DOI: 10.1002/ejoc.200800872

Prins Cyclization in Ionic Liquid Hydrogen Fluoride Salts: Facile and Highly Efficient Synthesis of 4-Fluorinated Tetrahydropyrans, Thiacyclohexanes, and Piperidines

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Keywords: Cyclization / Ionic liquids / Fluorine / Heterocycles

Prins cyclization of homoallylic alcohols with various aldehydes was investigated in ionic liquid hydrogen fluoride (HF) salts, which played roles as a reaction medium, a catalyst, and a fluorine source. The reaction afforded the corresponding 4-fluorinated tetrahydropyrans in excellent yields with a high stereoselectivity (*cis* form exclusively). When benzaldehydes having a strongly electron-donating group at the *para* position were used, the stereoselectivity was lost in this system. In order to apply this method to the synthesis of other 4-fluorinated heterocyclic compounds, we also carried out thia-Prins and aza-Prins cyclization in HF salt and successfully obtained 4-fluorinated thiacyclohexanes and piperidines, respectively.

Introduction

Organofluorine compounds are in great demand in medicinal, agrochemical, and material sciences. Because they are not always naturally occurring, selective fluorination of organic compounds is of much importance. Electrochemical selective fluorination has been established in our group by using ionic liquid hydrogen fluoride (HF) salts like Et_3N–*n*HF and Et_4NF–*n*HF (*n* = 3–5) 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 employed in organic synthesis as green reaction media instead of volatile organic compounds (VOC).[2] In recent years, we have developed VOC-free electrochemical selective fluorination systems in neat HF salts.[3] In contrast, ionic liquid HF salts such as Et_3N–3HF[4] and 1-ethyl-3-methylimidazolium fluoride–2.3HF [EMIMF$(HF)_{2.3}$][5] have been demonstrated to be safe and easy to handle for chemical fluorination.

Recent progress of Prins cyclization is noticeable in synthetic chemistry. It is well known as a powerful synthetic reaction that can produce halogenated, acetoxylated, and hydroxylated tetrahydropyrans.[6] A number of biologically active natural compounds containing tetrahydropyran rings have been discovered to date.[7] Hence, 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 byproducts were always formed in these cases.

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

In this paper, we report the highly efficient and stereoselective synthesis of 4-fluorinated tetrahydropyrans by Prins cyclization in ionic liquid HF salts. In addition, thia-Prins and aza-Prins cyclization in HF salts were also demonstrated to provide the corresponding 4-fluorinated thiacyclohexanes and piperidines, respectively.

Results and Discussion

At first, we investigated to find the most suitable ionic liquid HF salts as a protic acid catalyst for Prins cyclization. As shown in Figure 1, Et_3N–3HF and Et_3N–4HF hardly promoted the reaction of **1a** with **2a**, whereas Et_3N–5HF and Et_4NF–5HF catalyzed efficiently, and the reaction was finished in ca. 10 min. Therefore, it is clear that ionic liquid HF salts containing higher contents of hydrogen fluoride are effective. Olah et al. reported a similar tendency in the fluorination of alcohols with dimethyl ether–*n*HF.[9] An excess amount of acidic protons derived from the HF salt could protonate the contaminating H_2O, which would prohibit nucleophilic attack of H_2O.

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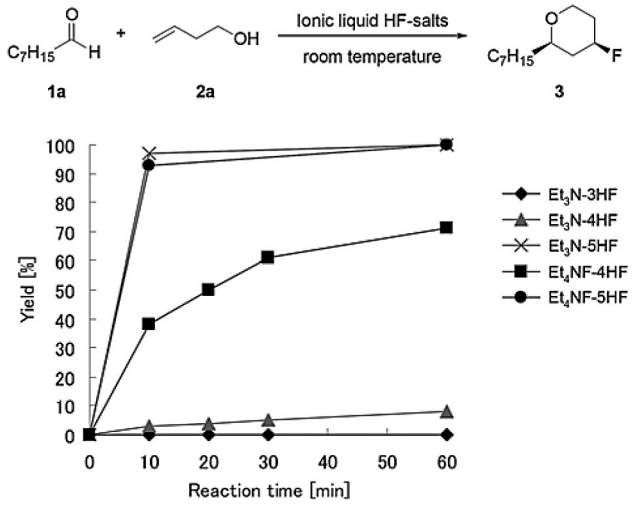
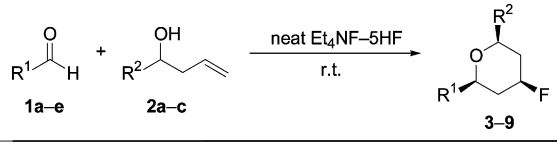


Figure 1. Time course of the yield of **3** in various HF salts.

We then investigated Prins cyclization of various aldehydes and homoallylic alcohols in Et_4NF–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**) was successfully carried out to afford the corresponding fluorinated tetrahydropyrans in excellent yields with high stereoselectivity (*cis* products were formed exclusively).[10] Regardless of the substituents at the *para* position of the benzaldehyde (Table 1, entries 4 and 5), the desired products were obtained in a similar manner. Furthermore, the reaction of 1-substituted homoallylic alcohols with aldehydes (Table 1, entries 6 and 7) also proceeded to provide 2,4,6-trisubstituted tetrahydropyrans quantitatively.

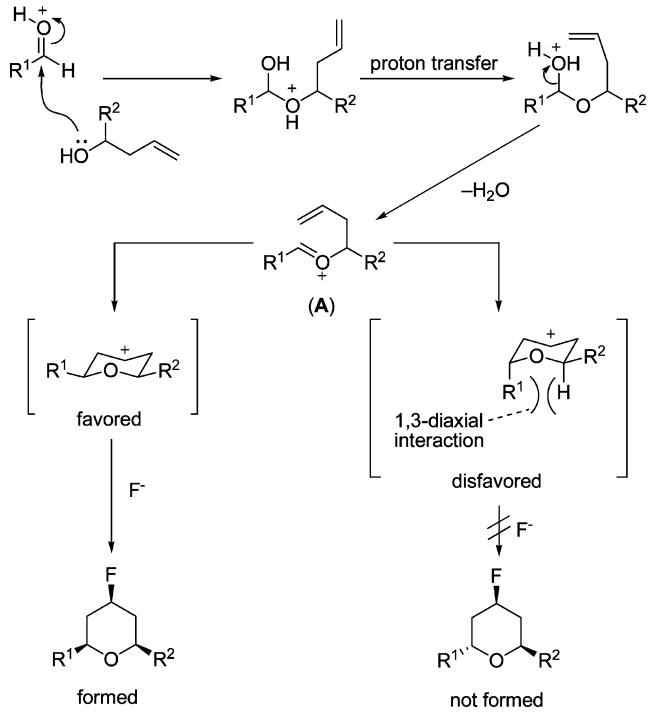
Table 1. Prins cyclization of various aldehydes with homoallylic alcohols in Et_4NF–5HF.



