Prins-type polymerization using ionic liquid hydrogen fluoride salts†

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We successfully carried out Prins-type polymerization for the first time to prepare 4-fluorinated tetrahydropyran-containing polymers in a highly stereoselective manner.

Recently, numerous reports on Prins cyclization have been published because it attracts much attention as a facile synthetic method to prepare tetrahydropyran (THP) derivatives, which are components of sugar derivatives, natural products, and so on.[1] Under acidic conditions, cyclization of homoallyic alcohols with aldehydes (and ketones) gives THP having a substituent such as hydroxide, halide, or acetate at the 4-position.[2] Very recently, we reported a facile and highly efficient synthesis of 4-fluorinated THP in ionic liquid hydrogen fluoride (HF) salts ($Et_3N{\cdot}n$HF or $Et_4NF{\cdot}n$HF).[3,4] These HF salts played roles as a non-volatile reaction medium, a Brønsted acid, and a fluorine source in this system. In addition, it was found that the fluorine atom was introduced into THP with high stereoselectivity.

To the best of our knowledge, there have been no reports on polymerization based on a Prins cyclization reaction to date. Furthermore, only a few reports on synthesis of THP-containing synthetic polymers by ring-opening polymerization of bicyclic compounds[5] and radical cyclopolymerization of an acrylate ether dimer[6] have been published. Herein, we wish to report the first example of polymer synthesis *via* Prins cyclization by using homoallylic alcohols having an aldehyde moiety (its acetal form) as monomers in ionic liquid HF salts. The resulting polymers include a 4-fluorinated THP unit in a highly stereoselective manner through selective fluorocyclization.

Monomers (**1**), composed of an homoallylic alcohol and an aldehyde moiety, were prepared with the aldehyde moiety protected. The acetal group of the monomers would turn into an activated aldehyde in the presence of HF salts (Scheme 1). A steric restriction of the *p*-phenylene spacers between the alcohol and the aldehyde moieties prevents an intramolecular reaction, but favors an intermolecular reaction towards polymerization. Then the formation of six-membered ring, followed by nucleophilic substitution of the fluoride ion at the 4-position of THP unit leads to 4-fluorinated THP-containing polymers. In a previous report, Prins cyclization was successfully performed when $Et_4NF{\cdot}5HF$ containing a high content of hydrogen fluoride was used as a HF salt.[3] Polymerization of the monomers was carried out by the addition of $Et_4NF{\cdot}5HF$ to a monomer solution in CH_2Cl_2 at room temperature. The reaction was quenched by the addition of water. The separated organic layer was repeatedly washed with $NaHCO_3$ (aq) and water. Purification by reprecipitation into CH_3OH afforded a light-yellow powder. Table 1 summarizes the results of polymerization conducted in various mixed solvents. In the case of using neat HF salt (entry 1), the purified polymer was partially soluble in $CHCl_3$. The insoluble part probably consists of a higher molecular weight polymer and/or a partially cross-linked polymer.[7] On the other hand, the addition of a co-solvent (CH_2Cl_2) suppressed the production of insoluble polymer in this polymerization system. Entry 3 (CH_2Cl_2–$Et_4NF{\cdot}5HF$ = 50 : 50) provided a soluble polymer in moderate yield. The gel permeation chromatography (GPC) analysis of polymer **2a** gave a unimodal profile (M_n = 3300, M_w/M_n = 1.7, where M_n and M_w are the number- and weight-average molecular weight, respectively). Lower HF ratio resulted in the decrease of the polymer product yield (entries 4 and 5).

The structure of **2a** was determined by ^{1}H-, ^{13}C- and ^{19}F-NMR. A comparison with the model compound, 4-fluoro-2,6-diphenyltetrahydropyran, gave information of the fine structure of **2a**. A characteristic coupled signal at 5 ppm indicated the selective introduction of a fluorine atom onto the 4-position of the THP ring[3] as shown in Fig. 1a. The small peaks at 10–7.5 ppm are assigned to the protons derived from a benzaldehyde at the terminal. A couple of peaks at around −94 ppm observed in the ^{19}F NMR spectrum (Fig. 1b) indicates the introduction of fluorine to the 4-position of 2,6-diphenyl THP with an all-*cis* form.[3] Elemental analysis data also support the structure of this polymer.[8] It should be noted that the stereoselective fluorocyclization by the Prins-type reaction successfully proceeded even in polymerization.

