through a tube filled with freshly activated molecular sieves (4 Å) during the bulb-to-bulb transfer process (Fig. 1).

In Trial 2, we investigated the effect of a stepwise increase in temperature, beginning at 0 °C and ending at 60 °C. This had little effect on yield and contamination with **1**; the significant increase



**Fig. 1.** Vacuum apparatus for isolation of reaction product: (A) Schlenk reaction tube (50 mL); (B) test tube for isolation of  $ZnCl_2$  catalyst; (C) solvent trap filled with molecular sieves (4 Å for methanol; 3 Å for water); (D) Schlenk collection tube (25 or 50 mL); (E) vacuum valve.

in the contribution of **3** to the overall product composition was due to removal of solvent during product isolation. Trial 3 was performed at room temperature but at a significantly higher reactant concentration ([2] in CH<sub>3</sub>OD  $\sim$ 3.1 M) than Trials 1 and 2; the apparent increase in production of **1** under these conditions was traced to incomplete exclusion of moisture. Ultimately, we minimized formation of **1** with rigorously dry technique (including the use of a glove box for loading the Schlenk tube) and by using deuterated solvents with very high isotopic purity (99 at% D in trials with CD<sub>3</sub>OD).

Trial 4 explored the use of completely deuterated methanol (Scheme 4,  $R = CD_3$ , 99.8 at% D), at an even higher concentration ([2] in  $CD_3OD \sim 4.1$  M), and provided the purest sample overall of 3, although the yield was still modest (46%). While this set of experiments did not exhaustively optimize zinc-mediated transformation of 2 to 3, the outcome of Trial 4 provided a sample of 3 that was both large and pure enough to make our vibrational overtone dynamics studies possible.

#### 2.2. Preparation of 1D-nFB in D<sub>2</sub>O, with and without ZnCl<sub>2</sub> catalyst

Of course, the solvents/deuterium sources (CH<sub>3</sub>OD and CD<sub>3</sub>OD) used in our studies above are prepared commercially from D<sub>2</sub>O, which is a significantly less expensive potential deuterium donor ( $p_2O = 1.00$ , CH<sub>3</sub>OD = 1.77, CD<sub>3</sub>OD = 16.71). These facts led us to wonder if transformation of **2** to **3** might be accomplished directly in D<sub>2</sub>O (Scheme 4, R = D) as effectively as in CH<sub>3</sub>OD and CD<sub>3</sub>OD. Results from our experiments exploring this possibility are summarized in Table 2. In each of these experiments, held constant were the amounts of **2** (2.7 g) and Zn° (1.5 equiv.) while reaction temperature, reaction time, external energy source, concentration, zinc metal/ion source, and amount of ZnCl<sub>2</sub> catalyst were varied.

Table 2	2
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Zinc-mediated preparation of 1D-nFB (3) from 4I-nFB (2) in D<sub>2</sub>O.

Trial	Reaction conditions <sup>a</sup>				Relative product composition $(\%)^h$				Calc'd yield (%) <sup>j</sup>
	$T(^{\circ}C)^{b}$ Rxn time (h)		Other modifications	3	2	1	6		
5	22	1	-	58	40	2	<1	124	58
6a	115	1	_	74	23	3	<1	28	18
6b	115	5	_	85	8	4	2	82	66
6c	115	5	$2 \times D_2 O$ vol.	95	<1	2	2	90	85
6d	135	9	$2 \times D_2 O$ vol.	88	9	3	1	91	74
6e	135	24	$2 \times D_2 O$ vol.; nano $Zn^c$	90	3	5	2	80	69
7a	35	1	Sonication <sup>d</sup>	94	3	3	1	64	57
7b	35	5	Sonication	94	1	3	1	81	75
7c	35	5	Sonication, ZnO <sup>e</sup>	87	7	4	1	58	48
7d	40	13	Sonication	81	12	6	1	73	55
8a	60	1	Microwave reactor <sup>f</sup>	90	7	2	1	53	45
8b	170	2	Microwave reactor <sup>f g</sup>	55	21	24	<1	92	45
9a	110-140	15	19 mol% ZnCl <sub>2</sub>	70	27	2	1	121	73
9b	165	15	48 mol% ZnCl <sub>2</sub>	50	46	3	1	149	59
9c	170	6	No ZnCl <sub>2</sub>	87	7	4	2	72	59

<sup>a</sup> Trials 5, 6a–6e, 7a–7d, 8a–8b: reaction conducted with 2.7 g (7.7 mmol) of **2** and 0.755 g (11.46 mmol; 1.5 equiv.) of Zn° dust in D<sub>2</sub>O (4.84 mL; 268 mmol; 34.8 equiv., except Trials 6c, 6d, and 6e which used 9.68 mL of D<sub>2</sub>O (536 mmol; 69.6 equiv.)) and included a catalytic amount (~10 mg, ~0.07 mmol, ~0.1mol%) of ZnCl<sub>2</sub>. Trials 9a,b: reaction conducted with 7.7 mmol of **2** and 1.5 equiv. of Zn° dust in 9.68 mL (535.9 mmol, 69.6 equiv.) of D<sub>2</sub>O in a 50 mL Schlenk tube. Trial 9c: reaction conducted with 4.0 mmol of **2** and 1.5 equiv. of Zn° dust in 6.26 mL (344 mmol, 86 equiv.) of D<sub>2</sub>O in a 50 mL Schlenk tube.

