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Self-Promoted Nucleophilic Addition of Hexafluoro-2-propanol to Vinyl Ethers

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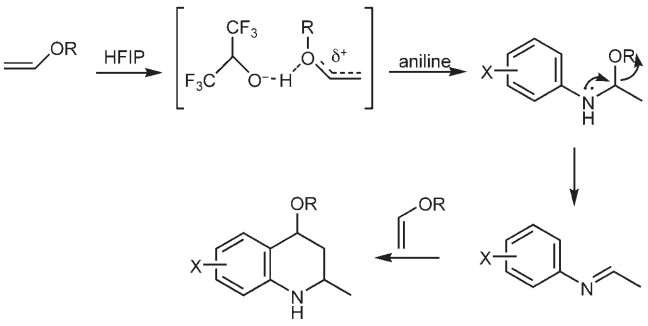
Abstract: In spite of its low nucleophilicity, hexafluoro-2-propanol easily adds to vinyl ethers, without catalyst, to afford a range of hexafluoroisopropyloxy acetals. This addition reaction also occurred in the presence of a competitive, more nucleophilic alcohol. Kinetic studies showed the importance of hydrogen bond parameters in the rate and course of the reaction.

Keywords: acetals; carbohydrates; fluorine; hexafluoro-2-propanol; protecting groups; solvent effect

Introduction

In recent years, the importance of fluoro alcohols as media for organic synthesis was illustrated by a huge number of articles.[1] The main advantage of these alcohols, for example, hexafluoroisopropanol (HFIP) and trifluoroethanol (TFE), is the possibility to carry out, in the absence of promoting agents, reactions that usually require the aid of Lewis acids or catalysts. In this connection, we reported the HFIP-promoted preparation of tetrahydroquinolines in a one-pot procedure from anilines and enol ethers (Scheme 1).[2] In this reaction HFIP facilitates the nucleophilic addition of anilines to vinyl ethers, probably through formation of an intermediate species with cationic character.

In order to extend the scope of this reaction we investigated other nucleophiles, such as alcohols. The addition of alcohols to 3,4-dihydro-2*H*-pyran (DHP) is a very useful reaction for the protection of alcohols and has been widely described in the presence of a variety of Lewis acids or strong protic acids.[3] The achievement of this reaction without the need of any metal or Lewis acid catalysis would be a great improvement.



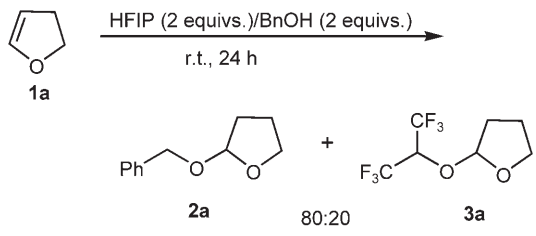
Scheme 1. Formation of tetrahydroquinolines by a domino reaction in HFIP.

Results and Discussion

In a preliminary experiment, equimolar amounts of benzyl alcohol and HFIP were allowed to stir at room temperature with dihydrofuran **1a** during one day (Scheme 2).

Surprisingly it was found that HFIP competed with the benzyl alcohol for the addition onto the vinyl ether, affording a non-negligible amount of 1,1,1,3,3,3-hexafluoroisopropoxytetrahydrofuran (**3a**).

The reaction was then investigated in pure HFIP without any other nucleophile. Reaction was carried out by dissolving dihydrofuran (12 mmol) in a four-fold excess of HFIP and allowing the mixture to stir at room temperature. The reaction was strikingly very fast (2 h) and, af-



Scheme 2.

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ter distillation of HFIP, the acetal **3a** was isolated in 86% yield.

Because of its very low nucleophilicity [N (HFIP) = −3.93],[4,5] interference of hexafluoro-2-propanol in reactions, when it is used as solvent, is rare. Nevertheless some nucleophilic additions of fluorinated alcohols to oxonium intermediates have been reported for the synthesis of fluoro acetals.[6] The acidity of fluorinated alcohols has also been exploited in the Mitsunobu reaction to efficiently synthesize, by nucleophilic substitution, polyfluoro ethers[7] and fluoroalkyl glycosides.[6b,8]

