Insight into the Ferrier rearrangement by combining flash chemistry and superacids

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COMMUNICATION

Insight into the Ferrier rearrangement by combining flash chemistry and superacids

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In memory of Professor Jun-ichi Yoshida

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Abstract: The transformation of glycals into 2,3-unsaturated glycosyl derivatives, reported by Ferrier in 1962, is supposed to involve an α,β unsaturated glycosyl cation, an elusive ionic species that has still to be observed experimentally. Herein, while combination of TfOH and flow conditions failed to observe this ionic species, its extended lifetime in superacid solutions allowed its characterization by NMR-based structural analysis, supported by DFT calculations. This allyloxycarbenium ion was further exploited in the Ferrier rearrangement to afford unsaturated nitrogen-containing *C*-aryl glycosides and *C*-alkyl glycosides under superacid and flow conditions respectively.

The Ferrier I rearrangement (or Ferrier reaction),[1-2] first reported in 1962 by Ferrier[3] and earlier observed by Fisher,[4] is considered as the prevalent route to hex-2-enopyranoses or pseudoglycals, species that hold a great synthetic potential in carbohydrate chemistry.[5,6] Typically, this reaction is carried out with a glycal **1** having a good leaving group (e.g., acetate, carbonate, or trichloroacetimidate) at C-3 position, which after activation and allylic rearrangement,[7] generates the corresponding pseudoglycal **2** (Figure 1A). It is now accepted that, in reactions involving alcohols as nucleophiles under acidic conditions, the resulting pseudoglycals are very labile and anomerize, favoring the α-*O*-glycosides as a reflection of a thermodynamic control. On the opposite, the stereoselective formation of *C*-glycosides, unlikely to be a reversible process, is supposed to be under kinetic control.[8] Undoubtedly, the conformation of glycal **1** plays an all-important role in the Ferrier rearrangement. The vinylogous anomeric effect, the anomeric effect extended through a C=C double bond, must dictate a preferred pseudoaxial orientation of the leaving group at C-3 in the starting glycal.[9]

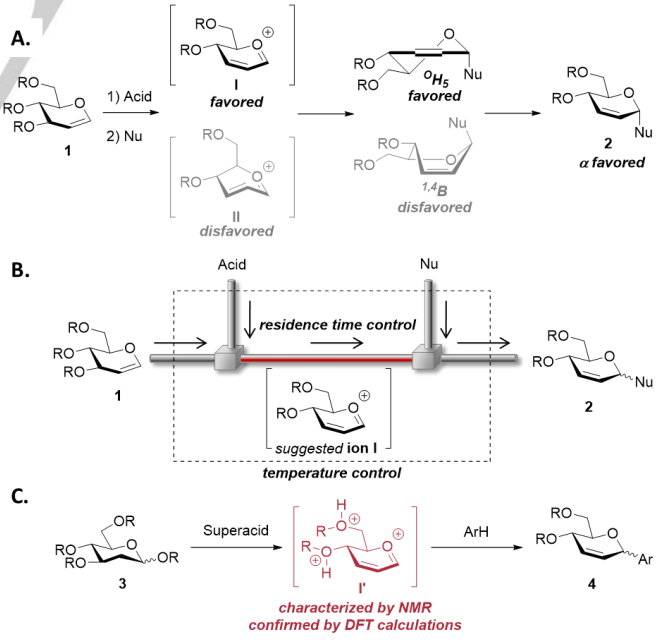


Figure 1. A. Ferrier rearrangement; **B.** Accumulation of allyloxycarbenium ion **I** under flash conditions and its reaction with *C*-nucleophiles in flow; **C.** Superacid-promoted generation, low-temperature *in situ* NMR characterization, conformational analysis and use in *C*-arylation of the short-lived protonated allyloxycarbenium ion **I'**.

The conformation of the postulated oxocarbenium ion intermediate (adopting the preferred conformation **I** over conformation **II** according to calculations)[10,11] as well as the favored product conformation ($^{O}H_5$ over $^{1,4}B$) must also contribute to the α-selectivity (Figure 1A).[12] The anchimeric assistance by the protecting group at C-4 to ease the departure of the leaving group at C-3 has also been postulated to rationalize the stereochemical outcome of the Ferrier rearrangement.[13] In comparison with a classical glycosyl cation, the additional conjugation into the vinyl group enhances the stabilization of the allyloxycarbenium ion, suggesting its classification as a stabilized ion,[14] thus theoretically favoring its direct observation by spectroscopic methods. Surprisingly, despite its crucial role in the Ferrier reaction, this species remains however hypothetical to the best of our knowledge. We report herein our efforts to characterize this elusive ion combining flow microreactors (Figure 1B), superacid chemistry, NMR analysis and DFT calculations and its use as a glycosyl donor to generate unprecedented nitrogen-containing *C*-aryl hex-2-enopyranosides (Figure 1C).