<sup>b</sup> Temperature of external heating/cooling bath.

<sup>c</sup> Nanoparticle Zn (Sigma-Aldrich 578002-5G, particle size < 50 nm).

<sup>d</sup> Branson Model 1510 Sonicator; sonicator bath filled with water.

e Reaction included a catalytic amount (~10 mg) of ZnO instead of ZnCl<sub>2</sub>.

<sup>f</sup> Biotage "Initiator" Microwave Reactor; reaction conducted in 20 mL microwave vial.

<sup>g</sup> Microwave apparatus recorded a pressure of 15 bar during this run.

<sup>h</sup> Relative composition was determined by integration of appropriate <sup>19</sup>F NMR signals in the product mixture following bulb-to-bulb transfer from the reaction flask. Percentages listed as <1% indicate that a trace of the specific product could be detected but not accurately integrated.</p>

<sup>i</sup> (Crude reaction mass/theoretical mass of  $\mathbf{3}$ ) × 100.

<sup>j</sup> See Section 4.4 for details.

We discovered in preliminary trials that mixtures of 2, Zn°, and ZnCl<sub>2</sub> in D<sub>2</sub>O did not react spontaneously at room temperature. Therefore, in the trials summarized in Table 2, reactants were simply added to a Schlenk tube in the glove box at room temperature, after which the sealed tube was subjected to the indicated conditions. As before, these trials culminated with a bulb-to-bulb vacuum transfer of the product mixture through a tube containing freshly activated molecular sieves (3 Å, Fig. 1) into a second, tared Schlenk tube. The mass of the product isolated at this stage provided the "Crude Yield" values reported in Table 2. Subsequent preparation of an NMR sample of product mixtures and analysis by <sup>19</sup>F NMR spectroscopy then provided the relative product composition data presented which, in turn, provided the corresponding "Calculated Yield" values. Since the techniques developed earlier minimized undesired proton sources, we were not surprised to observe that crude product mixtures contained very little 1; integration of appropriate <sup>19</sup>F NMR signals showed that **1** typically was present at a level of  $\sim 3\% \pm 2\%$ . (The uncertainties inherent in our NMR signal integration protocol suggest that these estimates actually *overstate* actual contamination by **1**).

Trial 5, in which the reactants were simply shaken periodically at room temperature for 1 h, provided baseline results for this entire study. Thus, we were gratified to learn that transformation of **2** to **3** can be accomplished in  $D_2O$  ([2] in  $D_2O \sim 1.6$  M), although NMR analysis showed that more than a third of the isolated product was unreacted starting material, indicating that the desired reaction is fairly slow under these conditions. However, we were encouraged that the crude product was otherwise relatively pure, containing only a trace of **1** and an even smaller amount of the dimer **6**. Subsequent experiments aimed to improve these results.

Trials 6a–6d examined the effect of running the reaction at higher temperatures, for longer periods of time, and at lower concentration. These results show that the reaction appears to operate best when conducted for at least 5 h at a temperature of at

least 115 °C. In addition, running the reaction at lower concentration (e.g. [2] in  $D_2O \sim 0.8$  M, Trials 6c, 6d) appeared to somewhat improve overall product purity. Under these conditions, crude yields of **3** settled out at about 90% (or, after correcting the crude yield for the presence of unreacted **2** and side products **1** and **6**, at a calculated yield of ~74–85%). These data also showed that overall conversion of **2** to **3** (including Trials from 6b through 7c and 8a) fluctuated a bit, but is generally quite high (as suggested by the **3**:**2** ratio observed in the isolated products: from ~10:1 in Trial 6d to a significantly higher value in Trial 6c). Running the reaction under these improved conditions but with 1.5 equiv. of Zn° nanoparticles in place of Zn° dust did not appreciably affect the overall outcome (Trial 6e). We had hoped these conditions might increase the overall Zn° particle surface area available to **2** thereby increasing conversion and yield.