However, to the best of our knowledge, only two examples of self-promoted nucleophilic reactions of HFIP have been reported. They concern oxirane ring opening. When HFIP was reacted with the 9,10-epoxy ether derivative of artemisinin, the corresponding 10-hexafluoropropyloxy acetal was obtained after 15 min at room temperature,[9] whereas the reaction of TFE with the same epoxy ether required the presence of *p*-toluenesulfonic acid.[10] When styrene was reacted with H_2O_2 in HFIP, α-hexafluoropropyloxy-β-hydroxyethylbenzene was formed as a secondary product, probably by HFIP-promoted opening of the intermediate epoxide.[11]

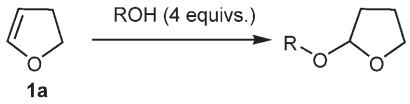
Despite of these examples showing that HFIP can act, to some extent, as a nucleophile, the more striking feature, in the present experiment, is the easy addition of HFIP to the enol ether, even in the presence of a more nucleophilic alcohol.

This prompted us to investigate this reaction in order to evaluate the promoting effect of HFIP and to have a better understanding of the competitive addition to the enol ether. Reactions were first studied using a range of alcohols alone, and then using mixtures of HFIP and a second alcohol.

The reaction of enol ethers with alcohols was first attempted with another fluorinated alcohol, trifluoroethanol (TFE), which is less acidic and a weaker hydrogen bond donor than HFIP (pK_a = 12.3 versus 9.3, and α = 1.51 versus 1.96),[5e] but slightly more nucleophilic [N (TFE) = −2.78]. Reactions were carried out with dihydrofuran **1** in excess of TFE (4 equivs.). The adduct **4a** was formed only upon refluxing and in a poor conversion rate (30%) (Table 1). The reaction was then performed with more nucleophilic non-fluorinated alcohols. With BnOH, MeOH and *i*-PrOH, the addition also occurred providing acetals, but in long reaction times and with 100%, 54% and 47% conversion, respectively.

These results indicate that the reaction is governed by several factors. It requires either an easy generation from the enol ether of an intermediate with a marked cationic character or a high nucleophilicity of alcohols. Alcohols have the double role of promoting agent and of nucleophile.[12] In this reaction, TFE is not able to satisfy any of these requirements and HFIP is the most efficient reagent. The intriguing easiness of addition of HFIP, despite of its poor nucleophilicity, can be rationalized by close associations of HFIP with dihydrofuran through hydrogen bonding, as already reported with THF.[13] In an intermediate involving one molecule of HFIP closely associated to one molecule of dihydrofuran, the development of a positive charge makes the dihydrofuran electrophilic, and the development of a negative charge makes HFIP nucleophilic (Scheme 3). The formed ion pair could then collapse to give the fluoro acetal. It is, however, not precluded that such associations involve more than one molecule of HFIP, this latter becoming a hydrogen bond acceptor, when its proton is strongly involved in a hydrogen bond with a good acceptor.[14]

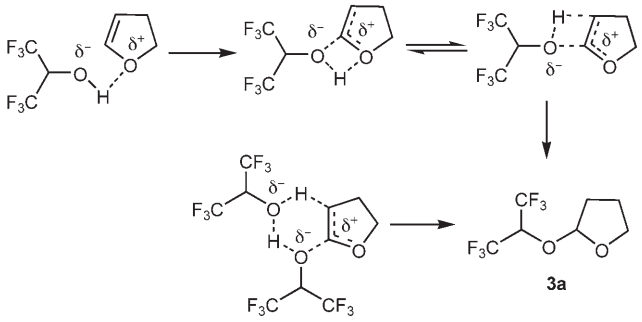
Table 1.



Entry	Alcohol	Reaction time	T [°C]	Product	Conversion
1	HFIP	2 h	r.t.	**3a**	100%
2	TFE	1d	Reflux[a]	**4a**	30%
3	BnOH	16 h	80 °C[a]	**2a**	100%
4	MeOH	16 h	80 °C[a]	**5a**	54%
5	*i*-PrOH	16 h	80 °C[a]	**6a**	47%

[a] Reaction performed in a bath at 80 °C (after 2 days at room temperature only starting material was recovered).

Competitive experiments have been performed with a mixture of HFIP and other alcohols in the view to obtain more information on the mechanism of this reaction. Taking into account these preliminary results, some questions arise. In the competition between benzyl alcohol and HFIP, the acetal **2a** could be the result of a substitution reaction of the fluorinated acetal **3a** by benzyl alcohol. Indeed, Matsumara reported that in the reaction of a nucleophile with the α-trifluoroethoxytetrahydrofuran, the trifluoroethoxide was a better leaving group than the alkoxide.[6d] The reaction with TMSCN provided no ring opening while the same reaction performed with no fluorinated cyclic acetals give a mixture



Scheme 3. Mechanism of the addition of HFIP to enol ethers.