The cation-flow method,[15] in which highly reactive cations are rapidly generated in the absence of nucleophiles using the integrated flow microreactor, is quite effective for the generation of alkoxycarbenium ions[16] and for performing glycosylation reactions involving glycosyl cation intermediates based on an indirect method.[17] To evaluate the ability of this method to generate and exploit the related Ferrier cation, the commercially available tri-*O*-acetyl-D-glucal **1a** was chosen as a model substrate. Using an integrated flow microreactor system consisting of two micromixers (M1 and M2) and two microtube reactors (R1 and R2), the treatment of a dichloromethane solution of **1a** with triflic acid (TfOH) followed by allyltrimethylsilane to generate the known *C*-glycoside **2a**[18] was examined (Figure 2).

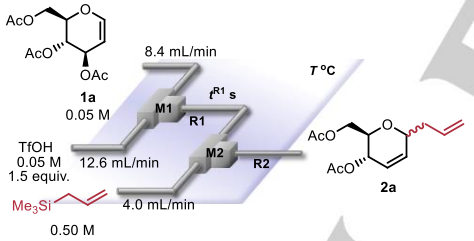


Figure 2. Integrated flow microreactor system for the production of *C*-allyl pseudo-glycal **2a** from glycal **1a**. T-shaped micromixers: M1 and M2, microtube reactors: R1 and R2.

The reactions were carried out at a range of residence times in R1 (t^{R1}) and a variety of temperatures (T). The results are summarized in Figure 3, in which the yield of **2a** is plotted against T and t^{R1} as a contour map with a scattered overlay. The yield of **2a** strongly depends on the residence time and the temperature. At high temperatures with longer residence times, the yield was low presumably because of the decomposition of the generated cation. At low temperatures, the yield was also low for a short t^{R1} probably because of the incomplete generation of the cation. However, **2a** was obtained in 83% yield (α/β = 91:9) by choosing T = -30 °C and t^{R1} = 0.6 seconds as the optimized conditions. Whatever the conditions used, it is worth noting that the α anomer is formed as the major isomer, in accordance with the kinetic trapping of cation of type **I** from the lower face of the sugar ring.

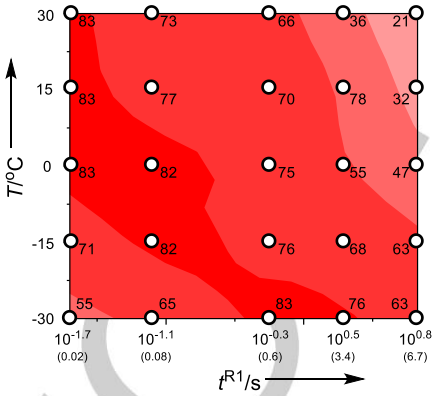
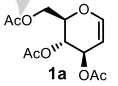
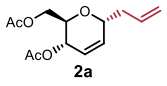
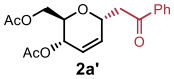
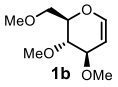
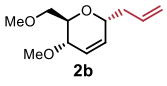
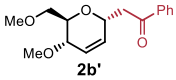
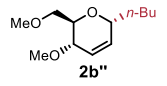


Figure 3. Effects of temperature (T) and residence time in R1 (t^{R1}) on the yield (%) of **2a** from the reaction of the glucal **1a** with triflic acid (TfOH) and subsequent reaction with allyltrimethylsilane in the flow microreactor system.

This result was further exemplified by applying the method to various nucleophiles and D-glucals to produce a set of pseudoglycals **2** (Table 1).

Table 1 : Flow microreactor synthesis of functionalized pseudo glycals **2** from D-glucals **1**.