Entry	Aldehyde **1**	Homoallylic alcohol **2**	Time [min]	Product	Yield [%][a]
1	**1a** ($R^1 = C_7H_{15}$)	**2a** (R^2 = H)	10	**3**	quant.
2	**1b** (R^1 = cyclohexyl)	**2a** (R^2 = H)	20	**4**	93
3	**1c** (R^1 = Ph)	**2a** (R^2 = H)	20	**5**	quant.
4	**1d** (R^1 = *p*-NO_2Ph)	**2a** (R^2 = H)	20	**6**	quant.
5	**1e** (R^1 = *p*-MePh)	**2a** (R^2 = H)	90	**7**	96
6	**1a** ($R^1 = C_7H_{15}$)	**2b** ($R^2 = C_7H_{15}$)	10	**8**	quant.
7	**1c** (R^1 = Ph)	**2c** (R^2 = Ph)	120	**9**	98

[a] Isolated yield.

According to the common reaction mechanism of Prins cyclization, high stereoselectivity observed here is explained as shown in Scheme 1. The intermediate oxonium ion (**A**) forms the more favorable chair-like transition state to avoid severe 1,3-diaxial interaction. Alder et al.[11] reported that the C^+–H bond was semiaxial 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.[12]



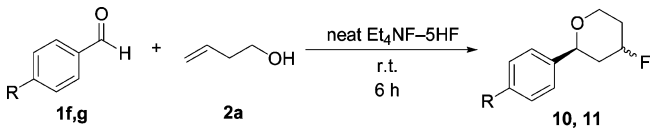
Scheme 1. Plausible mechanism of Prins cyclization.

As mentioned above, Prins cyclization in HF salts proceeded in a highly stereoselective manner. However, we could not control the stereoselectivity of the cyclization products when *p*-anisaldehyde (**1f**) and *p*-hydroxybenzaldehyde (**1g**) were used as aldehydes (Table 2). Despite the fact that such aldehydes gave the corresponding 4-fluorinated tetrahydropyrans in high yields, the stereochemistry of the products was found to be a mixture of *cis* and *trans* isomers. The plausible mechanism of this isomerization is shown in Scheme 2. Electron-donating group (OCH_3 or OH) at the *para* position o the benzene ring would promote ring opening and contribute to the stabilization of the resulting open-chain benzyl cation. The intermediate would undergo recyclization to form *trans* isomers in an equilibrium reaction. Indeed, the treatment of the separated *cis* isomer with HF salts for 6 h lead to a stereoisomeric mixture.

Next, we demonstrated Prins cyclization of various ketones and homoallylic alcohols for the scope and limitation of this reaction system. Notably, only cyclic ketones afforded the desired spiro-type products (Table 3). However, open-chain ketones like 2-octanone and aromatic ketone-like acetophenone did not afford the cyclized products at all. This is in sharp contrast to the successful trimethylsilyl iodide (TMSI) mediated Prins cyclization of various ketones with homoallylic alcohols.[13]

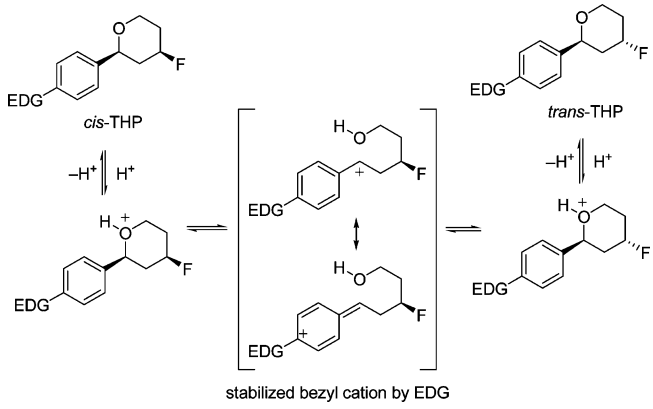
The reusability of the ionic liquid was studied on the reaction of **1a** (0.2 mmol) with **2a** (0.2 mmol) in Et_4NF–5HF (3 mL:78 mmol of HF). Fluorinated product **3** could be

Table 2. Prins cyclization of benzaldehyde derivatives having an electron-donating group at the *para* position with homoallylic alcohol.



Entry	Aldehyde **1**	Product	Yield [%][a] (*cis*/*trans*)
1	**1f** (R^1 = OMe)	**10**	90 (45:55)
2	**1g** (R^1 = OH)	**11**	88 (43:57)

[a] Determined by ^{19}F NMR spectroscopy.



Scheme 2. Mechanism of isomerization of 4-fluorotetrahydropyrans having an electron-donating group.

easily separated by simple extraction with hexane, and the residual ionic liquid was then reused for the reaction. The yield of **3** was more than 90% for up to five cycles, indicating the reusability of the ionic liquid for Prins cyclization. However, due to the generation of H_2O and the consumption of HF, the yield of **3** gradually decreased over the course of more cycles. If removal of H_2O from the "used" reaction media and addition of HF could be achieved, the ionic liquid HF salts would be an ideal reaction medium for Prins cyclization with reusability.

Table 3. Prins cyclization of various ketones with **2a** in Et_4NF–5HF.

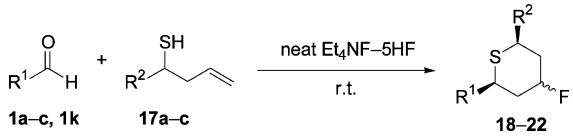
Entry	Aldehyde	Product	Yield [%]
1	**1h**	**12**	19[a]
2	**1i**	**13**	85[b]
3	**1j**	**14**	trace[a]

[a] Determined by ^{19}F NMR spectroscopy. [b] Isolated yield.