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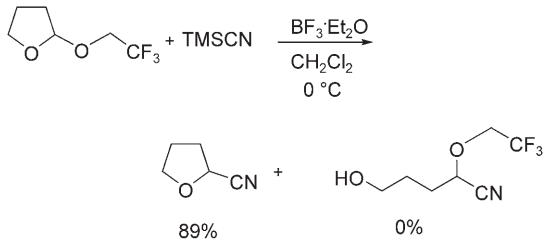
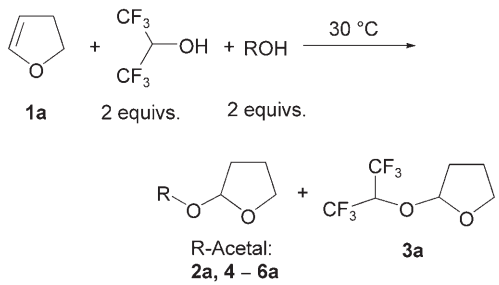


Scheme 4.



Scheme 5. Competitive experiments.

of cyclic and non-cyclic substituted compounds (Scheme 4).[6d,15]

Due to the presence of two CF_3 groups, the hexafluoroisopropyl moiety should behave as an even better leaving group. Consequently once formed, **3a** can easily be converted into **2a**. Alternatively the acetal **2a** can also be formed through a direct addition of benzyl alcohol on the enol ether activated by HFIP. Nevertheless, it has been shown that, because of its high hydrogen bond donor ability, HFIP can deactivate good nucleophiles such as aliphatic alcohols or amines, by means of acid-base interactions.[16]

First, it has been checked than **3a** is stable at room temperature in the presence of 1 equivalent of benzyl alcohol, which proves that the formation of acetals **2a** and **3a** are two competitive pathways. Then kinetic studies of the competition between HFIP and other alcohols (MeOH, BnOH, *i*-PrOH, TFE) were investigated. HFIP (2 equivs.), the second alcohol (2 equivs.) and dihydrofuran **1a** (1 equiv.) were introduced in an NMR tube, and the reaction was followed at 30 °C by ^{1}H NMR, measuring the integration of protons C(*H*)-O (Scheme 5). The initial rate of formation of products **R-Ac** (**2a**,**4a**–**6a**) and **3a** (evaluated from t_0 to time corresponding to 10% conversion of **1a**), and the **R-Ac/3a** ratios at reaction completion, are reported in Table 2. Figure 1 illustrates the kinetic profile of the reaction with BnOH.

It appeared that both acetals are stable under these conditions. Reaction times are not reflecting the nucleophilicity of alcohols. The faster reaction (12 h) is obtained when the second alcohol is TFE, which is the poorest nucleophile. This could be the result, as expected, of the deactivation of the competing alcohols by HFIP. However the addition of trifluoroethanol is disfavoured over that of HFIP with a **4a**/**3a** ratio of 0.67, while the addition of non-fluorinated alcohols is always favoured. An examination of the initial rates of reaction shows that the rate of formation of **3a** is also far slower than in the case of the reaction performed in HFIP alone and highly depending on the second alcohol: it is, for example, 10 times lower with *i*-PrOH than with TFE (entries 3 and 4). This indicates that the competitive path-

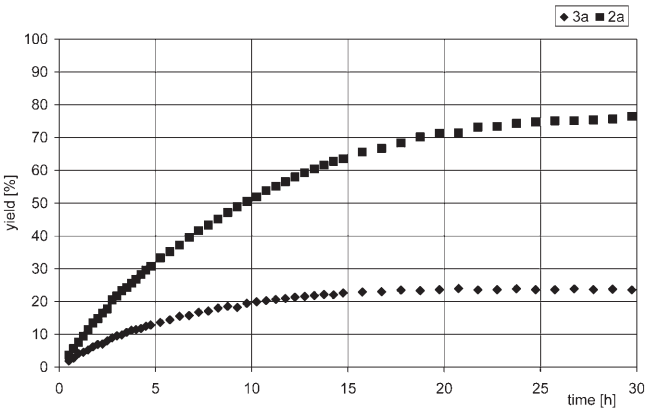


Figure 1. Kinetic profile for the competitive addition of HFIP and BnOH to dihydrofuran **1**.

