Facile and highly efficient synthesis of fluorinated heterocycles *via* Prins cyclization in ionic liquid hydrogen fluoride salts†

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Prins cyclization of homoallylic alcohols, thiols, and amines with various aldehydes in an ionic liquid HF salt ($Et_4NF{\cdot}5HF$) afforded the corresponding 4-fluorinated heterocycles in excellent yields.

Organofluorine compounds are key materials in medicinal, agrochemical, and material sciences. Hence, it is of great importance to develop environmentally benign selective fluorination systems. In our laboratory, electrochemical partial fluorination has been established by using ionic liquid HF salts like $Et_3N{\cdot}nHF$ and $Et_4NF{\cdot}nHF$ ($n = 3 \sim 5$) as a supporting electrolyte and a fluorine source.[1] Ionic liquids have unique physical and chemical properties, and have recently received much attention. For example, ionic liquids are used in organic synthesis as green solvents.[2] We have developed solvent-free electrochemical partial fluorination systems in recent years.[3] On the other hand, ionic liquid HF salts such as $Et_3N{\cdot}3HF$[4] and 1-ethyl-3-methylimidazolium fluoride·2.3HF [$EMIMF(HF)_{2.3}$][5] have been shown to be safe and easy to handle for chemical fluorination.

It is well known that Prins cyclization is a powerful synthetic reaction that can produce halogenated, acetoxylated, and hydroxylated tetrahydropyrans.[6] Many biologically active natural compounds containing tetrahydropyran rings have been discovered so far.[7] Therefore, the efficient synthesis of fluorinated tetrahydropyrans is useful for exploration of new pharmaceuticals. However, there have been only a few reports on the synthesis of fluorinated tetrahydropyrans.[8] Unfortunately, the yields were unsatisfactory and/or hydroxylated by-products were formed in these cases.

We focused our attention on the acidic protons and the fluoride ions that were contained at a high concentration in ionic liquid HF salts. The protons would catalyze Prins cyclization, furthermore, a wealth of fluoride ions would make fluorination smoother.

Herein we report the highly efficient synthesis of fluorinated six-membered heterocycles *via* Prins cyclization in ionic liquid HF salts without use of any organic solvents.

At first, we investigated to find the most suitable ionic liquid HF salts as a protic acid catalyst for Prins cyclization. As shown in Fig. 1, $Et_3N{\cdot}3HF$ and $Et_3N{\cdot}4HF$ hardly promoted the reaction of **1a** with **2a**, while $Et_3N{\cdot}5HF$ and $Et_4NF{\cdot}5HF$ catalyzed efficiently and the reaction finished in *ca.* 10 min. Therefore, it is clear that ionic liquid HF salts containing a higher content of hydrogen fluoride are effective. Excess acidic protons derived from the HF salt would protonate the contaminating H_2O, prohibiting the nucleophilic attack of H_2O.

We then investigated the Prins cyclization of various aldehydes and homoallylic alcohols in $Et_4NF{\cdot}5HF$ at room temperature. The generality of the reaction is shown in Table 1. Prins cyclization of an aliphatic aldehyde (**1a**), an alicyclic aldehyde (**1b**) and an aromatic aldehyde (**1c**) with a homoallylic alcohol (**2a**) has been successfully carried out to afford the corresponding fluorinated tetrahydropyrans in excellent yields with high stereoselectivity (*cis* products were formed exclusively).[9] Regardless of substituents at the *para* position of benzaldehyde (entries 4, 5), the desired products were obtained in a similar manner. Furthermore, the reaction of 1-substituted homoallylic alcohols with aldehydes (entries 6, 7) also proceeded to provide 2,4,6-trisubstituted tetrahydropyrans quantitatively.

According to a common reaction mechanism of Prins cyclization, the high stereoselectivity observed here is explained as shown in Scheme 1. The intermediate oxonium ion forms the more favorable chair-like transition state, avoiding a severe 1,3-diaxial interaction. Alder *et al.*[10] reported that the C^+–H bond was semi-axial in the chair 4-tetrahydropyranyl cation and it was the most stable conformation calculated by B3LYP/6-31G. Hence, the nucleophilic attack of complex polyhydrogen fluoride occurred from the equatorial position exclusively.[11]