Entry	**1** (glycal)	nucleophile	**2** (product)	Yield (%) (α/β)
1	 **1a**		 **2a**	83 (91:9)
2			 **2a'**	91 (78:22)
3	 **1b**		 **2b**	quant. (91:9)
4			 **2b'**	quant. (70:30)
5			 **2b"**	57 (58:42)

Under the optimized reaction conditions, the known[19] pseudoglycal **2a'** could be generated in 91% yield from **1a** and 1-phenyl-1-trimethylsiloxyethylene (Table 1, entry 2). The reactivity of trimethoxy D-glucal **1b** was also examined using the flow microreactor system. As summarized in Table 1, trimethoxy D-glucal **1b** was also effective as a glycosyl donor, allowing the coupling of various nucleophiles. Allyltrimethylsilane, 1-phenyl-1-trimethylsiloxyethylene and *n*-BuLi gave the corresponding *C*-alkyl glycosides **2b**,[20] **2b'** and **2b"** in good to excellent yields. In all cases, an α stereochemical outcome was observed that can be tentatively explained by the pseudo-axial attack on the α-face of the $^{4}H_3$ conformer of the transient 2-deoxyglucopyranosyl

oxycarbenium ion as previously observed[22a] while a long-range participation by the ester or ether at C-4 can not be excluded.[13c,13d] We finally evaluated the ability of the flow microreactor system to generate and accumulate ion **I** to allow its observation by NMR. Unfortunately, treatment of glucal **1** with TfOH failed to afford clean NMR spectra under these conditions (see SI).

Strongly inspired by the work of Olah and Prakash, who unlocked large areas of carbocation chemistry exploiting non nucleophilic superacid conditions,[21] our team has used HF/SbF_5 superacid as both reagent and solvent to generate and characterize several glycosyl cations in the condensed phase.[22] Following this strategy, we challenged the generation of ion **I** in superacid solutions and its observation by low-temperature NMR spectroscopy. The tri-*O*-acetyl-D-glucal **1a** was first submitted to HF/SbF_5 and furnished a mixture of two polycationic species which were analyzed by NMR spectroscopy (Figure 4A).

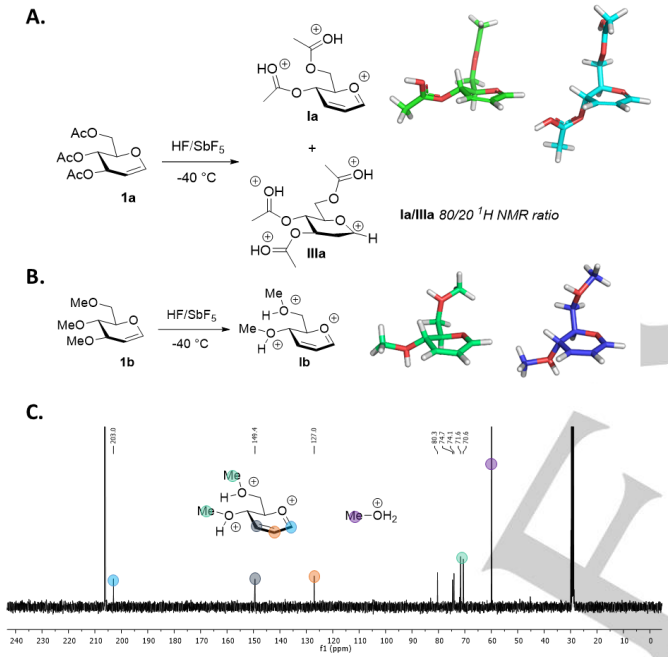


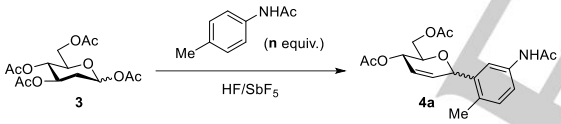
Figure 4. A. Generation of conjugated allyloxycarbenium ion **Ia** (conformations in solution confirmed by DFT analysis) and glycosyl cation **IIIa** from tri-*O*-acetyl-D-glucal **1a** in HF/SbF_5 at -40 °C (conformations in solution confirmed by DFT analysis); **B.** Generation of allyloxycarbenium ion **Ib** from tri-*O*-methyl-D-glucal **1b** in HF/SbF_5 at -40 °C (conformations in solution confirmed by DFT analysis); **C.** Low-temperature ^{13}C NMR spectrum of cation **Ib** in HF/SbF_5 solution.