Table 2. Initial rate of formation and products ratio in the competitive addition of HFIP and another alcohols to dihydrofuran **1a** at 30 °C.

Entry	ROH	Initial reaction rate · $k_{in} \times 10^5$ (mol/(L·s))	Initial reaction rate ratio (**R-Ac**/**3a**)	Products ratio at completion (time)
1	BnOH	k_{in} (**2a**) = 4.18 ± 0.08 k_{in} (**3a**) = 1.73 ± 0.13	**2a**/**3a** = 2.42	**2a**/**3a** = 3.2 (30 h)
2	MeOH	k_{in} (**5a**) = 1.48 ± 0.03 k_{in} (**3a**) = 0.99 ± 0.02	**5a**/**3a** = 1.49	**5a**/**3a** = 2.25 (60 h)
3	*i*-PrOH	k_{in} (**6a**) = 1.10 ± 0.04 k_{in} (**3a**) = 0.64 ± 0.02	**6a**/**3a** = 1.71	**6a**/**3a** = 3.0 (88 h)
4	TFE	k_{in} (**4a**) = 2.99 ± 0.04 k_{in} (**3a**) = 6.93 ± 0.25	**4a**/**3a** = 0.43	**4a**/**3a** = 0.67 (12 h)

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Table 3. Initial rates of formation of **3a** and values of β.[17]

Alcohol	*i*-PrOH	MeOH	BnOH	TFE	HFIP
β	0.95	0.62[4a,17c]	0.50[17c]	0	0
k_{in} (**3a**) $\times 10^5$	0.64 ± 0.02	0.99 ± 0.02	1.73 ± 0.13	6.93 ± 0.25	

ways are strongly depending on interactions between HFIP and the other alcohol. It was found in fact that one important factor governing the reaction is the hydrogen bond acceptor ability of the competing alcohol (parameter β, Table 3).[17] There is an excellent correlation observed between the logarithm of the initial rates of formation of **3a** and β values (Figure 2). This clearly indicates that hydrogen bonding between HFIP and the competing alcohol plays an important role in the reaction mechanism, both disfavouring the "protonation" of dihydrofuran and reducing the nucleophilicity of alcohols. TFE, which is the weaker hydrogen bond acceptor, allows the generation by HFIP of the zwitterion intermediate postulated in Scheme 3, and thus a faster reaction, with nevertheless a predominant formation of product **3a**.

This unexpected and efficient reaction of addition of HFIP to dihydrofuran could be extended to the synthesis of a range of fluorinated acetals by reaction with other vinyl ethers in pure HFIP. A solution of the enol ethers **1b**–**f** (12 mmol) in HFIP (4 equivs.) was stirred at room temperature and monitored by ^{19}F NMR until complete reaction. Excess of HFIP was then recovered by distillation of the reaction mixture, and acetals **3b**–**f** were isolated pure from the residue in good to excellent yields (Table 4).

The reactions with the enol ethers **1b**,**c** were fast (1 to 2 h) and exothermic. The low isolated yield in acetal **3b** (entry 2) is attributed to its high volatility. With enol ethers **1d**,**e** reaction times were much longer (1 day) but yields in acetals were high. In the reaction of HFIP with the methoxydihydropyran, products resulting from the ring opening of the bis-acetal **3f** were present in the distillation residue.

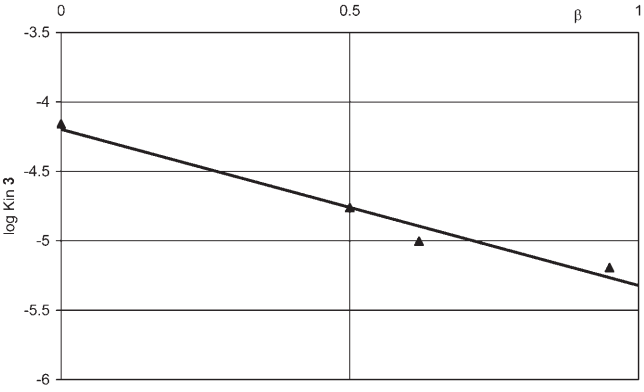


Figure 2. Correlation between the logarithm of the initial rate of formation of **3** and β. The equation obtained is: $\log k_{in} = -1.124\beta - 4.20$ with $R^2 = 0.97$.

Table 4. Formation of hexafluoropropyloxy acetals.