As a counter experiment, we investigated the Prins-type polymerization in $BF_3{\cdot}OEt_2$–CH_2Cl_2[9] without HF salts. Although the polymerization proceeded, the ^{1}H NMR spectrum of the obtained polymer indicated the complex mixture of 4-fluorinated THP and 4-hydroxylated THP.[10] In this case, undesired nucleophilic attack by the generated water occurred, whereas the protonation of water prevents such side reactions to afford the predominantly fluorinated product in the case of using HF salts.[3] Hence, the use of HF salt as the acid and fluorine source was found to be the most ideal way to produce the well-defined polymer.

Polymerization of monomer **1b** having a tetrafluorobenzene ring under the optimized conditions (Table 1, entry 3) did not afford any polymeric products (Table 2, entry 1). Instead, the deprotection of the acetal group in **1b** was observed solely. This result indicated that the acidity of HF salt was not enough to start the cyclization due to the lowered

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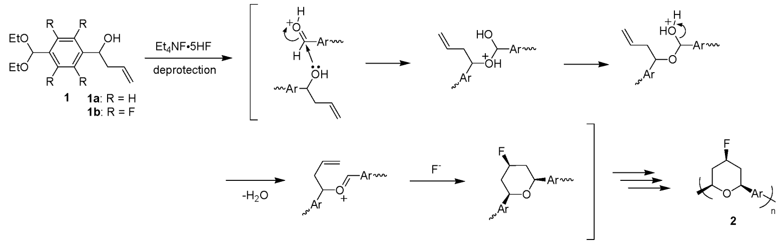
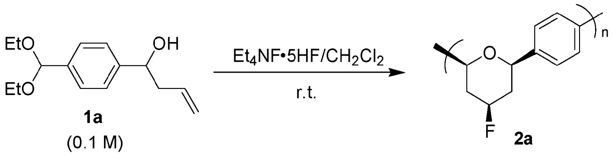
† Electronic supplementary information (ESI) available: Experimental section, ^{13}C NMR spectrum of **2a** and ^{19}F NMR spectrum of **2b**. See DOI: 10.1039/b902713k



Scheme 1 Plausible mechanism of Prins-type polymerization of monomer **1**.

Table 1 Results of polymerization of **1a** under various conditions



Entry	$Et_4NF{\cdot}5HF–CH_2Cl_2$ (v/v)	Reaction time/h	M_w	M_n	M_w/M_n	Yield (%)	Solubility in $CHCl_3$
1	100 : 0	24	—	—	—	69	P-soluble[a]
2	75 : 25	24	—	—	—	60	P-soluble[a]
3	50 : 50	24	5700	3300	1.7	42	Soluble
4	25 : 75	24	4000	3400	1.2	17	Soluble
5	10 : 90	24	—	—	—	No polymer	
6	50 : 50	6	3500	2500	1.4	13	Soluble
7	50 : 50	2	2800	2000	1.4	Trace	Soluble

[a] Partially soluble.