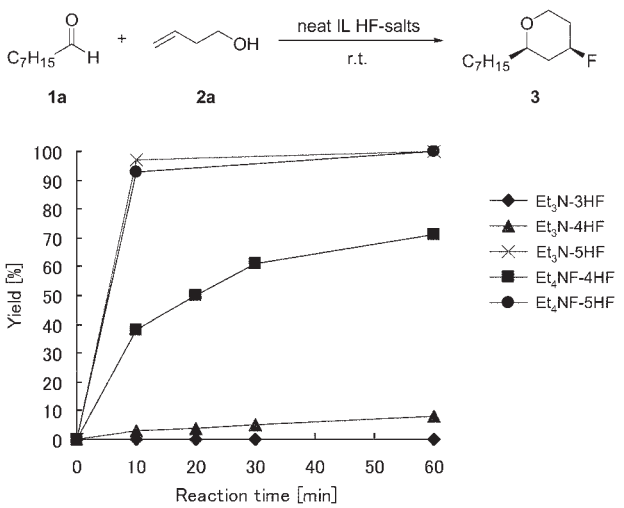

Fig. 1 Time course of the product yield in various HF salt ionic liquids at room temperature.

Department of Electronic Chemistry, Tokyo Institute of Technology, 4259 Nagatsuta, Midori-ku, Yokohama 226-8502, Japan. E-mail: fuchi@echem.titech.ac.jp; Fax: +81-45-924-5406; Tel: +81-45-924-5406

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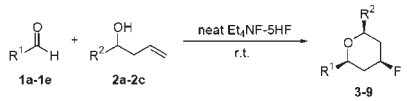
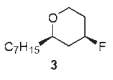
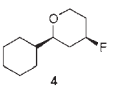
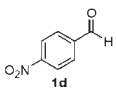
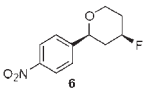
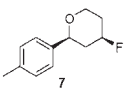
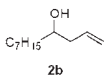
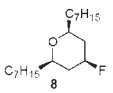
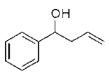
Table 1 Prins cyclization of various aldehydes with homoallylic alcohols in $Et_4NF{\cdot}5HF$



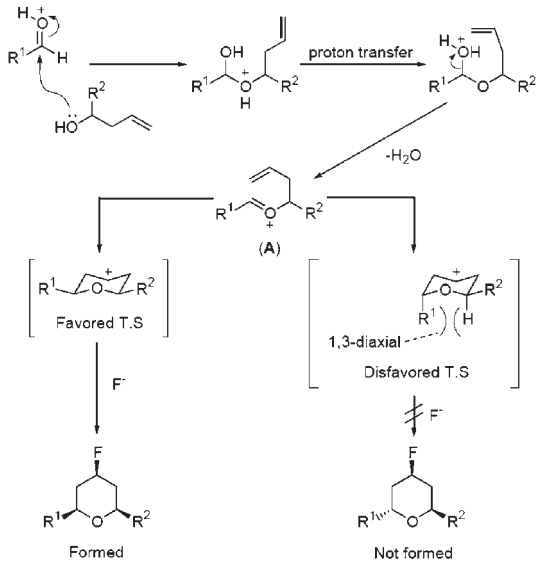
Entry	Aldehyde	Homoallylic alcohol	Reaction time/min	Product	Yield[a] (%)
1	 1a	 2a	10	 3	Quant.
2	 1b		20	 4	93
3	 1c		20	 5	Quant.
4	 1d		20	 6	Quant.
5	 1e		90	 7	96
6	 1a	 2b	10	 8	Quant.
7	 1c	 2c	120	 9	98

[a] Isolated yield.

Next, we hoped to demonstrate the Prins cyclization of various ketones and homoallylic alcohols with this reaction system. However, the ketones have shown quite low or no reactivity. On the other hand, Sabitha *et al.* reported trimethylsilyl iodide (TMSI) mediated Prins cyclization of various ketones and homoallylic alcohols.[12] Therefore, this result indicates that the protons of $Et_4NF{\cdot}5HF$ have a poor ability to activate the carbonyl groups. However, interestingly, only a cyclic ketone reacted to afford the spiro product (Scheme 2).