Entry	Vinyl ether **1**	Product **3**	Reaction time	Yield [%][a]
1	**1a**	**3a**	2 h	86
2	**1b**	**3b**	1 h	63
3	**1c**	**3c**	2 h	75
4	**1d**	**3d**	1 day	81
5	**1e**	**3e**	1 day	95
6	**1f**	**3f**	2 days	52[b]

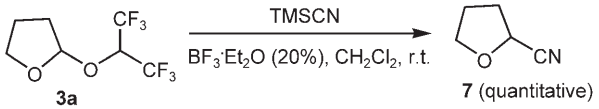
Reaction conditions: vinyl ether (12 mmol) in 5 mL of HFIP (4 equivs.), room temperature.

[a] Isolated yields.

[b] Ring opening compounds are observed in the crude reaction mixture.

As an example the reactivity of the acetal **3a** towards nucleophiles was evaluated with TMSCN. The reaction was performed at room temperature in presence of $BF_3 \cdot Et_2O$. The cyclic substitution product **7** was obtained in quantitative yield, with no trace of the ring opening product (Scheme 6).

This easy preparation of fluorinated acetals was then applied to the carbohydrate series. When placed in HFIP, the peracetylated glucal **1g** reacted slowly at room temperature providing in quantitative yields a 3:1 α:β mixture of the allylic fluoroalkyl acetals **3g**, resulting from a Ferrier reaction (Scheme 7).[18] When the reaction was conducted at reflux, the reaction time was



Scheme 6. Substitution of hexafluoropropyloxy acetal **3a**.

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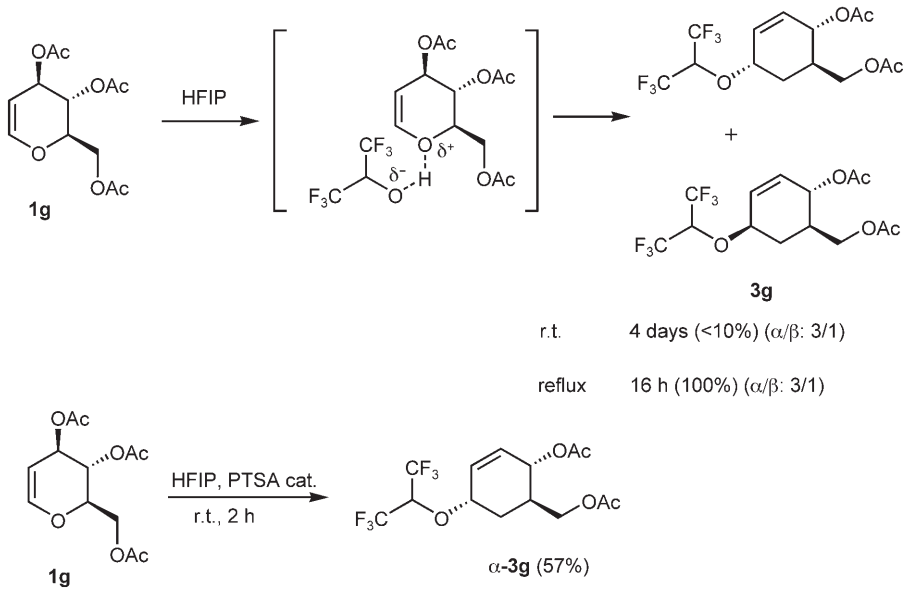
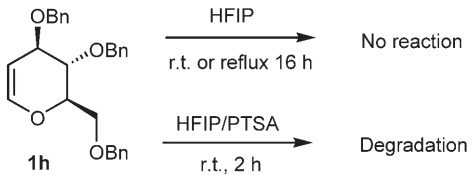


Scheme 7.

shorter (16 h), but same ratio of stereoisomers was obtained. The reaction was also checked in the presence of a catalytic amount of *p*-TSA in order to promote the intermediate formation of an oxonium ion postulated in the Ferrier reaction. The reaction was much faster and the only product formed was α-**3g** (the β isomer was not detected by NMR in the crude product). However, the moderate yield (57%) strongly suggests the degradation of the β isomer in the reaction medium.

The mechanism suggested above (see Scheme 3), involving hydrogen bond association of HFIP with the glucal, could explain the addition of HFIP with an approach depending on the steric hindrance of the two faces of the intermediate. The lost of an acetoxy group instead of a proton migration prompted us to investigate the reaction from the parent perbenzyloxy compound **1h**. No reaction occurred in HFIP after 16 h at room temperature or at reflux (Scheme 8).