Detailed NMR analysis confirmed the presence the resonance-stabilized glycosyl cation **Ia** (anomeric proton at $\delta = 8.30$ ppm and anomeric carbon at $\delta = 202.4$ ppm). The shielding of the anomeric carbon and proton compared to the 2-deoxyglucosyl cation[22a] can be rationalized by the increased stabilization of the carbocation by conjugation. The presence of a C=C bond in this species was evidenced by two signals at 6.29 and 6.75 ppm in the ^1H NMR spectrum and two peaks at 152.3 and 125.4 ppm in the ^{13}C NMR spectrum. In addition, the protonated acetates are characterized by two singlets at 12 ppm < δ < 14 ppm in the ^1H NMR spectrum. Beside ion **Ia**, the presence of the known 2-deoxyglucosyl cation **IIIa** was also detected in the reaction crude according to characteristic NMR signals (see SI).[22a] In the presence of Brønsted acid catalysts, glycals undergo nucleophilic displacement (Ferrier-type reaction) but can also experience functionalization at C1 to yield 2-deoxy derivatives, *via* postulated oxycarbenium ions.[23] Here, the observation of ion **IIIa** further reinforces this hypothesis. Performing the reaction at higher temperatures increased the **Ia**/ **IIIa** ratio suggesting that ion **IIIa** is a precursor of ion **Ia** in this process (ref SI). To drive the reaction to the exclusive formation of conjugated glycosyl cation, we switched to trimethoxy D-glucal **1b** and submitted it to the same superacid conditions (Figure 4B). Unlike in a classical organic environment,[24] the methoxy substituent has proved to be a superior leaving group under superacid activation compared to the acetyl group. Satisfyingly, one major polycationic species was observed by NMR whose signals were in good agreement with the conjugated glycosyl cation **Ib** displaying an anomeric proton at $\delta = 8.45$ ppm and an anomeric carbon at $\delta = 203.0$ ppm (Figure 4C). The protonation of the methoxy groups was evidenced by a signal at 9.81 ppm (^1H-NMR) and two signals at 70.6 and 71.6 ppm (^{13}C-NMR). The departure of the CH_3O group at C-3 was confirmed by the observation of the methyloxonium ion at 60.0 ppm,[25] and the formation of a C=C bond evidenced by two doublets of doublets at 6.86 ppm ($J = 9.8$ Hz and $J = 4.2$ Hz) and 6.48 ppm ($J = 9.9$ Hz and $J = 1.9$ Hz) in the ^1H-NMR spectrum and two signals at 149.4 and 127.0 ppm (^{13}C-NMR). The quality of the recorded NMR spectra allowed complete analysis of the homonuclear ^1H-NMR coupling constants for both species **Ia** and **Ib**, enabling access to their conformational preferences in solution, by comparing the experimental $^3J(H,H)$ coupling constants with those predicted for DFT calculated structural models (see SI). The planarity of the sugar ring at the O5-C1-C2-C3 moiety was thus confirmed, while the situation around the C3-C4-C5-O5 bonds was demonstrated to be more flexible. Indeed, for both species the experimental values $^3J(H3,H4)$= 4.3-4.5Hz, and $^3J(H4,H5)$= 5.0-5.2Hz (see SI) necessarily entailed the existence of a conformational equilibrium. DFT calculations (see SI) identifed two enery minima very close in energy (0.8 and 3.2 kJ/mol for **Ia** and **Ib** respectively) (Figures 4A and 4B and SI) for which the combination of their NMR parameters fulfill the experimentally observed ones.

Because of the potential bioactivity as well as the synthetic challenges associated with aryl *C*-glycosides, this class of carbohydrates has attracted considerable interest and extensive research aiming at developing new chemical strategies and tactics toward aryl *C*-glycosides.[26] The carbon-Ferrier rearrangement is considered as one of the most prevalent and straightforward approaches to access *C*-glycosides,[2c] that are distinct motifs embedded in various biologically active natural products.[6d,26] Acid-promoted reaction of glycals with good nucleophiles such as alkynyl and allylsilanes, silyl enol ethers or organometallics is especially efficient to generate *C*-glycosides.[2c] However, standard procedures to generate *C*-aryl glycosides through acid-promoted Ferrier rearrangement with aromatics is scarcely reported[27] and subject to the undesired formation of rearranged products when dealing with functionalized aromatics due to heteroatom nucleophilicity.[28] Capitalizing on the ability to generate Ferrier cation of type **I** in HF/SbF_5 solution, on previous Friedel-Crafts type reactions achieved in superacid[29] and on the protection of the nitrogen atom(s) by protonation in superacid, the generation of nitrogen-containing aryl *C*-glycosides from Ferrier cation precursor in superacid was explored. In batch conditions, the tri-*O*-acetyl-D-glucal **1a** was submitted to HF/SbF_5 conditions