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.[14] Li et al.[15] reported thia-Prins cyclization and Martin et al.[16] demonstrated aza-Prins cyclization. However, there has been no report on synthesis of fluorinated thiacyclohexanes and few reports on the synthesis of fluorinated piperidines by Prins-type cyclization.[17]

As shown in Table 4, Prins cyclization of various kinds of aldehydes and homoallylic thiol (**17a**) was successfully performed to provide 4-fluorothiacyclohexanes in excellent yields. Although *cis* products were obtained selectively (higher than 92%),[18] a small amount of *trans* product was also formed. When we used 1-substituted homoallylic thiols (Table 4, entries 4 and 5), 2,4,6-trisubstituted 4-fluorothiacyclohexanes were obtained in high-to-excellent yields. Before the reactions were complete, we could detect the dithioacetal compound, which is one of the intermediates of this reaction. Under the acidic conditions, the dithioacetal would be deprotected again and form the cyclic products.

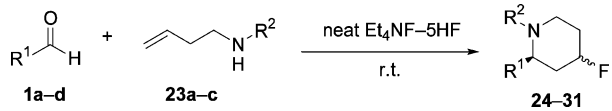
Table 4. Prins cyclization of various aldehydes with homoallylic thiols in Et_4NF–5HF.



Entry	Aldehyde **1**	Homoallylic thiol **17**	Time [min]	Product	Yield [%][a] (*cis*/*trans*)[b]
1	**1a** ($R^1 = C_7H_{15}$)	**17a** (R^2 = H)	40	**18**	98 (92:8)
2	**1b** (R^1 = cyclohexyl)	**17a** (R^2 = H)	60	**19**	98 (95:5)
3	**1c** (R^1 = Ph)	**17a** (R^2 = H)	60	**20**	quant. (96:4)
4	**1k** ($R^1 = C_5H_{11}$)	**17b** ($R^2 = C_5H_{11}$)	90	**21**	72 (96:4)
5	**1c** (R^1 = Ph)	**17c** (R^2 = Ph)	10	**22**	quant. (96:4)

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

Table 5. Prins cyclization of various aldehydes with homoallylic thiols in Et_4NF–5HF.



1a–d 23a–c 24–31

Entry	Aldehyde **1**	Homoallylic alcohol **23**	Time [h]	Product	Yield [%] (*cis*/*trans*)[b]
1	**1a** (R^1 = C_7H_{15})	**23a** (R^2 = H)	24	**24**	0
2	**1a** (R^1 = C_7H_{15})	**23b** (R^2 = Ts)	1	**25**	quant.[a] (88:12)
3	**1b** (R^1 = cyclohexyl)	**23b** (R^2 = Ts)	2	**26**	quant.[a] (92:8)
4	**1c** (R^1 = Ph)	**23b** (R^2 = Ts)	24	**27**	17[b] (82:18)
5	**1d** (R^1 = *p*-NO_2Ph)	**23b** (R^2 = Ts)	24	**28**	18[b] (83:17)
6	**1a** (R^1 = C_7H_{15})	**23c** (R^2 = CO_2Me)	0.5	**29**	92[a] (93:7)
7	**1b** (R^1 = cyclohexyl)	**23c** (R^2 = CO_2Me)	0.5	**30**	97[a] (95:5)
8	**1c** (R^1 = Ph)	**23c** (R^2 = CO_2Me)	24	**31**	29[a] (97:3)

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

Furthermore, we carried out Prins cyclization of various aldehydes and homoallylic amines.[10] The reaction of **1a** with homoallylic amine **23a** did not proceed at all, because of the predominant protonation of the amino group of **23a** in Et_4NF–5HF. To solve the problem, we introduced an electron-withdrawing tosyl group onto the nitrogen atom of **23a**. Because the basicity of **23a** decreased, aza-Prins cyclization proceeded smoothly to provide 4-fluoropiperidines in excellent yields (Table 5, entries 2 and 3). However, the reaction of benzaldehyde (**1c**) with **23b** did not proceed well, because the reactivity of aromatic aldehydes was lower than that of aliphatic aldehydes (Table 5, entry 4). The nucleophilicity of homoallylic amine can be controlled by introduction of the weaker electron-withdrawing ester group.[19] Consequently, the yield of the reaction with benzaldehyde was improved (Table 5, entry 8). Similarly to the case of thia-Prins cyclization, *cis* products were obtained as the main stereoisomers; however, the stereoselectivity in these cases was slightly lower relative to that observed in the thia-Prins cyclization.

Conclusions

We successfully carried out the synthesis of various 4-fluorinated tetrahydropyrans in excellent yields by Prins cyclization in ionic liquid HF salts. The stereochemistry of the products was controlled except for the use of *p*-anisaldehyde and *p*-hydroxybenzaldehyde. We also demonstrated successful thia-Prins and aza-Prins reactions in Et_4NF–5HF. The synthetic method is very convenient and widely applicable, and it is an environmentally friendly process, because VOCs are not required. Through this study, it has been suggested that ionic liquid HF salts would be usable for a variety of fluorination reactions.

Experimental Section

General: ^1H, ^{13}C, and ^{19}F NMR spectra were recorded with a JEOL JNM EX-270 (^1H: 270 MHz, ^{13}C: 67.8 MHz, ^{19}F: 254 MHz) spectrometer in $CDCl_3$. The chemical shifts for ^1H, ^{13}C, and ^{19}F NMR spectra are given in δ (ppm) from internal TMS, $CDCl_3$, and monofluorobenzene (–36.5 ppm), respectively. EI mass spectra were recorded with a Shimadzu GCMS-QP5050A mass spectrometer. HR mass spectra were recorded with a JEOL The MStation JMS-700.