This observation suggests that the addition of HFIP can only occur through a concerted mechanism where the nucleophile entering pushes the double bond towards the leaving group. In the absence of a leaving group, the postulated ion pair does not collapse. As expected, glucals are not as reactive towards HFIP than simple cyclic vinyl ethers.



Scheme 8.

Conclusion

In conclusion, this study shows that HFIP, in spite of its very low nucleophilicity, easily adds to vinyl ethers with no need of a catalyst. This reaction also occurred when a competitive, more nucleophilic alcohol was present. Kinetic studies showed the importance of hydrogen bonding in the reaction mechanism, demonstrating that the expected deactivation of nucleophiles by HFIP is also accompanied by the deactivation of HFIP by good hydrogen bond acceptor solvents. Evidence suggests that HFIP promotes its own addition reaction by favouring the formation of an intermediate species with a cationic character, with which it is closely associated, thus liberating the conjugated base with a high degree of anionic character. This reaction was exploited to prepare a range of fluorinated acetals, but is efficient for glucals only when an allylic leaving group is present.

Starting from the cyclic fluorinated acetals, the hexafluoroisopropyloxy moiety being an excellent leaving group, some examples of clean and selective nucleophilic substitutions with no ring opening products are reported.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were recorded on either a 200 MHz or a 400 MHz multinuclear Bruker spectrometer. COSY, NOESY, HSQC and HMBC experiments were performed on a 400 MHz multinuclear Bruker spectrometer. Chemical shifts (δ) are given in ppm relative to TMS. Coupling constants are given in Hz. GC analyses were performed using a SE 30 capillary column (12 m). All starting materials are commercially available. HFIP was provided by Central Glass Co. Ltd.

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Typical Procedure for the Synthesis of Fluorinated Acetals 3

The enol ether (12 mmol) was added to HFIP (5 mL, 4 equivs.) in a flask and stirred at room temperature for the time indicated in Table 4. The reaction was followed by ^{19}F NMR and after completion, distillation allowed us to recover HFIP and pure products in 52–95% yields.

***Fluorinated Acetal* 3a:** Yield: 2.45 g (86%); ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 5.42$ (m, 1H), 4.59 (sept, 1H, $J = 6.2$ Hz), 4.12–3.91 (m, 2H), 2.35–1.74 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 122.2$ (q, $J = 282$ Hz), 122.0 (q, $J = 282$ Hz), 104.5, 70.6 (sept, $J = 33$ Hz), 68.3, 32.2, 22.3; ^{19}F ($CDCl_3$, 188 MHz): $\delta = -74.24$ (qd, 3F, $J = 8.7$ Hz, $J = 6.2$ Hz), -74.75 (qd, 3F, $J = 8.7$ Hz, $J = 6.2$ Hz, CF_3); IR (neat): $\nu = 1217$, 1186, 1100, 1072, 939, 922, 898, 878, 687 cm^{-1}; anal. calcd. for $C_7H_8O_2F_6$: C 35.31, H 3.39; found: C 35.24, H 3.25.

***Fluorinated Acetal* 3b:** Yield: 1.8 g (63%); ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 5.07$ (q, 1H, $J = 5.4$ Hz), 4.51 (sept, 1H, $J = 6.1$ Hz), 3.85–3.54 (m, 2H), 1.47 (d, 3H, $J = 5.4$ Hz), 1.26 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 121.3$ (q, $J = 282$ Hz), 121.2 (q, $J = 282$ Hz), 101.5, 70.6 (sept, $J = 32$ Hz), 60.4, 19.0, 14.5; ^{19}F ($CDCl_3$, 188 MHz): $\delta = -74.32$–73.92 (m, 6F); IR (neat): $\nu = 1219$, 1187, 1100, 1066, 888, 688 cm^{-1}.

***Fluorinated Acetal* 3c:** Yield: 2.4 g (75%), ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 5.06$ (q, 1H, $J = 5.3$ Hz), 4.50 (sept, 1H, $J = 6.2$ Hz), 3.76–3.47 (m, 2H), 1.71–1.31 (m, 9H), 0.98 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 121.7$ (q, $J = 287$ Hz), 121.4 (q, $J = 287$ Hz), 101.6, 71.2 (sept, $J = 33$ Hz), 64.8, 31.4, 19.4, 18.9, 13.5; ^{19}F ($CDCl_3$, 188 MHz): $\delta = -74.40$ to -74.08 (m, 6F); IR (neat): $\nu = 1219$, 1194, 1159, 1100, 950, 908, 689 cm^{-1}; anal. calcd. for $C_9H_{14}O_2F_6$: C 40.30, H 5.72; found: C 40.05, H 5.60.