Trials 7a–7d investigated accelerating the reaction with sonication rather than heat. Ultimately, although sonication at 35 °C for 5 h (Trial 7b) appeared to be somewhat superior to heating the for the same time period (T = 115 °C, Trial 6b), we found that sonication gave results that were difficult to reproduce and understand (e.g. Trial 7d: sonication for a long period resulted in a lower conversion of **2** to **3**). Trial 7c showed that replacing ZnCl<sub>2</sub> with a different source of Zn<sup>2+</sup> catalyst (ZnO) also did not improve the reaction outcome.

Trials 8a and 8b illustrate several attempts to activate the desired transformation using microwave irradiation. Relatively brief (1 h) treatment in a sealed microwave reaction vessel at moderate temperature (60 °C, Trial 8a) gave overall results similar to those achieved by heating for 5 hr at 115 °C (Trial 6b); doubling irradiation time and increasing temperature (170 °C; Trial 8b) gave inferior results.

Trials 9a–9d summarize experiments that led to an optimized method for preparation of **3**. These experiments involve the effect of varying the amount of  $ZnCl_2$  catalyst present, reaction time and reaction temperature. Trials 9a and 9b demonstrate that increasing

the amount of ZnCl<sub>2</sub> catalyst surprisingly caused a marked decrease in the conversion of 2 to 3, even when reaction temperature is raised significantly. We don't have an explanation for this outcome but speculate that high levels of ZnCl<sub>2</sub> may coat the particles of metallic zinc, decreasing metal surface availability for reaction with substrate. Trial 9c reports a completely serendipitous result: conversion of 2 to 3 proceeded (6 h at 170 °C with 1.5 equiv. of  $Zn^{\circ}$ ) even when  $ZnCl_2$  was mistakenly omitted from the reaction mixture! Moreover, this reaction proceeded in 59% yield and with only 2% contamination with dimer 6. Ultimately, we found it was most convenient to conduct reactions under these simplified conditions by simply heating "overnight" (12–18 h) at 170 °C with only Zn° and D<sub>2</sub>O present. We believe the overall modest yield for this process mainly reflects the challenges inherent in removing the product from the reaction system and then separating it from solvent.

## 2.3. Method generality: Preparation of deuterofluorocarbons closely related to 4D-nFB

Successful preparation of **3** with  $D_2O$  led us to attempt our simplified deuteration method with other suitable substrates; results are reported in Table 3. For example, deuteration of primary iodoperfluroroalkanes closely related to **2** proceeded smoothly in good yield and high levels of purity. Thus, 5iodoundecafluoropentane (**7**) and 6-iodotridecafluorohexane (**8**), homologues of **2**, gave the corresponding deuterated products **9** and **10** [12] when heated overnight (12 h for **9**; 18 h for **10**) at 170 °C in  $D_2O$  with 1.5 equiv. of Zn°. In both of these examples, if the corresponding dimeric and protonated side products were produced, levels were so low they could not be detected by NMR spectroscopy.

Unfortunately, our deuteration method with  $D_2O$  only and no  $ZnCl_2$  is less successful with 1-iodoheptafluoropropane, **11**, the homologous substrate one  $CF_2$  unit *smaller* than **2**: our standard reaction conditions (170 °C, 18 h in a 50 mL Schlenk tube) produced a mixture of the desired product **12** [13] contaminated with unreacted starting material and the "dimeric" side product, tetradecafluorohexane, in a 1.0:2.6:0.53 ratio. Extensive experimentation aimed at improving this outcome explored increasing the reaction temperature, returning to the use of catalytic ZnCl<sub>2</sub>,

and even significantly decreasing the volume of the reaction Schlenk tube from 50 mL to 3 mL. We were led to decreasing the reaction tube volume by reasoning that since **11** is significantly more volatile than **2**, it will be present to a larger extent in the head space of the reaction tube, decreasing its contact with the zincbased reagent and, hence, its conversion to the deuterated product. In the smaller reaction vessel, containing the usual amounts of Zn° and D<sub>2</sub>O and 20 mol% of ZnCl<sub>2</sub>, heated to 223 °C for 45 h, the best outcome we could achieve was a product mixture showing 80% conversion of **11** to **12**, but, significantly, with *none* of the dimeric side product perfluorohexane observed. Although this result represented a significant improvement overall, we deemed it inferior, in overall practicality, to our result for synthesis of 12, reported in Table 3, using the original method with CD<sub>3</sub>OD as deuterium source: 12 produced in 39% isolated yield (contaminated with 7% of the dimeric side product). We have not yet studied deuteration of 1-iodoperfluorethane using D<sub>2</sub>O, but our results indicate that this process is difficult with substrates smaller than 4-iodononafluorobutane.