Materials: 1-Octanal (**1a**), cyclohexanecarboxaldehyde (**1b**), benzaldehyde (**1c**), 4-nitrobenzaldehyde (**1d**), *p*-tolualdehyde (**1e**), *p*-anisaldehyde (**1f**), *p*-hydroxybenzaldehyde (**1g**), cyclopentanone (**1h**), cyclohexanone (**1i**), cycloheptanone (**1j**), 1-hexanal (**1k**), 3-buten-1-ol (**2a**), 1-phenyl-3-buten-1-ol (**2c**), and 3-buten-1-amine (**23a**) were purchased and used without purification. 1-Undecen-4-ol (**2b**),[10b] 3-buten-1-thiol (**17a**),[20] 1-nonene-4-thiol (**17b**),[15] 1-phenyl-3-butene-1-thiol (**17c**),[15] and *N*-(3-butenyl)-*p*-toluenesulfonamide (**23b**)[21] were synthesized according to literature procedures. Et_3N–3HF, Et_3N–4HF, Et_3N–5HF, Et_4NF–4HF, and Et_4NF–5HF were kindly supplied by Morita Chemical Industries Co. Ltd. (Japan). *Caution:* Ionic liquid HF salts are toxic and may cause serious burns if they come in contact with unprotected skin. Therefore, they should be handled carefully at all times. It is recommended to use hand protection.

***N*-(3-Butenyl)carbamate (23c):**[22] To a stirred solution of 3-buten-1-amine (0.36 g, 5.0 mmol) and potassium carbonate (0.90 g, 6.5 mmol) in CH_3OH (30 mL) was added methyl chloroformate (1.18 g, 12.5 mmol) dropwise at 0 °C. The reaction mixture was stirred for 2 h at room temperature and then water (50 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the organic phase was evaporated to give a clear oil (0.57 g, 4.4 mmol, 88%).

General Procedure for Prins Cyclization: Prins cyclization of various aldehydes or ketones (0.2 mmol) and homoallylic alcohols, thiols, or amines (0.2 mmol) was carried out in Et_4NF–5HF (3 mL) by using a plastic cell at room temperature. The conversion of starting materials was monitored by TLC. After the starting materials were consumed, the reaction mixture was passed through a short column of silica gel eluting with ethyl acetate to remove the fluoride salt. The eluent was evaporated under vacuum. Then, the almost-pure product was obtained. For the thia- or aza-Prins cyclization, the products were obtained as stereoisomeric mixtures of *cis* and *trans* forms. Then, the diastereomeric ratio was calculated by ^{19}F NMR spectroscopy. Next, after the products were purified by silica gel column chromatography (hexane/ethyl acetate), the total isolated yields of both stereoisomeric mixtures were calculated.

***cis*-4-Fluoro-2-phenyltetrahydropyran (5):** Colorless oil. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 5 H), 4.95–4.65 (m, $J_{H,F}$ =

49.1 Hz, 1 H), 4.33–4.27 (m, 1 H), 4.24–4.15 (m, 1 H), 3.60–3.49 (m, 1 H), 2.38–2.28 (m, 1 H), 2.15–2.06 (m, 1 H), 1.94–1.68 (m, 2 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 141.1 (d, J = 1.7 Hz), 128.3, 127.7, 125.7, 89.3 (d, J = 176.1 Hz), 77.8 (d, J = 11.2 Hz), 65.4 (d, J = 12.1 Hz), 40.5 (d, J = 17.2 Hz), 33.0 (d, J = 17.3 Hz) ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –93.1 (m) ppm. MS: m/z = 80 $[M]^+$, 179 $[M – H]^+$, 105, 91, 77, 51. HRMS: calcd. for $C_{11}H_{13}FO$ 180.0950; found 180.0949.

***cis*-4-Fluoro-2-(4-nitrophenyl)tetrahydropyran (6):** Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.21 (d, J = 8.9 Hz, 2 H), 7.52 (d, J = 8.5 Hz, 2 H), 5.00–4.70 (m, $J_{H,F}$ = 49.0 Hz, 1 H), 4.46–4.42 (m, 1 H), 4.29–4.20 (m, 1 H), 3.65–3.54 (m, 1 H), 2.42–2.34 (m, 1 H), 2.20–2.12 (m, 1 H), 1.95–1.58 (m, 2 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 148.4 (d, J = 1.7 Hz), 147.2, 126.3, 123.6, 88.7 (d, J = 176.8 Hz), 76.5 (d, J = 11.4 Hz), 65.4 (d, J = 12.1 Hz), 40.5 (d, J = 17.9 Hz), 32.8 (d, J = 17.7 Hz) ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –93.7 (m) ppm. MS: m/z = 224 $[M – H]^+$, 208, 178, 150, 107, 77, 59. HRMS: calcd. for $C_{11}H_{12}FNO_3$ 225.0801; found 225.0803.

***cis*-4-Fluoro-2-*p*-tolyltetrahydropyran (7):** Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.22 (d, J = 8.1 Hz, 2 H), 7.14 (d, J = 8.1 Hz, 2 H), 4.92–4.62 (m, $J_{H,F}$ = 49.1 Hz, 1 H), 4.28–4.12 (m, 2 H), 3.57–3.47 (m, 1 H), 2.32 (s, 3 H), 2.30–2.24 (m, 1 H), 2.12–2.04 (m, 1 H), 1.92–1.66 (m, 2 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 138.1 (d, J = 1.7 Hz), 137.3, 128.9, 125.7, 89.3 (d, J = 175.9 Hz), 77.6 (d, J = 11.2 Hz), 65.3 (d, J = 12.1 Hz), 40.5 (d, J = 16.7 Hz), 33.0 (d, J = 17.3 Hz), 21.1 ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –93.0 (m) ppm. MS: m/z = 194 $[M]^+$, 179, 119, 105, 91, 77, 65, 55. HRMS: calcd. for $C_{12}H_{15}FO$ 194.1107; found 194.1107.

***cis*-4-Fluoro-2,6-diheptyltetrahydropyran (8):** Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.80–4.50 (m, $J_{H,F}$ = 49.4 Hz, 1 H), 3.22 (m, 2 H), 2.10–2.03 (m, 2 H), 1.64–1.27 (m, 26 H), 0.88 (t, J = 6.4 Hz, 6 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 89.8 (d, J = 174.0 Hz), 74.9 (d, J = 11.2 Hz), 38.7 (d, J = 16.2 Hz), 36.1 (d, J = 1.7 Hz), 31.9, 29.6, 29.3, 25.7, 22.7, 14.2 ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –93.1 (m) ppm. MS: m/z = 300 $[M]^+$, 201, 181, 163, 127, 113, 95, 81, 69, 55. HRMS: calcd. for $C_{19}H_{37}FO$ 300.2828; found 300.2823.

