Synthesis of Organofluorine Compounds Using the Ene Reaction of *N*-(*p*-Toluenesulfonyl)trifluoroacetaldehyde Imine[1)]

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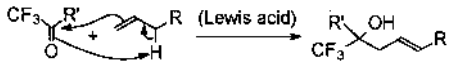
***N*-Tosyltrifluoroacetaldehyde imine (4) reacted with terminal olefins by only heating together to give the ene reaction products. This means the imine is much more reactive than trifluoroacetaldehyde (2) itself as an enophile. However, 4 was very sensitive to moisture and the yields were low even if it was used without isolation. Further, it did not react with non-terminal olefins. In the course on study of the mechanism of this reaction, we found that *N*-(2,2,2-trifluoro-1-ethoxyethyl)tosylamide (12), obtained by the reaction of trifluoroacetaldehyde ethyl hemiacetal (1) with tosylamide (3) in the presence of titanium(IV) chloride followed by addition of ethanol, reacted in the presence of sodium hydride and titanium(IV) chloride to give the same products from the ene reaction of 4 in much better yields. Interestingly, this reaction proceeded with non-terminal olefins.**

Key words trifluoromethyl; trifluoroacetaldehyde; imine; ene reaction; amide acetal; *N*-(2,2,2-trifluoro-1-ethoxyethyl)tosylamide

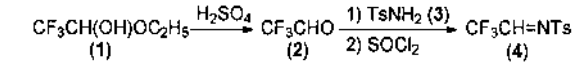
Nowadays, organofluorine compounds are attracting much attention in biomedicinal fields, and some new medicines containing fluorine substituents have been developed.[2)] New methodologies for synthesis of fluorine compounds have been found, too. However, new methods for syntheses of new types of fluorine compounds are still required. We are engaged in developing new synthetic methodology for trifluoromethyl compounds, and we reported the ene reaction of trifluoromethyl carbonyl compounds in the presence or absence of a Lewis acid to give a wide range of α-(trifluoromethyl)-homoallyl alcohols.[3)]



(1)

Some of the products from this ene reaction were converted to trifluoro analogs of terpenes[4)] and sesquiterpenes.[5)] The homoallyl alcohols from trifluoroacetaldehyde were successfully oxidized by Dess-Martin reagent to trifluoromethyl allyl ketones, which were transformed to various trifluoromethyl compounds.[6)] As an extension of this ene reaction of trifluoromethyl carbonyl compounds, we examined the ene reaction of *N*-tosylhexafluoroacetone imine, and found that it reacted as a good enophile to give *N*-tosyl-α,α-bis(trifluoromethyl)homoallylamines.[7)] Here, we would like to report the ene reaction of *N*-tosyltrifluoroacetaldehyde imine (**4**) and related reactions to give *N*-tosyl-α(trifluoromethyl)-homoallylamines.

First, *N*-tosyltrifluoroacetaldehyde imine (**4**) was synthesized to compare the ene reaction of trifluoromethyl carbonyl compounds with that of their imines. Thus, trifluoroacetaldehyde ethyl hemiacetal (**1**) was treated with concentrated sulfuric acid, and the generated trifluoroacetaldehyde (**2**) was introduced to a solution of *p*-toluenesulfonamide (tosylamide, **3**) and a catalytic amount of pyridine in tetrahydrofuran (THF). The mixture was kept at room temperature for 48 h. After evaporation of the solvent, the residue was treated with thionyl chloride to give the imine (**4**) (Eq. 2). This imine was very sensitive to moisture and was used for ene reaction without purification.

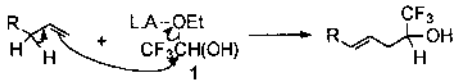


(2)

Reaction of **4** with terminal ene compounds, 1-decene (**5**) and allylbenzene (**7**), proceeded in boiling xylene to give *N*-[1-(trifluoromethyl)-3-undecenyl]tosylamide (**6**) and *N*-[4-phenyl-1-(trifluoromethyl)-3-butenyl]tosylamide (**8**), respectively, while internal ene compounds, cyclohexene (**9**) and 2-octene (**10**), hardly reacted, as shown in Chart 1.

The ene reaction of trifluoroacetaldehyde itself does not proceed at all without a Lewis acid.[6)] This means that a tosylimino group is a better group as an enophile than a carbonyl group, while the two large substituents of **4**, a trifluoromethyl and a *p*-toluenesulfonyl group, make non-terminal disubstituted olefins unreactive. The stereochemistry of the double bonds of **6** and **8** was determined from the coupling constants between the olefinic protons to be *E*-configuration. Thus, *N*-tosyltrifluoroacetaldehyde imine (**4**) was found to react as a good enophile. However, it is highly sensitive to moisture and difficult to deal with. This could be the reason why the yields of the reaction were not satisfactory. Another difficulty of this reaction was that gaseous trifluoroacetaldehyde must be evolved for the synthesis of **4**.

Previously, we found that the hemiacetal (**1**) reacted with ene compounds in the presence of Lewis acids (Eq. 3).[8)]



(3)

If this could be applied here, the above difficulty would be removed (see Chart 2).