The final entry in Table 3 reports a completely unanticipated result: a nonperfluorinated primary iodosubstrate also smoothly underwent zinc-mediated deuteration. Thus, substrate 13 (1,1,1,2,2,3,3,4,4-nonafluoro-6-iodohexane), when treated with  $Zn^{\circ}$  alone in D<sub>2</sub>O at 170 °C for 9 h produced the corresponding deuterated product 14 in 69% yield, with no unreacted starting material or possible dimeric products detected by <sup>1</sup>H or <sup>19</sup>F NMR analysis. This surprising outcome allows us to draw two conclusions: (a) that fluorine substitution at the carbon atom undergoing zinc-mediated deuteration is unnecessary to allow C-I bond scission (surprising if a carbanion intermediate, as suggested above in Scheme 2, is actually involved), and (b) that possible  $\beta$ elimination of H-I from 13 (which would produce alkene 15, Scheme 6) does not compete with the desired deuteration process. The lack of elimination side products is particularly surprising since the deuteration process must produce  $Zn(OD)_2$  as it proceeds. In broader terms, efficient production of **14** suggests that substrates other than just iodoperfluorocarbons are susceptible to zinc-mediated deuteration in  $D_2O$ . We are currently conducting a more extensive exploration of this general methodology. We can make a preliminary report here, however, in support of our conclusion (a), above, that under our general reaction

#### Table 3

Zinc-mediated preparation of deuterofluorocarbons closely related to 4D-nFB.

$R_{F} - I \xrightarrow[XOD(X=CD_{3},D)]{\text{ZD} (X=CD_{3},D)} R_{F} - D$				
Substrate, R <sub>F</sub> =	Deuteron source	Reaction time (h)	Deuteration product (calculated yield, %) <sup>b</sup>	Comments
<ol> <li>7, CF<sub>3</sub>CF<sub>2</sub>CF<sub>2</sub>CF<sub>2</sub>CF<sub>2</sub>CF<sub>2</sub></li> <li>8, CF<sub>3</sub>CF<sub>2</sub>CF<sub>2</sub>CF<sub>2</sub>CF<sub>2</sub>CF<sub>2</sub>CF<sub>2</sub></li> <li>11, CF<sub>3</sub>CF<sub>2</sub>CF<sub>2</sub></li> <li>13, CF<sub>3</sub>CF<sub>2</sub>CF<sub>2</sub>CF<sub>2</sub>CF<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub></li> </ol>	$D_2O^a$ $D_2O^a$ $CD_3OD^c$ $D_2O^a$	12 18 0.5 9	<b>9</b> (64) <b>10</b> (56) <b>12</b> (39) <b>14</b> (69)	$R_F-H$ , $R_F-R_F$ contaminants below NMR detection limits $R_F-H$ , $R_F-R_F$ contaminants below NMR detection limits Product contained 7% of $R_F-R_F$ dimer $R_F-H$ , $R_F-R_F$ contaminants below NMR detection limits

<sup>a</sup> Standard reaction conditions: used 2.5–6 mmol (1 equiv.) of  $\mathbf{R_{F}-I}$  and  $Zn^{\circ}$  dust (1.5 equiv.) in  $D_2O$  (69 equiv.;  $[\mathbf{R_{F}-I}] \sim 0.8 \text{ M}$ ) overnight (9–18 h) at 170 °C in a 50 mL Schlenk tube.

<sup>b</sup> Yield was calculated (see Table 2) by integration of appropriate NMR signals (<sup>19</sup>F, and <sup>1</sup>H for **14**) in the isolated product mixture following bulb-to-bulb transfer from the reaction flask.

<sup>c</sup> Reaction conducted using **11** (13.8 g, 46.7 mmol), Zn° dust (4.58 g, 70.1 mmol, 1.5 equiv.) and catalytic ZnCl<sub>2</sub> (~60 mg) in CD<sub>3</sub>OD (11.26 mL, 277 mmol, 5.93 equiv.) at room temperature (0.5 h) in a 50 mL Schlenk tube.



Scheme 6. Zinc-mediated synthesis of 6D-1,1,1,2,2,3,3,4,4-nonafluorohexane 14.

conditions 1-iodobutane gives 1-deuterobutane in greater than 80% yield. We will report full details in a future publication.