in the presence of *p*-methylacetanilide as a model arene, affording the desired *C*-aryl hex-2-enopyranoside **4a** albeit in low yield with the formation of several side products with undetermined structure. A similar trend was observed with other arenes, definitely discarding the use of glycals as glycosyl donors to generate *C*-aryl glycosides in HF/SbF_5. As mentioned above, the glycosyl cation **IIIa** can lead to a conjugated ion **Ia** upon acid activation and subsequent elimination of the C-3 acetate group. This suggests that the treatment of a 2-deoxy glycosyl donor in the presence of an arene under superacid conditions at a temperature above -40 °C might generate a *C*-aryl glycoside intermediate that would undergo further elimination to afford the desired *C*-aryl-hex-2-enopyranoside. This hypothesis was confirmed by the direct observation of **Ia** (and **IIIa**) when submitting 2-deoxy glucosyl donor **3** to superacid solution the **Ia/IIIa** ratio increasing over time and temperature increase (see SI). A preliminary trial at -40 °C with donor **3** and *p*-methylacetanilide yielded **4a** in 16% yield (Table 2, entry 1). Performing the reaction at lower acidity failed to furnish the desired compound even on a prolonged reaction time (Table 2, entry 2).[30] However, carrying out the reaction at slightly higher temperature and at a lower concentration proved beneficial (Table 2, entries 3-5). Conducting the reaction with a substrate concentration in solution of 0.038 mol.L^{-1} was found to be the best compromise for a good conversion and a selective transformation, decreasing the amount of undetermined side products (Table 2, entries 6-7). The amount of nucleophilic partner could even be reduced to 1.5 equiv. by performing the reaction at -20 °C for 10 min, affording the desired product **4a** in 72% yield (Table 2, entry 8).

Table 2. Optimization of C-arylation conditions applied to 2-deoxyglucosyl donor **3** to access pseudoglycal **4a**.



Entry	[**3**][a] (mol.L^{-1})	[SbF_5][b] (mol%)	**n**	Conditions	Yield (%)[c]
1	0.15	8	3	-40 °C, 10 min	16
2	0.15	4	3	-40 °C, 4 h	-[d]
3	0.075	8	3	-20 °C, 10 min	19
4	0.019	8	3	-20 °C, 10 min	38
5	0.019	8	3	-20 °C, 2 min	46
6	0.038	8	3	-20 °C, 4 min	71
7	0.038	8	2	-20 °C, 5 min	66
8	0.038	8	1.5	-20 °C, 10 min	72

[a] Substrate concentration in HF/SbF5 solution. [b] Concentration of SbF_5 relative to HF in HF/SbF_5 solution. [c] Isolated yield. [d] No reaction.

Interestingly, this Friedel-Crafts reaction is regioselective, as the carbohydrate unit is selectively inserted in ortho position to the methyl group of the acetanilide. This result can be correlated to the behaviour of nitrogen containing species in superacid solutions as in HF/SbF_5. Neutral acetamide function must be in equilibrium with its protonated form and the methyl group therefore orientates the electrophilic addition.[31] The reaction is also stereoselective, the *α*-isomer being formed predominantly through this process, whatever the conditions used (α/β ratio = 85:15; entries 1 and 3-8). As demonstrated by low-temperature in situ NMR, **4a** results from the concomitant nucleophilic trapping of **Ia** and **IIIa** (followed by elimination) in solution (see SI).

To define the scope of this reaction, we screened a series of substituted arenes and heteroarenes (Figure 5). As previously observed for the formation of product **4a**, the reaction proceeded regioselectively and efficiently in the presence of methylated acetanilides (products **4b** and **4c**). The structure of **4b** was also confirmed by X-ray analysis of the collected crystals obtained after reaction of substrate **3** (see SI).[32] Gratifyingly, halogenated aromatics could also be coupled to pseudo glycals, as shown by the formation of *α*-product **4d**. Here again, the fluorine atom orientates the regioselectivity. More importantly, the Ferrier cation **I** was found to react with aniline with excellent stereoselectivity, albeit in a moderate yield (product **4e**). Considering that anilines must react in their protonated forms in superacid solutions, and thus acting as very poor ammonium-substituted nucleophiles, this result emphasizes the superelectrophilic character of the protonated Ferrier cation in superacid.[33] The reaction was also operative with a protected phenol, expanding the method to oxygenated aromatics (product **4f**).