***cis*-4-Fluoro-2-(4-methoxyphenyl)tetrahydropyran (*cis*-10):** Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.28–7.23 (m, 2 H), 6.90–6.85 (m, 2 H), 4.93–4.63 (m, $J_{H,F}$ = 49.1 Hz, 1 H), 4.27–4.12 (m, 2 H), 3.78 (s, 3 H), 3.58–3.48 (m, 1 H), 2.33–2.25 (m, 1 H), 2.13–2.05 (m, 1 H), 1.95–1.66 (m, 2 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 159.0, 133.3 (d, J = 2.1 Hz), 127.1, 113.7, 89.3 (d, J = 176.3 Hz), 77.4 (d, J = 11.7 Hz), 65.3 (d, J = 11.7 Hz), 55.2, 40.3 (d, J = 17.0 Hz), 32.9 (d, J = 17.3 Hz) ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –93.0 (m) ppm. MS: m/z = 210 $[M]^+$, 209 $[M – H]^+$, 179, 135, 122, 108, 91, 77, 65, 55. HRMS: calcd. for $C_{12}H_{15}FO_2$ 210.1056; found 210.1055.

***trans*-10:** Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.28–7.25 (m, 2 H), 6.90–6.84 (m, 2 H), 5.16–4.97 (m, $J_{H,F}$ = 48.0 Hz, 1 H), 4.72–4.67 (m, 1 H), 4.01–3.96 (m, 2 H), 3.78 (s, 3 H), 2.16–1.69 (m, 4 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 158.8, 134.1, 127.0, 113.6, 86.9 (d, J = 167.9 Hz), 73.7, 63.1, 55.2, 38.4 (d, J = 20.1 Hz), 30.7 (d, J = 20.2 Hz) ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –109.1 (m) ppm. MS: m/z = 210 $[M]^+$, 209 $[M – H]^+$, 179, 135, 122, 108, 91, 77, 65, 55. HRMS: calcd. for $C_{12}H_{15}FO_2$ 210.1056; found 210.1058.

***cis*-4-Fluoro-2-(4-hydroxylphenyl)tetrahydropyran (*cis*-11):** Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.19–7.14 (m, 2 H), 6.69–6.63 (m, 2 H), 6.32 (s, 1 H), 4.94–4.64 (m, $J_{H,F}$ = 49.1 Hz, 1 H), 4.27–4.12 (m, 2 H), 3.60–3.50 (m, 1 H), 2.32–2.23 (m, 1 H), 2.15–2.06 (m, 1 H), 1.93–1.72 (m, 2 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 155.4, 132.5 (d, J = 1.8 Hz), 127.5, 115.3, 89.3 (d, J = 175.9 Hz), 77.7 (d, J = 11.3 Hz), 65.4 (d, J = 11.7 Hz), 40.0 (d, J = 17.2 Hz), 32.9 (d, J = 17.6 Hz) ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –93.1 (m) ppm. MS: m/z = 196 $[M]^+$, 179, 131, 121, 107, 94, 77, 65, 55. HRMS: calcd. for $C_{11}H_{13}FO_2$ 196.0900; found 196.0895.

***trans*-11:** Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.26–7.19 (m, 2 H), 6.81–6.75 (m, 2 H), 5.20–4.98 (m, $J_{H,F}$ = 48.1 Hz, 1 H), 4.94 (s, 1 H), 4.71–4.66 (m, 1 H), 4.02–3.97 (m, 2 H), 2.19–1.71 (m, 4 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 155.4, 133.0, 127.5, 115.3, 86.7 (d, J = 167.9 Hz), 74.2, 63.1, 38.0 (d, J = 20.4 Hz), 30.5 (d, J = 20.5 Hz) ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –109.1 (m) ppm. MS: m/z = 196 $[M]^+$, 179, 131, 121, 107, 94, 77, 65, 55. HRMS: calcd. for $C_{11}H_{13}FO_2$ 196.0900; found 196.0899.

9-Fluoro-6-oxaspiro[4.5]decane (12): Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.94–4.67 (m, $J_{H,F}$ = 49.3 Hz, 1 H), 3.91–3.81 (m, 1 H), 3.60–3.51 (m, 1 H), 2.02–1.37 (m, 12 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 88.0 (d, J = 171.8 Hz), 83.4 (d, J = 6.7 Hz), 58.9 (d, J = 7.8 Hz), 41.0 (d, J = 17.3 Hz), 38.9 (d, J = 2.1 Hz), 36.0, 32.3 (d, J = 18.4 Hz), 23.8, 23.5 ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –99.5 (m) ppm. MS: m/z = 158 $[M]^+$, 129, 116, 101, 84, 67, 55. HRMS: calcd. for $C_9H_{15}FO$ 158.1107; found 158.1105.

4-Fluoro-1-oxaspiro[5.5]undecane (13): Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.01–4.73 (m, $J_{H,F}$ = 49.3 Hz, 1 H), 3.91–3.82 (m, 1 H), 3.64–3.54 (m, 1 H), 2.04–1.25 (m, 14 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 87.3 (d, J = 171.3 Hz), 73.2 (d, J = 7.3 Hz), 57.5 (d, J = 7.8 Hz), 41.6 (d, J = 17.2 Hz), 37.3 (d, J = 2.2 Hz), 33.7, 32.5 (d, J = 18.4 Hz), 25.9, 21.7, 21.4 ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –99.1 (m) ppm. MS: m/z = 172 $[M]^+$, 129, 116, 55. HRMS: calcd. for $C_{10}H_{17}FO$ 172.1263; found 172.1262.

4-Fluoro-1-oxaspiro[5.6]dodecane (14): Colorless oil. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –97.9 (m) ppm. MS: m/z = 186 $[M]^+$, 143, 129, 116, 84, 69, 55.

***cis*-4-Fluoro-2-heptylthiacyclohexane (*cis*-18):** Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.54–4.25 (m, $J_{H,F}$ = 46.9 Hz, 1 H), 2.83–2.60 (m, 3 H), 2.42–2.33 (m, 2 H), 1.83–1.27 (m, 14 H), 0.88 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 91.6 (d, J = 170.6 Hz), 42.1 (d, J = 12.3 Hz), 41.2 (d, J = 18.8 Hz), 35.8, 34.0 (d, J = 20.1 Hz), 31.8, 29.5, 29.2, 26.9, 26.6 (d, J = 13.4 Hz), 22.7, 14.2 ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –90.4 (m) ppm. MS: m/z = 218 $[M]^+$, 161, 143, 119, 101, 99, 73, 67, 55. HRMS: calcd. for $C_{12}H_{23}FS$ 218.1504; found 218.1507.