In order to survey the versatility of this methodology, we applied it to the synthesis of 4-fluorothiacyclohexanes and 4-fluoropiperidines. Thiacyclohexane rings and piperidine rings are key components contained in many natural products and possessing peculiar biological activities.[13] Li *et al.*[14] reported a thia-Prins cyclization and Martin *et al.*[15] demonstrated an aza-Prins cyclization. However, there has been no report on the synthesis of fluorinated thiacyclohexanes and few reports on the synthesis of fluorinated piperidines *via* a Prins-type cyclization.[16]

As shown in Table 2, Prins cyclizations of various kinds of aldehydes and a homoallylic thiol (**11a**) have been successfully



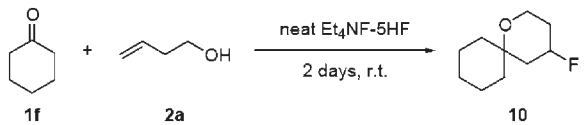
Scheme 1 Plausible mechanism of Prins cyclization.

performed to provide 4-fluorothiacyclohexanes in excellent yields. Although *cis* products were obtained selectively (higher than 92%), a small amount of *trans* products were also formed.

Furthermore, we carried out Prins cyclization of various aldehydes with homoallylic amines. The reaction of **1a** with homoallylic amine (**15a**) did not proceed at all because of the predominant protonation of amino group of **15a** in $Et_4NF{\cdot}5HF$. To solve this problem, we introduced an electron-withdrawing tosyl group into the nitrogen atom of **15a**. Since the basicity of **15a** decreased, aza-Prins cyclization proceeded smoothly to provide 4-fluoropiperidines (Table 3, entries 2 and 3). However, the reaction of benzaldehyde (**1c**) with **15b** hardly proceeded, because the reactivity of aromatic aldehydes was lower than that of aliphatic aldehydes. Similarly to the case of thia-Prins cyclization, *cis* products were obtained as a main stereoisomer, however the stereoselectivity in these cases was little lower compared with that observed in the case of thia-Prins cyclization.

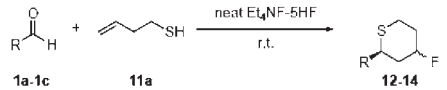
Finally, the reusability of the ionic liquid was demonstrated on the reaction of **1a** (0.2 mmol) with **2a** (0.2 mmol) in $Et_4NF{\cdot}5HF$ (3 ml). The fluorinated product **3** could be easily separated by extraction with hexane and the residual ionic liquid was then reused for the repeating reaction. The yield of **3** was more than 90% for up to 5 cycles, indicating the reusability of the ionic liquid for Prins cyclization.

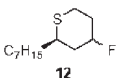
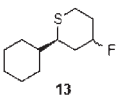
In conclusion, we successfully carried out the synthesis of various fluorinated six-membered heterocycles in excellent yields *via* Prins cyclization in ionic liquid HF salts. This synthetic method is very convenient and widely applicable, and an environmentally friendly process because no organic solvents are required. Through this study, it has been



Scheme 2 Prins cyclization of cyclic ketone with homoallylic alcohol in $Et_4NF{\cdot}5HF$.

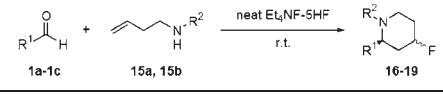
Table 2 Prins cyclization of various aldehydes with homoallylic thiols in $Et_4NF{\cdot}5HF$

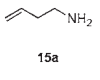
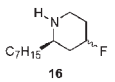
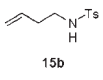
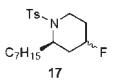
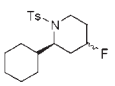


Entry	Aldehyde	Homoallylic thiol	Reaction time/min	Product	Yield[a] (%) (*cis*/*trans*)[b]
1	 1a	 11a	40	 12	98 (92 : 8)
2	 1b		60	 13	98 (95 : 5)
3	 1c		60	 14	Quant. (96 : 4)

[a] Total isolated yields of both diastereomers. [b] Determined by ^{19}F NMR.

Table 3 Prins cyclization of various aldehydes with homoallylic amines in $Et_4NF{\cdot}5HF$



Entry	Aldehyde	Homoallylic amine	Reaction time/h	Product	Yield (%) (*cis*/*trans*)[b]
1	 1a	 15a	24	 16	0
2	 1a	 15b	1	 17	Quant.[a] (88 : 12)
3	 1b		2	 18	Quant.[a] (92 : 8)
4	 1c		24	 19	17[b] (82 : 13)

[a] Total isolated yields of both diastereomers. [b] Determined by ^{19}F NMR.

suggested that ionic liquid HF salts would be usable for a variety of fluorination reactions.

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