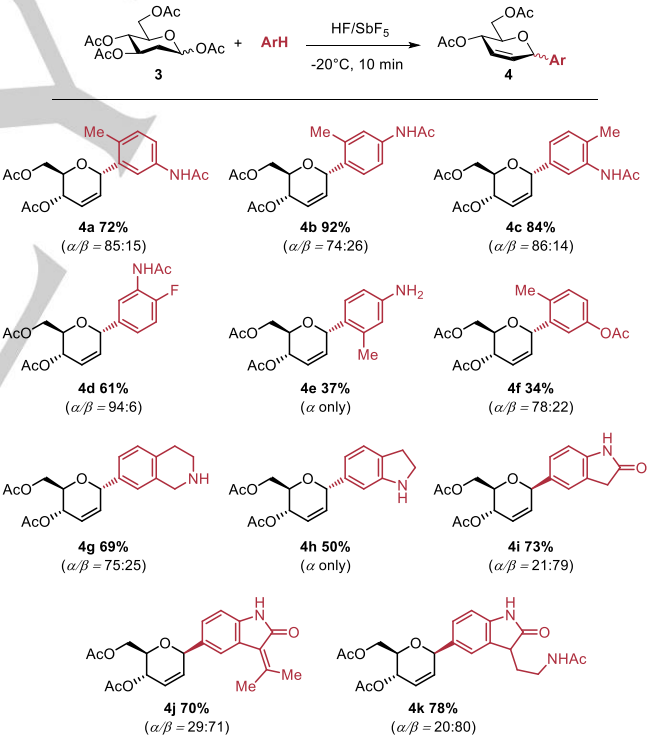


Figure 5. Scope of the C-arylation of peracetylated 2-deoxyglucopyranose mediated by HF/SbF_5. Conditions from Table 2, entry 8.

The direct modification of nitrogen-containing natural products at a late stage of a synthetic plan is now considered as a tool of choice in drug discovery programs.[34] To test the potential of our methodology in this context, the reactivity of the Ferrier cation **Ia** with several nitrogen containing aromatics was explored. To our delight, tetrahydroisoquinoline, indoline, oxindole as well as functionalized oxindoles could be stereoselectively and efficiently *C*-glycosylated in a regioselective manner (products **4g-k**). Noteworthy, the *β*-isomer is predominantly formed when glycosyl

cation is trapped by oxindoles, a stereochemical outcome that is difficult to rationalize.

In conclusion, this study enabled to convert the cyclic allyloxycarbenium ion **I**, the key intermediate in the Ferrier rearrangement, from an elusive species to a well-defined molecule. This cation was suggested to accumulate in the presence of triflic acid under flow conditions, and was further trapped by anionic C-nucleophiles. Exploiting non-nucleophilic HF/SbF_5 superacid solution, this cation was fully characterized by combining low-temperature NMR spectroscopy and DFT calculation. Its synthetic application in Ferrier rearrangements starting from 2-deoxyglucosyl donor produced a series of unprecedented nitrogen-containing *C*-aryl pseudoglycals.

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Keywords: glycosylation • oxycarbenium • Ferrier • superelectrophile • *C*-glycoside

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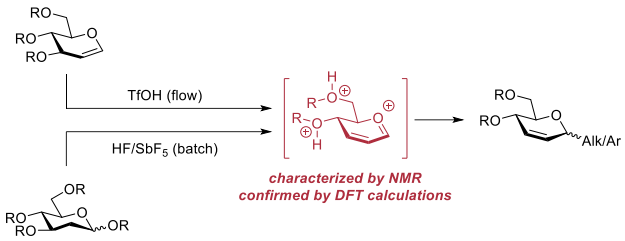

The cyclic allyloxycarbenium ion, the key intermediate in the Ferrier rearrangement, has been generated and accumulated under TfOH flow conditions. It has also been shown to be stable under superacid HF/SbF_5 solutions. Its long-lived character in these non-nucleophilic conditions allowed its full characterization by low-temperature NMR combined with DFT calculations. This ionic species proved to be synthetically useful and produced a range of original heteroatom-containing *C*-aryl pseudoglycals under these superacid conditions.