***trans*-18:** ^{19}F NMR (254 MHz, $CDCl_3$): δ = –108.7 (m) ppm.

***cis*-2-Cyclohexyl-4-fluorothiacyclohexane (*cis*-19):** White solid; m.p. 39–40 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.52–4.23 (m, $J_{H,F}$ = 46.8 Hz, 1 H), 2.79–2.57 (m, 3 H), 2.43–2.33 (m, 2 H), 1.83–1.05 (m, 13 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 92.3 (d, J = 170.1 Hz), 48.4 (d, J = 11.7 Hz), 42.5, 38.3 (d, J = 19.0 Hz), 34.2 (d, J = 20.1 Hz), 30.4, 30.3, 26.6 (d, J = 13.9 Hz), 26.4 ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –89.5 (m) ppm. MS: m/z = 202 $[M]^+$, 119, 99, 85, 73, 55. HRMS: calcd. for $C_{11}H_{19}FS$ 202.1191; found 202.1189.

***trans*-19:** ^{19}F NMR (254 MHz, $CDCl_3$): δ = –108.8 (m) ppm.

***cis*-4-Fluoro-2-phenylthiacyclohexane (*cis*-20):** White solid; m.p. 54–55 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 5 H), 4.66–4.37 (m, $J_{H,F}$ = 46.6 Hz, 1 H), 3.96–3.90 (m, 1 H), 2.93–2.73 (m, 2 H), 2.61–2.43 (m, 2 H), 2.18–2.03 (m, 1 H), 1.94–1.76 (m, 1 H)

ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 140.4, 128.6, 127.6, 127.3, 91.8 (d, J = 171.2 Hz), 46.2 (d, J = 13.4 Hz), 41.5 (d, J = 19.4 Hz), 33.6 (d, J = 20.1 Hz), 28.1 (d, J = 14.4 Hz) ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –90.2 (m) ppm. MS: m/z = 196 $[M]^+$, 176, 161, 147, 135, 121, 105, 91, 77, 65, 51. HRMS: calcd. for $C_{11}H_{13}FS$ 196.0722; found 196.0718.

***trans*-20:** ^{19}F NMR (254 MHz, $CDCl_3$): δ = –110.2 (m) ppm.

***cis*-4-Fluoro-2,6-dipentylthiacyclohexane (*cis*-21):** Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.53–4.24 (m, $J_{H,F}$ = 46.8 Hz, 1 H), 2.82–2.73 (m, 2 H), 2.42–2.34 (m, 2 H), 1.60–1.27 (m, 18 H), 0.89 (t, J = 6.8 Hz, 6 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 91.9 (d, J = 170.0 Hz), 41.3 (d, J = 12.7 Hz), 41.1 (d, J = 19.0 Hz), 35.6, 31.7, 26.6, 22.5, 14.1 ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –90.9 (m) ppm. MS: m/z = 260 $[M]^+$, 231, 189, 119, 115, 87, 67, 55. HRMS: calcd. for $C_{15}H_{29}FS$ 260.1974; found 260.1980.

***trans*-21:** ^{19}F NMR (254 MHz, $CDCl_3$): δ = –107.2 (m) ppm.

***cis*-4-Fluoro-2,6-diphenylthiacyclohexane (*cis*-22):** White solid; m.p. 104–106 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.39–7.22 (m, 10 H), 4.82–4.53 (m, $J_{H,F}$ = 46.4 Hz, 1 H), 4.12–4.07 (m, 2 H), 2.69–2.61 (m, 2 H), 2.25–2.10 (m, 2 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 139.8 (d, J = 1.1 Hz), 128.6, 127.7, 127.3, 46.5 (d, J = 13.9 Hz), 40.7 (d, J = 19.7 Hz) ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –90.3 (m) ppm. MS: m/z = 272 $[M]^+$, 239, 181, 167, 147, 137, 121, 115, 91, 77, 65, 51. HRMS: calcd. for $C_{17}H_{17}FS$ 272.1035; found 272.1039.

trans-**22**: ^{19}F NMR (254 MHz, $CDCl_3$): δ = –108.8 (m) ppm.

***cis*-4-Fluoro-2-heptyl-*N*-tosylpiperidine (*cis*-25):** Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.1 Hz, 2 H), 7.29 (d, J = 8.1 Hz, 2 H), 4.86–4.57 (m, $J_{H,F}$ = 48.5 Hz, 1 H), 4.18–4.16 (m, 1 H), 3.97–3.92 (m, 1 H), 3.08–2.98 (m, 1 H), 2.42 (s, 3 H), 1.96–1.90 (m, 2 H), 1.52–1.23 (m, 14 H), 0.88 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 143.1, 138.1, 129.6, 126.7, 87.0 (d, J = 172.4 Hz), 53.6 (d, J = 12.8 Hz), 38.8 (d, J = 12.8 Hz), 34.2 (d, J = 18.3 Hz), 31.8, 31.3 (d, J = 18.8 Hz), 31.1, 29.2, 29.1, 26.5, 22.7, 21.6, 14.1 ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –99.9 (m) ppm. MS: m/z = 256, 236, 155, 91, 55. HRMS: calcd. for $C_{19}H_{30}FNO_2S$ 355.1981; found 355.1989.

trans-**25**: ^{19}F NMR (254 MHz, $CDCl_3$): δ = –104.2 (m) ppm.

***cis*-2-Cyclohexyl-4-fluoro-*N*-tosylpiperidine (*cis*-26):** Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.73 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 8.2 Hz, 2 H), 4.81–4.51 (m, $J_{H,F}$ = 48.7 Hz, 1 H), 3.98–3.92 (m, 1 H), 3.82 (m, 1 H), 3.03–2.93 (m, 1 H), 2.42 (s, 3 H), 2.17–2.10 (m, 1 H), 1.87–0.88 (m, 14 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 143.1, 138.3, 129.7, 126.7, 86.8 (d, J = 172.3 Hz), 58.8 (d, J = 12.8 Hz), 39.2 (d, J = 12.8 Hz), 36.6, 31.0 (d, J = 13.9 Hz), 30.7 (d, J = 14.5 Hz), 30.3, 30.1, 26.1, 26.0, 25.9, 21.5 ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –98.5 (m) ppm. MS: m/z = 256, 236, 155, 91, 55. HRMS: calcd. for $C_{18}H_{26}FNO_2S$ 339.1668; found 339.1671.

trans-**26**: ^{19}F NMR (254 MHz, $CDCl_3$): δ = –106.0 (m) ppm.