#### 3. Conclusions

Our studies provide a practical route for the preparation of monodeuterofluorocarbons from the corresponding monoiodofluorocarbons using zinc dust and a suitable solvent as deuterium source in sealed Schlenk tubes. Reaction with CD<sub>3</sub>OD and Zn° (with or without ZnCl<sub>2</sub> catalyst) with primary iodo-perfluorocarbons provides the corresponding 1-deuteroperfluorocarbons in moderate yield and good purity. With 4-iodononafluorobutane (2), 5iodoundecafluoropentane (7) and 6-iodotridecafluorohexane (8), the reaction can be simplified by elimination of the ZnCl<sub>2</sub> catalyst and replacing  $CD_3OD$  with (significantly less expensive)  $D_2O$ . These conditions require longer reaction times and higher temperatures but produce the corresponding 1-deuterononafluorobutane (3), 1-deuteroundecafluoropentane (9) and 1-deuterotridecafluorohexane (10) products in excellent yield and purity. Surprisingly, these conditions work smoothly and efficiently with 1,1,1,2,2,3,3,4,4nonafluoro-6-iodohexane (13) to produce 14, indicating that the deuteration method can tolerate iodofluorocarbon substrates lacking fluorine atoms at the  $\alpha$ - and  $\beta$ -positions.

#### 4. Experimental

#### 4.1. General information

All reactions were performed in 50 mL Schlenk tubes (Chemglass Life Sciences, AF-0096) that were charged with reagents and a small magnetic stir bar at room temperature under an atmosphere of dry nitrogen in a glove box (Vacuum Atmospherics Co., HE-493) before the Schlenk tube valve was closed and they were removed from the glove box. Liquids were added to the Schlenk tube using new disposable plastic syringes (NormJect) of the appropriate size and 6-inch stainless steel needles (Sigma-Aldrich, Z219363). Reactions were conducted in a fume hood behind an explosion shield. Reactions conducted above room temperature were heated at the desired temperature by inserting the Schlenk tube in a sandfilled heating mantle; gentle agitation was provided by spinning the magnetic stir bar.

D<sub>2</sub>O was obtained from Cambridge Isotope Laboratories (99.9 atD %, DLM-4-100). 4-iodononafluorobutane (98%, 1100-J-06), 5-iodoundecafluoropentane (97%, 1100-J-51), 6-iodotridecafluorohexane (98%, 1100-J-12), and 1-iodoheptafluoropropane (95%, 1100-J-07) were obtained from SynQuest Labs, Inc. 1,1,1,2,2,3,3,4,4-nonafluoro-6-iodohexane (95%, 07387-5G-F) and CH<sub>3</sub>OD (99 atD %, 15,193-9) were obtained from Sigma-Aldrich. CD<sub>3</sub>OD was obtained from Cambridge Isotope Laboratories (99.8 atD %, DLM-24-S-10). These reagents were stored in the glove box: iodine-containing precursors were wrapped in foil to minimize exposure to light. Zinc dust (98%,  $<10 \,\mu$ m, 209988-100G), anhydrous zinc chloride (99.99%, 429430-5G) and nanopowder zinc (99%, 578002-5G) were obtained from Sigma-Aldrich. CDCl<sub>3</sub> (99.8%D with 0.05% TMS, DLM-7-t-b) was obtained from Cambridge Isotope Laboratories and was stored in a desiccator; CFCl<sub>3</sub> (99%, 254991) was obtained from Sigma-Aldrich and was stored in a refrigerator. Molecular sieves were obtained from Sigma-Aldrich (3 Å, 208574; 4 Å, 208590) and were activated by heating in a vacuum drying oven (National Appliance Co., Model 5831) overnight at 160 °C followed by cooling to room temperature in a desiccator.

Reaction products (and any un-reacted starting materials) were separated from zinc, zinc chloride and reaction solvents/deuterium sources by bulb-to-bulb distillation into a dry, tared 25 mL Schlenk tube employing a vacuum transfer line. Interposed between the reaction and collection Schlenk tubes, and used to remove reaction solvents/deuterium sources, was a hand-fashioned drying tube (forged by joining two 2 "long, 9 mm diameter Pyrex tubes to a 5" long, 14 mm Pyrex tube; see Fig. 1) filled with lightly pulverized, activated molecular sieves (3 Å sieves were used to remove  $D_2O$ ; 4 Å sieves were used to remove CH<sub>3</sub>OD and CD<sub>3</sub>OD). Cooling of Schlenk tubes during the bulb-to-bulb transfer operations, and freeze/pump/thaw degassing steps, was provided by immersion in liquid-nitrogen-filled Dewar flasks.

#### 4.2. Exclusion of proton sources

In order to minimize the inclusion of proton ( $^{1}$ H) sources during the synthesis of deuterofluorocarbons, all necessary steps were taken to exclude water. All glassware, syringe needles, and tools were washed with water, rinsed with methanol, and then ovendried at 160 °C (Fisher Isotemp 230G oven) and allowed to cool to room temperature in a desiccator before use. Used reaction vessels containing zinc were washed with cycles of concentrated HCl (aq), distilled water, 1 M NaOH, distilled water, and methanol, followed by oven drying. Schlenk tube valves and syringe needles were cleaned by rinsing with methanol and wiping dry with Kimwipes followed by storage overnight in a desiccator before reuse.