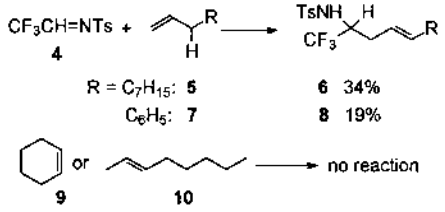


Chart 1

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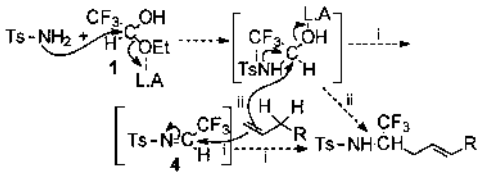


Chart 2

Table 1. Reaction of **5** in the Presence of $TiCl_4$

R (eq) **5**	$TiCl_4$ (eq)	Yield (%)		
		6	**12**	**13**
C_7H_{15} (0.9)	0.9	Trace	60	—
C_7H_{15} (0.9)	1.8	34	24	Trace
C_7H_{15} (0.9)	3.6	22	21	16
C_7H_{15} (1.8)	1.8	66	19	—

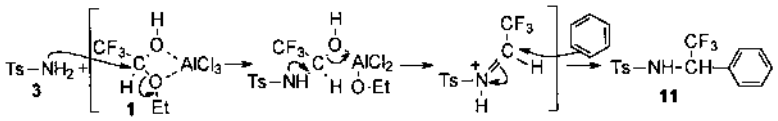


Chart 3

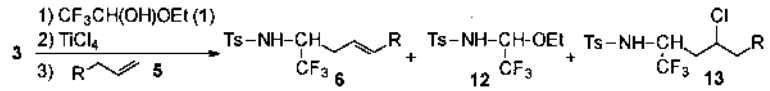


Chart 4

Namely, if **1** reacts with tosylamide in the presence of a Lewis acid to give α-tosyl-amidoalcohol and this forms the imine **4** (route i) or reacts directly with an ene compound in the presence of the Lewis acid (route ii), the same product from the ene reaction will be obtained. Weingarten *et al*. reported formation of an imine by the reaction of an amine and an aldehyde in the presence of titanium(IV) chloride.[9] If this could be applied to amide, the imine would be formed. With this expectation, we examined the reaction of **1** and **3** with 1-decene (**5**) in the presence of aluminum chloride.

When **1**, **3** and **5** were heated in benzene in the presence of aluminum chloride, *N*-(2,2,2-trifluoro-1-phenylethyl)tosylamide (**11**) was obtained in the yield of 65%, but no ene reaction products were observed. The same reaction in other solvents resulted in the recovery of starting materials. Formation of **11** is explained as shown in Chart 3.

This means that the imine or its comparable compound did not react with the ene compound **5**, but reacted with benzene in a Friedel-Crafts type reaction. To avoid this, we examined other Lewis acids in other solvents. Boron trifluoride etherate and zinc chloride did not afford **6**. When 0.9 eq of titanium (IV) chloride ($TiCl_4$) was used in dichloromethane in a closed vessel, *N*-(2,2,2-trifluoro-1-ethoxyethyl)tosylamide (**12**) was obtained in high yield. As the amount of $TiCl_4$ was increased, **6** was obtained and formation of **12** was decreased. The best result was obtained when 1.8 eq of $TiCl_4$ was used. If more $TiCl_4$ was used, formation of *N*-[3-chloro-1-(trifluoromethyl)undecyl]tosylamide (**13**), an apparent adduct of hydrogen chloride to **6**, became appreciable. The reaction is shown in Chart 4 and the results are summarized in Table 1.

Thus, when approximately two equivalents of **5** and $TiCl_4$ were used for one equivalent of **1** and **3**, a good yield of **6** was obtained. This reaction is superior to the former ene reaction of the imine (**4**), since this procedure eliminated the preliminary formation of trifluoroacetaldehyde and its imine **4**.

To examine the scope and limitation of this reaction, we examined the reaction of some other ene compounds. Allylbenzene (**7**) gave the ene product (**8**) and the iminoacetal (**12**)

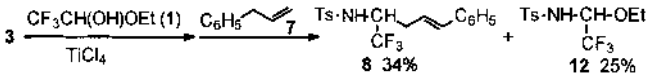


Chart 5

in moderate yields in the presence of two equivalents of $TiCl_4$. When one equivalent of the acid was used, only a trace of **8** was obtained with a much larger amount of **12** (Chart 5). Interestingly, when $AlCl_3$ was used in benzene at 90 °C, **8** was obtained in 31% yield. This suggests that the double bond of **7** might be more reactive than that of **5**, since the latter did not react under the same conditions and **11** was obtained.