***cis*-4-Fluoro-2-phenyl-*N*-tosylpiperidine (*cis*-27):** Colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.78–7.75 (m, 2 H), 7.35–7.22 (m, 7 H), 5.43 (m, 1 H), 4.73–4.44 (m, $J_{H,F}$ = 48.6 Hz, 1 H), 4.02–3.95 (m, 1 H), 3.07–2.96 (m, 1 H), 2.70–2.60 (m, 1 H), 2.44 (s, 3 H), 1.87–1.82 (m, 1 H), 1.76–1.62 (m, 1 H), 1.52–1.33 (m, 1 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 143.4, 137.7, 137.5, 129.8, 128.7, 127.2, 126.8, 126.3, 86.6 (d, J = 173.1 Hz), 55.5 (d, J = 12.6 Hz), 39.9 (d, J = 12.3 Hz), 33.5 (d, J = 19.1 Hz), 31.1 (d, J = 19.0 Hz), 21.6 ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –99.4 (m) ppm. MS: m/z = 333 $[M]^+$, 256, 178, 155, 144, 130, 115, 104, 91, 77, 65, 51. HRMS: calcd. for $C_{18}H_{20}FNO_2S$ 333.1199; found 333.1199.

trans-**27**: ^{19}F NMR (254 MHz,$CDCl_3$): δ = –105.4 (m) ppm.

***cis*-4-Fluoro-2-(4-nitrophenyl)-*N*-tosylpiperidine (*cis*-28):**[23] ^{19}F NMR (254 MHz, $CDCl_3$): δ = –100.1 (m) ppm.

trans-**28**: Yellow solid; m.p. 155–157 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.15 (d, J = 8.7 Hz, 2 H), 7.74 (d, J = 8.0 Hz, 2 H), 7.50 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.4 Hz, 2 H), 5.36–5.34 (m, 1 H), 4.98–4.80 (m, $J_{H,F}$ = 46.9 Hz, 1 H), 3.87–3.83 (m, 1 H), 3.40–3.29 (m, 1 H), 2.73–2.64 (m, 1 H), 2.45 (s, 3 H), 2.12–1.23 (m, 3 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 147.2, 143.8, 137.4, 129.9, 127.3, 127.2, 126.8, 123.4, 85.8 (d, J = 171.5 Hz), 52.9, 36.7 (d, J = 2.1 Hz), 32.1 (d, J = 19.4 Hz), 28.8 (d, J = 21.2 Hz), 21.7 ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –107.0 ppm. MS: m/z = 378 $[M]^+$, 256, 223, 155, 91. HRMS: calcd. for $C_{18}H_{19}FN_2O_4S$ 378.1050; found 378.1060.

***cis*-4-Fluoro-*N*-methoxycarbonyl-2-phenylpiperidine (*cis*-31):** Yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.39–7.21 (m, 5 H), 5.67 (m, 1 H), 4.82–4.52 (m, $J_{H,F}$ = 48.8 Hz, 1 H), 4.27–4.22 (m, 1 H), 3.76 (s, 3 H), 2.88–2.74 (m, 2 H), 2.08–1.93 (m, 2 H), 1.80–1.61 (m, 1 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 156.2, 138.4, 128.8, 126.9, 125.8, 87.1 (d, J = 172.9 Hz), 53.3 (d, J = 13.2 Hz), 53.0, 38.2 (d, J = 12.4 Hz), 34.3 (d, J = 18.8 Hz), 32.3 (d, J = 18.8 Hz) ppm. ^{19}F NMR (254 MHz, $CDCl_3$): δ = –99.2 (m) ppm. MS: m/z = 237 $[M]^+$, 205, 190, 178, 160, 143, 130, 118, 104, 91, 77, 59, 51. HRMS: calcd. for $C_{13}H_{16}FNO_2$ 237.1165; found 237.1169.

trans-**31**: ^{19}F NMR (254 MHz, $CDCl_3$): δ = –105.4 (m) ppm.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13} C NMR spectra of new compounds.

Acknowledgments

This study was supported by a Grant-in-Aid for Scientific Research (No. 17073008) in Priority Area "Science of Ionic Liquids" (Area Number 452) and a Grant-in-Aid for Scientific Research (B) (No. 20350071).

[1] a) T. Fuchigami, M. Shimojo, A. Konno, K. Nakagawa, *J. Org. Chem.* **1990**, *55*, 6074–6075; b) T. Fuchigami, S. Narizuka, A. Konno, *J. Org. Chem.* **1992**, *57*, 3755–3757; c) Y. Hou, S. Higashiya, T. Fuchigami, *J. Org. Chem.* **1997**, *62*, 8773–8776; d) D. Baba, H. Ishii, S. Higashiya, K. Fujisawa, T. Fuchigami, *J. Org. Chem.* **2001**, *66*, 7020–7024; e) K. Suzuki, T. Fuchigami, *J. Org. Chem.* **2004**, *69*, 1276–1282; f) Y. Cao, A. Hidaka, T. Fuchigami, *J. Org. Chem.* **2005**, *70*, 9614–9617; g) A. Hidaka, B. Zagipa, H. Nagura, T. Fuchigami, *Synlett* **2007**, 1148–1152; h) H. Nagura, T. Fuchigami, *Synlett* **2008**, 1714–1718.

[2] a) R. D. Rogers, K. R. Seddon, *Science* **2003**, *302*, 792–793; b) T. Welton, *Chem. Rev.* **1999**, *99*, 2071–2083; c) J. Dupont, R. F. de Souza, P. A. Z. Suarez, *Chem. Rev.* **2002**, *102*, 3667–3692; d) Y. Hamashima, H. Takano, D. Hotta, M. Sodeoka, *Org. Lett.* **2003**, *5*, 3225–3228; e) T. Itoh, E. Akasaki, Y. Nishimura, *Chem. Lett.* **2002**, 154–155.