***Fluorinated Acetal* 3d:** Yield: 2.42 g (81%), ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 5.05$ (m, 1H), 4.57 (sept, 1H, $J = 6.2$ Hz), 3.93 (m, 1H), 3.65 (m, 1H), 1.99–1.54 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 121.9$ (q, $J = 285$ Hz), 121.3 (q, $J = 285$ Hz), 99.2, 71.2 (sept, $J = 33$ Hz), 61.7, 29.3, 24.7, 17.5; ^{19}F ($CDCl_3$, 188 MHz): $\delta = -74.15$ (m, 3F), -73.90 (m, 3F); IR (neat): $\nu = 1185$, 1144, 1099, 953, 904, 687 cm^{-1}.

***Fluorinated Acetal* 3e:** Yield: 2.75 g (95%), ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 4.56$ (sept, 1H, $J = 6.1$ Hz), 3.33 (s, 3H), 1.49 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 121,6$ (q, $J = 284$ Hz), 104.3, 68.5 (sept, $J = 33$ Hz) 50.3, 30.5, 24.4; ^{19}F ($CDCl_3$, 188 MHz): $\delta = -73.44$ to -73.20 (m, 6F); IR (neat): $\nu = 1287$, 1217, 1178, 1064, 893, 841, 686 cm^{-1}.

***Fluorinated Acetal* 3f:** Yield: 1.76 g (52%); two isomers a/b 1:1; ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 5.25$–5.18 (m, 1Ha + 1Hb), 4.79 (d, 1Ha, $J = 1.9$ Hz), 4.75 (d, 1Hb, $J = 2.6$ Hz), 4.6 (sept, 1Ha + 1Hb, $J = 6.1$ Hz), 3.49 (s, 3Ha + 3Hb), 1.95–1.44 (m, 6Ha + 6Hb); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 121.6$ (q, $J = 284$ Hz), 121.4 (q, $J = 284$ Hz), 99.7, 98.7, 71.8 (sept, $J = 33$ Hz), 55.5, 29.8, 28.8, 16.3; ^{19}F ($CDCl_3$, 188 MHz): $\delta = -74.30$ (m, 3F), -73.8 (m, 3F); IR (neat): $\nu = 1264$, 1218, 1190, 1126, 1099, 943, 890, 687 cm^{-1}.

***Fluorinated Acetal* 4a:** Yield: 450 mg (30%), ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 5.13$–5.10 (m, 1H), 4.00–3.55 (m, 4H), 2.07–1.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 124.0$ (q, $J = 278$ Hz), 103.9, 67.3, 63.4 (q, $J = 34$ Hz), 32.1, 22.8; ^{19}F ($CDCl_3$, 188 MHz): $\delta = -74.81$ (t, 3F, $J = 9.4$ Hz); IR (neat): $\nu = 1154$, 1116, 1060, 1035, 960, 919, 663 cm^{-1}.

Typical Procedure for Acetals 2a, 5a and 6a

2,3-Dihydrofuran (12 mmol) was added to an alcohol (4 equivs.) in a flask and stirred at 80 °C during 16 h. ^1H NMR allowed estimation of the conversion rate. All these acetals were already described in the literature.[19]

Typical Procedure for Ferrier-Type Reactions

In pure HFIP: A flask containing 100 mg of tri-*O*-acetyl-D-glucal and 3 mL of HFIP was heated for 16 h at reflux. Vacuum evaporation of the solvent and silica gel chromatography (ethyl acetate/petroleum ether, 2:3) of the crude residue afforded 106 mg of α-**3g** (76%) and 34 mg of β-**3g** (24%).

Catalyzed with* p-*TSA: To a flask containing 100 mg of tri-*O*-acetyl-D-glucal and 3 mL of HFIP was added 75 mg (1.07 equivs.) of *p*-TSA at room temperature. The reaction mixture turned black within a few minutes and was monitored by TLC. After 2 h, the reaction mixture was poured into a saturated solution of sodium hydrogen carbonate (10 mL) and extracted with dichloromethane (2×10 mL). The combined organic phases were dried on $MgSO_4$, filtrated and evaporated under vacuum. The crude residue gave after silica gel chromatography (ethyl acetate/petroleum ether, 2:3) 79 mg of α-**3g** (57%).