#### 4.3. NMR analysis

<sup>1</sup>H and <sup>19</sup>F NMR spectra were measured using a Brüker Avance DRX 500 MHz NMR spectrometer operating at frequencies of 500.150  $(^{1}\text{H})$  and 470.611  $(^{19}\text{F})$  MHz using the proton coil (which was separately retuned to observe <sup>19</sup>F frequencies) in a standard 5 mm broadband multinuclear (PABBO) probehead (90° pulse widths: <sup>1</sup>H, 11.5 µs; <sup>19</sup>F, 10.0 µs). <sup>1</sup>H NMR spectra were measured at 298 K while <sup>19</sup>F NMR spectra were measured at 273 K using the NMR spectrometer's BVT-2000 variable temperature unit. Measuring <sup>19</sup>F spectra at the lower temperature reduced <sup>19</sup>F signal complexity, which we tentatively ascribed to a decrease in conformational isomer distribution. <sup>19</sup>F NMR spectra were not proton decoupled. <sup>1</sup>H chemical shifts (ppm) were measured relative to internal TMS ( $\delta$  = 0 ppm); <sup>19</sup>F shifts were measured relative to internal CFCl<sub>3</sub> ( $\delta$  = 0 ppm). Spectral windows for <sup>19</sup>F acquisitions were set at 200 ppm; the recycle delay (D1) was set at 5 s. Sample spectra for compounds 3, 9, 10, 12, and 14 are presented in the Supplementary Data section.

In order to assess reaction product purity, and to provide a calculated reaction yield, a small sample of each reaction product was transferred, using the vacuum transfer line, to a 5 mm NMR tube equipped with a J. Young valve (Wilmad 507-JY-7). Samples were prepared by pre-filling an NMR tube with  ${\sim}700\,\mu\text{L}$  of a premade mixture of CDCl<sub>3</sub> and CFCl<sub>3</sub> ( $\sim$ 0.05% (v/v)) using a 1000 µL gas tight syringe. The J. Young valve was then closed and the NMR tube was attached to the vacuum manifold and immersed in the liquid nitrogen bath and then evacuated to 17-20 mTorr. A Schlenk collection tube containing a reaction product was then attached to the vacuum line and immersed in liquid nitrogen. Once the sample was cold, the Schlenk collection tube valve was opened and the liquid nitrogen Dewar flask under the tube was removed. Transfer of the reaction product into the NMR tube was then allowed to proceed until it was evident that the column of liquid in the NMR tube had increased in depth by a few millimeters. The J. Young valve and the Schlenk collection tube valves were then closed and both tubes were allowed to warm to room temperature.

## 4.4. Assessment of product purity and reaction yield calculation by NMR analysis

Relative product composition (Tables 1–3) and calculated yield (Table 2) for all deuteration reactions were determined by

measurement of relative integral areas of <sup>19</sup>F NMR signals for the deutero-product, hydro-product, unreacted starting material, and "dimer" following assignment of unique and well-resolved characteristic signals for each material. Relative integral areas (which are equivalent to the mole fraction of each material in the isolated product mixture) led directly to the relative product composition data reported. Calculated yield was determined by comparing the actual moles of deutero-product produced, measured by <sup>19</sup>F NMR signal integration, with the theoretical moles of deuteroproduct calculated from the mass of starting iodofluorocarbon used in each reaction. The total moles of all materials in the isolated product could be calculated by dividing the total isolated product mass by the sum of the mole fraction for each material times their respective molecular weights. Actual moles of deutero-product could be calculated by dividing the numerical difference of the total isolated product mass and the measured mass of the deuteroproduct by the molecular weight of the deutero-product. Finally, the measured mass of the deutero-product was equal to the total moles of all materials in the isolated product times the sum of the mole fractions for the hydro-product, unreacted starting material and dimer times their respective molecular weights.

#### 4.5. 1-Deutero-1,1,2,2,3,3,4,4,4-nonafluorobutane, 3

The preparation of 1-D-nonafluorobutane **3** (1D-nFB) serves as a general guide for the synthesis of deuterofluorocarbons. Preparation of compounds reported in Sections 4.6–4.8 below employed these methods.

Inside a glove box, reactants were added to a 50 mL Schlenk tube (containing a  $10 \times 5$  mm Teflon-coated magnetic stir bar) under an atmosphere of nitrogen. Zinc dust (0.497 g, 7.6 mmol, 1.5 equiv.) was added to the Schlenk tube using a spatula, taking care to keep the neck of the Schlenk tube free of zinc dust, which could impair sealing the tube. Deuterium oxide (D<sub>2</sub>O, 6.26 mL, 345 mmol, 86 equiv.) and 4-iodononafluorobutane **2** (41-nFB, 0.65 mL, 4.0 mmol, 1.0 equiv.) were added by gas-tight syringe. The Schlenk tube was sealed, removed from the glove box and then shaken vigorously for a few minutes to mix the contents.