[3] a) M. Hasegawa, H. Ishii, T. Fuchigami, *Tetrahedron Lett.* **2002**, *43*, 1503–1505; b) M. Hasegawa, H. Ishii, T. Fuchigami, *Green Chem.* **2003**, *5*, 512–515; c) M. Hasegawa, T. Fuchigami, *Electrochim. Acta* **2004**, *49*, 3367–3372; d) M. Hasegawa, H. Ishii, Y. Cao, T. Fuchigami, *J. Electrochem. Soc.* **2006**, *153*, D162-D166; e) S. Inagi, T. Sawamura, T. Fuchigami, *Electrochem. Commun.* **2008**, *10*, 1158–1160.

[4] a) M. A. McClinton, *Aldrichimica Acta* **1995**, *28*, 31–35; b) G. Haufe, *J. Prakt. Chem.* **1996**, *338*, 99–113.

[5] a) H. Yoshino, S. Matsubara, K. Oshima, K. Matsumoto, R. Hagiwara, Y. Ito, *J. Fluorine Chem.* **2004**, *125*, 455–458; b) H.

Yoshino, K. Nomura, S. Matsubara, K. Oshima, K. Matsumoto, R. Hagiwara, Y. Ito, *J. Fluorine Chem.* **2004**, *125*, 1127–1129; c) H. Yoshino, K. Matsumoto, R. Hagiwara, Y. Ito, K. Oshima, S. Matsubara, *J. Fluorine Chem.* **2006**, *127*, 29–35.

[6] a) J. S. Yadav, B. V. S. Reddy, M. S. Reddy, N. Niranjan, A. R. Prasad, *Eur. J. Org. Chem.* **2003**, 1779–1783; b) J. S. Yadav, B. V. S. Reddy, M. S. Reddy, N. Niranjan, *J. Mol. Catal. A* **2004**, *210*, 99–103; c) X. L. Zhao, L. Liu, Y. J. Chen, D. Wang, *Tetrahedron* **2006**, *62*, 7113–7120.

[7] a) J. D. White, P. R. Blakemore, C. C. Browder, J. Hong, C. M. Lincoln, P. A. Nagornyy, L. A. Robarge, D. J. Wardrop, *J. Am. Chem. Soc.* **2001**, *123*, 8593–8595; b) C. H. A. Lee, T. P. Loh, *Tetrahedron Lett.* **2006**, *47*, 1641–1644; c) X. Tian, J. J. Jaber, S. D. Rychnovsky, *J. Org. Chem.* **2006**, *71*, 3176–3183; d) R. Nannei, S. Dallavalle, L. Merlini, A. Bava, G. Nasini, *J. Org. Chem.* **2006**, *71*, 6277–6280; e) K. P. Chan, Y. H. Ling, T. P. Loh, *Chem. Commun.* **2007**, 939–941.

[8] a) K. Kataoka, Y. Ode, M. Matsumoto, J. Nokami, *Tetrahedron* **2006**, *62*, 2471–2483; b) E. H. Al-Mutairi, S. R. Crosby, J. Darzi, J. R. Harding, R. A. Hughes, C. D. King, T. J. Simpson, R. W. Smith, C. L. Willis, *Chem. Commun.* **2001**, 835–836; c) J. J. Jaber, K. Mitsui, S. D. Rychnovsky, *J. Org. Chem.* **2001**, *66*, 4679–4686.

[9] I. Bucsi, B. Török, A. I. Marco, G. Rasul, G. K. S. Prakash, G. A. Olah, *J. Am. Chem. Soc.* **2002**, *124*, 7728–7736.

[10] We determined the relative stereochemistry of the fluorinated tetrahydropyrans and piperidines according to the previous reports by Yoshida et al: a) J. Yoshida, Y. Ishichi, S. Isoe, *J. Am. Chem. Soc.* **1992**, *114*, 7594–7595; b) J. Yoshida, M. Sugawara, M. Tatsumi, N. Kise, *J. Org. Chem.* **1998**, *63*, 5950–5961.

[11] R. W. Alder, J. N. Harvey, M. T. Oakley, *J. Am. Chem. Soc.* **2002**, *124*, 4960–4961.

[12] T. Fuchigami, S. Narizuka, A. Konno, K. Momota, *Electrochim. Acta* **1998**, *43*, 1985–1989.

[13] G. Sabitha, K. B. Reddy, M. Bhikshapathi, J. S. Yadav, *Tetrahedron Lett.* **2006**, *47*, 2807–2810.

[14] a) S. Ohuchida, N. Hamanaka, M. Hayashi, *Tetrahedron Lett.* **1981**, *22*, 1349–1352; b) C. Boglio, S. Stahlke, S. Thorimbert, M. Malacria, *Org. Lett.* **2005**, *7*, 4851–4854; c) A. Kato, N. Kato, E. Kano, I. Adachi, K. Ikeda, L. Yu, T. Okamoto, Y. Banba, H. Ouchi, H. Takahata, N. Asano, *J. Med. Chem.* **2005**, *48*, 2036–2044.

[15] X. F. Yang, J. T. Mague, C. J. Li, *J. Org. Chem.* **2001**, *66*, 739–747.

[16] a) R. M. Carballo, M. A. Ramirez, M. L. Rodriguez, V. S. Martin, J. L. Padrón, *Org. Lett.* **2006**, *8*, 3837–3840; b) M. S. R. Murty, K. R. Ram, J. S. Yadav, *Tetrahedron Lett.* **2008**, *49*, 1141–1145.

[17] J.-P. Gesson, J. C. Jacquesy, D. Rambaud, *Tetrahedron* **1993**, *49*, 2239–2248.

[18] The relative stereochemistry of the 4-fluorothiacyclohaxanes was determined according to NOE experiments of the 2,4,6-trisubstituted compound (**22**).

[19] Group electronegativities: -SO_2Ph = 3.01, -COOR = 2.83 were referred to N. Inamoto, S. Masuda, *Chem. Lett.* **1982**, 1003–1006.

[20] M. Minozzi, D. Nanni, J. C. Walton, *Org. Lett.* **2003**, *5*, 901–904.

[21] S. Handa, M. S. Kachala, S. R. Lowe, *Tetrahedron Lett.* **2004**, *45*, 253–256.

[22] N. Kise, H. Yamazaki, T. Mabuchi, T. Shono, *Tetrahedron Lett.* **1994**, *35*, 1561–1564.

[23] This compound was separated only in *trans* form after purification by column chromatography (silica gel).

Received: September 9, 2008
Published Online: November 18, 2008