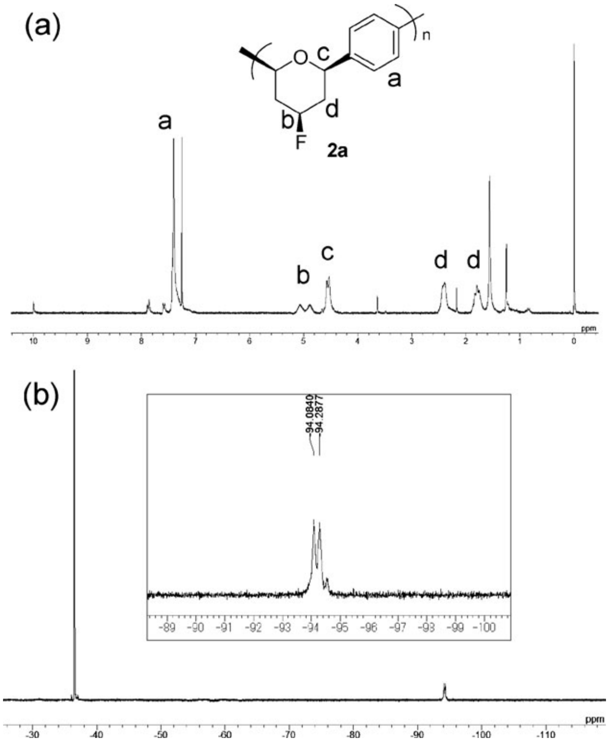


Fig. 1 ^1H (a) and ^{19}F (b) NMR spectra of polymer **2a** in $CDCl_3$. Monofluorobenzene (−36.5 ppm) was used as an internal standard in ^{19}F NMR.

nucleophilicity of the alcohol bearing the electron-withdrawing tetrafluorobenzene unit. Thus, we employed an additional Lewis acid ($BF_3{\cdot}OEt_2$ and trifluoroacetic acid) to further activate the carbonyl group. When the Lewis acid (about 5 equivalents or more to the monomer) was used, a successive polymerization was confirmed (entries 2–4). However, the obtained polymer (**2b**) had low solubility in $CHCl_3$, thus only the soluble part of the polymer was used for GPC and NMR measurements. In the ^{19}F NMR spectrum of **2b**, a new peak appeared at a higher magnetic field than the peaks derived from tetrafluorobenzene moiety and *cis*-4-fluoroTHP (see ESI, Fig. S2†). This is assigned to the peak of *trans*-4-fluoroTHP.[3,11] By comparing the intensities of the peaks of these *cis* and *trans* isomers, the *cis*/*trans* ratio was estimated as 2 : 1. The foregoing results indicated that the use of **1b** having an electron-withdrawing spacer decreased the stereoselectivity of fluorocyclization.

In conclusion, we have successfully demonstrated the synthesis of a 4-fluorinated THP-containing polymer *via* Prins cyclization using $Et_4NF{\cdot}5HF$ as an acid and a fluorine source. The 4-fluorinated THP was efficiently incorporated into the polymer in a stereoselective manner. This facile and selective polymerization method is expected to be widely applicable to the creation of new materials containing 4-substituted THP, thiacyclohexane, and piperidine. Further detailed properties of these polymers are now under investigation in our laboratory.

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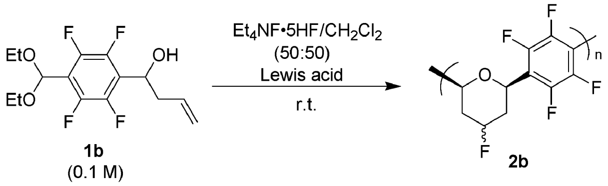
Table 2 Results of polymerization of **1b** under various conditions



1b
(0.1 M)

2b

Entry	Lewis acid	Reaction time/h	M_w	M_n	M_w/M_n	Yield (%)	Solubility in CHCl$_3$
1	—	24	—	—	—	No polymer[b]	
2	0.5 M BF$_3$·OEt$_2$	24	—	—	—	Trace	Soluble
3	1 M BF$_3$·OEt$_2$	24	3200[a]	2100[a]	1.5[a]	13	P-soluble[c]
4	1 M BF$_3$·OEt$_2$	48	4100[a]	2700[a]	1.5[a]	42	P-soluble[c]
5	1 M TFA	24	—	—	—	No polymer	

[a] GPC data of the soluble part of **2b**. [b] Deprotection of acetal was observed. [c] Partially soluble.

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4 Although ionic liquid HF salt is easily handled, proper safety precautions should be taken at all times. Therefore, it is recommended to use hand protection.

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7 Cross-linking possibly occurs by acetal formation between one aldehyde and two homoallylic alcohols.

8 Anal. calcd. for $(C_{11}H_{11}FO)_n$: C, 74.2; H, 6.2; F, 10.6; O, 9.0. Found: C, 76.2; H, 6.4; F, 8.7%.

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