The Schlenk tube was then heated at 170 °C in a sand bath for 6 h. Vigorous bubbling was observed to commence in the tube shortly after the heating period began. The tube was removed from the sand bath, allowed to cool to room temperature, and then was attached to a vacuum transfer line. To isolate the desired product from the reaction vessel, a bulb-to-bulb transfer was performed, beginning with the removal of nitrogen gas (from the glove box operations) through a series of freeze-pump-thaw cycles using liquid nitrogen. While removing nitrogen gas, this step retained D<sub>2</sub>O and all reactants and reaction products as frozen solids. This degassing was repeated (usually 3–7 cycles) until the vacuum manifold pressure remained below 20 mTorr when the Schlenk tube was opened to the frozen solids.

After this initial de-gassing process was complete, a collection apparatus, including a clean, empty Schlenk tube and a drying tube (containing oven-dried 3 Å molecular sieves, see above, and Fig. 1) was attached to the vacuum system in order to isolate the product from the crude reaction mixture. The product isolation process began by flushing the collection tube and drying tube with nitrogen to displace water, and then evacuating. The collection tube valve was closed and the collection tube was removed from the vacuum line and tared. The collection tube was then returned to the vacuum line, its valve was opened, and then reaction tube was cooled in a water ice bath to prevent excessive vaporization of D<sub>2</sub>O during the bulb-to-bulb transfer. The evacuated collection tube was then placed in a liquid-nitrogen-filled Dewar flask and main vacuum valve E (Fig. 1) was closed in order to isolate the transfer line system from the vacuum pump.

While the reaction mixture was rapidly agitated with a magnetic stir bar, the reaction tube valve was opened slowly until the reaction mixture began visibly bubbling. During this process, the denser and more volatile deuterofluorocarbon product could be seen rising through the D<sub>2</sub>O solvent. Care was taken to avoid "bumping" of the solvent: if D<sub>2</sub>O rose near the level of the neck of the flask, the product transfer rate was slowed by slightly closing the reaction Schlenk tube valve. Product transfer progress was evidenced both by a decrease in the pressure observed in the transfer line and by the physical descent of the light gray, oxidized zinc solid in the reaction tube. (Variation in the transfer efficiency of the variety of fluorinated materials involved in this study made it difficult to standardize the process for bulb-to-bulb transfer. In some cases, the reaction tube was connected to a second, clean collection flask and the process was repeated if the yield from the first transfer appeared abnormally low.) To complete the transfer, the collection tube valve was closed. At this point, if the vacuum line pressure had not dropped below 1 Torr, or if there had been bumping during the transfer, the reaction flask was placed in a liquid-nitrogen-filled Dewar flask in order to condense and retain any volatile compounds remaining in the line. The transfer line was only opened to the vacuum pump once both Schlenk flasks had been closed. The collection flask was then allowed to warm to room temperature.

The product was a homogenous colorless liquid when the collection tube was immersed in liquid nitrogen, but was invisible gas at room temperature. The mass of the collection tube was then measured; the isolated product weighed 0.631 g (59% calculated yield; Table 2). By <sup>19</sup>F NMR analysis, this sample was composed of a mixture of **3** (87%), **2** (7%), **1** (4%), and **6** (2%). **3**: <sup>19</sup>F NMR  $\delta$  –81.5 (t, 3F, F-4); –128.3 (m, 2F, F-3); –130.9 (m, 2F, F-2); 138.4 (m, 2F, F-1).

#### 4.6. 1-Deutero-1,1,2,2,3,3,4,4,5,5,5-undecafluoropentane, 9

A 50-mL Schlenk flask was charged with 2.42 g of 5iodoundecafluoropentane **7** (1.15 mL, 6.12 mmol), 7.5 mL of D<sub>2</sub>O (421 mmol, 69 equiv.), 0.596 g of Zn dust (9.16 mmol, 1.5 equiv.), and a magnetic spin bar under an atmosphere of nitrogen inside a glove box. The Schlenk tube was sealed, removed from the glove box and then heated in a sand bath at 170 °C for 12 h. The tube was then removed from the sand bath, allowed to cool to room temperature, and the crude product mixture was transferred, using a vacuum transfer line, into a tared 25-mL Schenk tube. The product (1.038 g, 64% yield) was a colorless oil. <sup>19</sup>F NMR  $\delta$  –81.1 (t, 3F, F-5); -124.6 (m, 2F, F-4); -126.6 (m, 2F, F-3); -129.8 (m, 2F, F-2); -137.9 (m, 2F, F-1).