***Fluorinated Acetal* α-3g:** ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 6.03$ (bd, 1H, $J = 11$ Hz), 5.86 (ddd, 1H, $J = 11$ Hz, $J = 3$ Hz, $J = 1$ Hz), 5.34 (ddd, 1H, $J = 10$ Hz, $J = 2$ Hz, $J = 2$ Hz), 5.30–5.23 (bs, 1H), 4.57 (sept, 1H, $J = 6$ Hz), 4.21 (d, 2H, $J = 4$ Hz), 4.13–4.02 (m, 1H), 2.09 (s, 3H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 170.6$, 170.1, 131.5, 124.9, 121.7 (q, $J = 284$ Hz), 121.2 (q, $J = 283$ Hz), 95.4, 72.0 (sept, $J = 33$ Hz), 68.1, 64.6, 62.2, 20.8, 20.5; ^{19}F ($CDCl_3$, 376 MHz): $\delta = -73.85$ (q, 3F, $J = 9$ Hz), -74.03 (q, 3F, $J = 9$ Hz); IR (neat): $\nu = 2954$, 1743, 1371, 1216, 1187, 1101, 1088, 959, 758, 728 cm^{-1}; HR-MS: calcd. for $C_{13}H_{14}F_6NaO_6^+$: 403.0587; found: 403.0586; anal. calcd. for $C_{13}H_{14}F_6O_6$: C 41.06, H 3.71; found: C 41.30, H 3.85; $[\alpha]_D$: 208.2 (*c* 0.8, CH_2Cl_2).

***Fluorinated Acetal* β-3g:** ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 6.16$ (dd, 1H, $J = 4$ Hz, $J = 2$ Hz), 6.12 (dd, 1H, $J = 4$ Hz, $J = 2$ Hz), 6.00 (dd, 1H, $J = 2$ Hz, $J = 1$ Hz), 5.95 (dd, 1H, $J = 2$ Hz, $J = 1$ Hz), 5.42 (bs, 1H), 5.24 (dd, 1H, $J = 4$ Hz, $J = 4$ Hz), 4.57 (sept, 1H, $J = 6$ Hz), 4.26–4.18 (m, 2H), 4.16–4.04 (m, 1H), 2.08 (s, 3H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 170.5$, 170.0, 128.1, 127.7, 121.7 (q, $J = 290$ Hz), 95.7, 73.2, 72.2 (sept, $J = 35$ Hz), 63.5, 62.5, 20.8, 20.6; ^{19}F NMR ($CDCl_3$, 376 MHz): $\delta = -73.40$ (q, 3F, $J = 8.2$ Hz), -73.50 (q, 3F, $J = 8.2$ Hz).

Typical Procedure for the Nucleophilic Substitutions

***Tetrahydrofuran-2-carbonitrile* (7):** 184 mg (1 mmol) of **3a** were dissolved in 1 mL of dichloromethane in a flask placed in a water-ice bath. To the resulting solution under argon were added dropwise 200 μL (1.5 mmol) of TMSCN and 130 μL of $BF_3 \cdot Et_2O$. After 2 h, GC indicated that the reaction was complete. The solution was then quenched with a saturated solution of $NaHCO_3$ (5 mL) and extracted with dichloromethane (3×10 ml). The combined organic extracts were washed with brine and dried with $MgSO_4$. Evaporation under reduced

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pressure afforded tetrahydrofuran-2-carbonitrile; yield: 970 mg (quantitative).[6d]

Typical Procedure for Kinetic Measurements

Competition between HFIP and benzyl alcohol at 30 °C: 216 mg (2 mmol) of benzyl alcohol and 336 mg (2 mmol) of HFIP were weighed in an NMR tube. To this mixture was added enough C_6D_6 to reach a total reaction volume of 550 μL. The reaction was started by addition of 70 mg (1 mmol) of dihydrofuran **1a**. The tube was immediately inserted in a 400 MHz multinuclear Bruker spectrometer thermostatted at 30 °C, and ^{1}H NMR spectral data were acquired at regular intervals. Concentrations of the starting material and the two products **2a** and **3a** were calculated from the integration of peaks corresponding to the −OC*H*O− of the two acetals and the −C*H*=C*H*O− of **1a**. Initial rates were calculated from best fits of the obtained plots for the first 10% of conversion. Values of R^2 were always higher than 0.993.

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