#### 4.7. 1-Deutero-1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexane, 10

A 50-mL Schlenk flask was charged with 2.23 g of 6iodotridecafluorohexane **8** (1.08 mL, 5.0 mmol), 6.26 mL of D<sub>2</sub>O (345 mmol, 69 equiv.), 0.497 g of Zn dust (7.60 mmol, 1.5 equiv.), and a magnetic spin bar under an atmosphere of nitrogen inside a glove box. The Schlenk tube was sealed, removed from the glove box and then heated in a sand bath at 170 °C for 18 h. The tube was then removed from the sand bath, allowed to cool to room temperature, and the crude product mixture was transferred, using a vacuum transfer line, into a tared 25-mL Schenk tube and weighed. The product (0.900 g, 56% yield) was a colorless oil. <sup>19</sup>F NMR  $\delta$  –81.2 (t, 3F, F-6); –123.6 (m, 2F, F-5); –124.2 (m, 2F, F-4); –126.9 (m, 2F, F-3); –130.1 (m, 2F, F-2); –138. 3 (m, 2F, F-1).

#### 4.8. 6-Deutero-1,1,1,2,2,3,3,4,4-nonafluorohexane, 14

A 50-mL Schlenk flask was charged with 0.93 g of 1,1,1,2,2,3,3,4,4-nonafluoro-6-iodohexane **13** (0.48 mL, 2.5 mmol), 3.13 mL of  $D_2O$  (173 mmol, 69 equiv.), 0.244 g of Zn dust

(3.75 mmol, 1.5 equiv.), and a magnetic spin bar under an atmosphere of nitrogen inside a glove box. The Schlenk tube was sealed, removed from the glove box and then heated in a sand bath at 170 °C for 9 h. The tube was then removed from the sand bath, allowed to cool to room temperature, and the crude product mixture was transferred, using a vacuum transfer line, into a tared 25-mL Schenk tube and weighed. The product (0.432 g, 69% yield) was a colorless oil. <sup>1</sup>H NMR  $\delta$  1.13 (br. t, 2H, H-6); 2.10 (m, 2H, H-5). <sup>19</sup>F NMR  $\delta$  –81.5 (t, 3F, F-1); –117.4 (m, 2F, F-2); –125.2 (m, 2F, F-3); –126.8 (m, 2F, F-4).

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#### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2015.10.002.

#### References

- [1] B.G. Saar, G.P. O'Donoghue, A.H. Steeves, J.W. Thoman Jr., Chem. Phys. Lett. 417 (2006) 159–163.
- [2] T. Hudlicky, R. Fan, J.W. Reed, D.R. Carver, M. Hudlicky, E.I. Eger II, J. Fluorine Chem. 59 (1992) 9–14.
- [3] W.T. Miller Jr., E. Bergman, A.H. Fainberg, J. Am. Chem. Soc. 79 (1957) 4159–4164.
- [4] R.N. Haszeldine, Nature 168 (1951) 1028–1031.
- [5] R.N. Haszeldine, E.G. Walaschewski, J. Chem. Soc. (1953) 3607-3610.
- [6] J.L. Howell, B.J. Muzzi, N.L. Rider, E.M. Aly, M.K. Abouelmagd, J. Fluorine Chem. 72 (1995) 61–68.
- [7] A.T. Yarnell, Sci. Technol. 87 (2009) 36-39.
- [8] A.W. Czarnik Protia, LLC, USA (2009) U.S. Pat, Appl. Publ. (2009) US 2009062373 A1 20090305.
- [9] A.W. Czarnik Protia, LLC, USA (2008) U.S. Pat, Appl. Publ. (2008) US 2008319007 A1 20081225.
- [10] K.C. Hwang, C.C. Tong, T.H. Yeh U.S. Pat, Appl. Publ. (2009) US 2009295274 A1 20091203.
- [11] (a) For references detailing <sup>1</sup>H and <sup>19</sup>F NMR data for 1 and 3 H. Blancou, P. Moreau, A. Commeyras, Tetrahedron, 33 (1977) 2061–2067;
  (b) A. Foris, Magn. Reson. Chem. 42 (2004) 534–555;
  (c) J. Gil-Rubio, J. Vicente, J. Guerrero-Leal, M. Blaya, D. Bautista, P.G. Jones,
  - Organometallics 31 (2012) 1287–1299.
- [12] J. Paterová, M. Skalický, M. Rybáčková, M. Kvíčalová, J. Cvačka, J. Kvíčala, J. Fluorine Chem. 131 (2010) 1338–1343.
- [13] G. Giacometti, E.W.R. Steacie, Can. J. Chem. 36 (1958) 1483-1500.