Although the yields were not satisfactory, the same products from the ene reaction of the imine (**4**) were obtained from monosubstituted olefins by a much easier procedure. However, this procedure was found to be ineffective for disubstituted olefins. Thus, reaction of *cis*-2-heptene (**14**) gave *N*-[2-methyl-1-(trifluoromethyl)-3-heptenyl]tosylamide (**15**) and *N*-[1-(trifluoromethyl)-2-vinylhexyl]tosylamide (**16**) in a total yield of only 11%. Reaction of cyclohexene (**9**) gave a mixture of ene reaction products (**17**, **18**) and their hydrogen chloride adduct (**19**) in very small amounts. The structures of these products were determined by comparison of NMR spectra with those obtained by the reaction discussed in the latter part of this report. Methylenecyclohexane (**21**), which reacted with trifluoromethyl carbonyl compounds as a good ene compound,[10] did not give the expected product (**22**) at all. These results are shown in Chart 6.

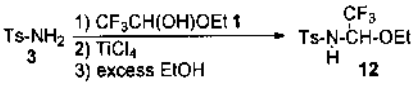
The above results suggest that disubstituted olefins are much less reactive than monosubstituted ones. This may be due to the larger steric hindrance of the reactive intermediate of this reaction than those in the reaction of trifluoromethyl carbonyl compounds.

To clarify the mechanism of this reaction, a mixture of tosylamide, $TiCl_4$ and **1** (1 : 2 : 1) in $CDCl_3$ was followed by ^{19}F-NMR. The signal due to **1** disappeared in 30 min, and new peaks at −14.0, −16.7 and −17.3 ppm were observed. After 2 h, only the peak at −14.0 ppm was observed. Treat-

ment of this mixture with water gave amidoacetal (**12**) and amidoalcohol (**23**). Formation of these products were tentatively speculated as shown in Chart 7.

Addition of **1** to a mixture of **3** and $TiCl_4$ caused slow evolution of gas, probably HCl. Addition of **5** to the mixture showing −14.0 ppm did not give the ene product (**6**). Thus, evolution of HCl inactivates the complex for the ene reaction. Namely, reaction of **1** and $TiCl_4$ made a complex, and addition of **3** gave a complex with the titanium oxide group through two intermediates with loss of HCl as shown at the top of Chart 7. The two intermediates showing at −17.3 and −16.7 ppm must react with **5** in a closed system to give **6**. As mentioned above, the reaction only proceeded in a closed vessel inhibiting evolution of HCl. The complex showing −14.0 ppm, which was formed in an open system by loss of HCl, was much less reactive and hydrolyzed to **23** or **12** through a or b routes.

As shown above, we could obtain ene type products using $TiCl_4$ much easier than by the reaction of the imine **4**. However, non-terminal olefins did not react in this condition, and the terminal olefins did not always give the products in high yields. To improve these point, we tried to use *N*-(2,2,2-trifluoro-1-ethoxyethyl)tosylamide (**12**) as an intermediate for the ene type reaction. This reagent is a colorless crystal and stable enough to keep on the shelf. It was obtained on a preparative scale by the reaction of the hemiacetal **1**, tosylamide **3** and $TiCl_4$, followed by addition of ethanol to the mixture (Eq. 4).



(4)

Reaction of **12** with **5** in the presence of $TiCl_4$ was found to give the ene product **6** in 29% yield after 20 h. This showed that **12** could be used as an intermediate, but its reaction was very slow. Since the *N*-proton was observed clearly in the mixture of **12** and $TiCl_4$ in ^{1}H-NMR, the free imine **4** did not seem to be formed. Thus, the mechanism of this reaction was temporarily speculated as shown in Chart 8.

To improve this deficiency, **12** was treated with sodium hydride and then with $TiCl_4$. Namely, we postulated formation of a highly reactive four-membered complex by this procedure, as shown in Chart 9.

After **12** was treated with one equivalent of sodium hydride and then with two equivalents of $TiCl_4$, one equivalent of 1-decene (**5**) was added to the mixture to afford the ene reaction product (**6**) in 87% yield. When **12** was treated with sodium hydride and $TiCl_4$ in a NMR tube, a new peak was observed in ^{19}F-NMR at −7.8 ppm, much lower field than that of **12**. The ethyl protons were observed at a similar fields as the former complex in Chart 7, but the methine proton moved from 5.89 ppm to 8.48 ppm. This suggested formation of the four-membered complex shown in Chart 9.

This procedure seemed to be much superior to the aforementioned reactions, since this need not isolation of the unstable imine **4**. The amidoacetal **12** is a stable crystal and easy to work with. The yield was satisfactorily high. Therefore, we examined the scope and limitation of this procedure. The major results are shown in Chart 10, and the characteris-

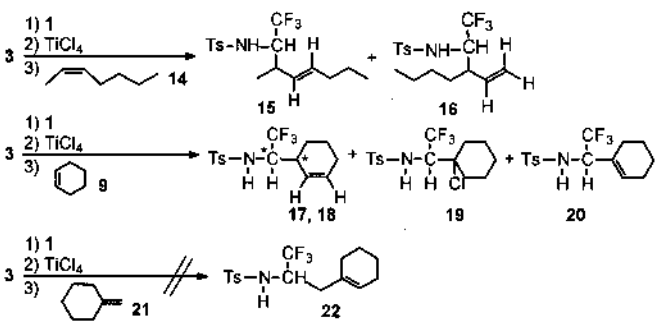


Chart 6

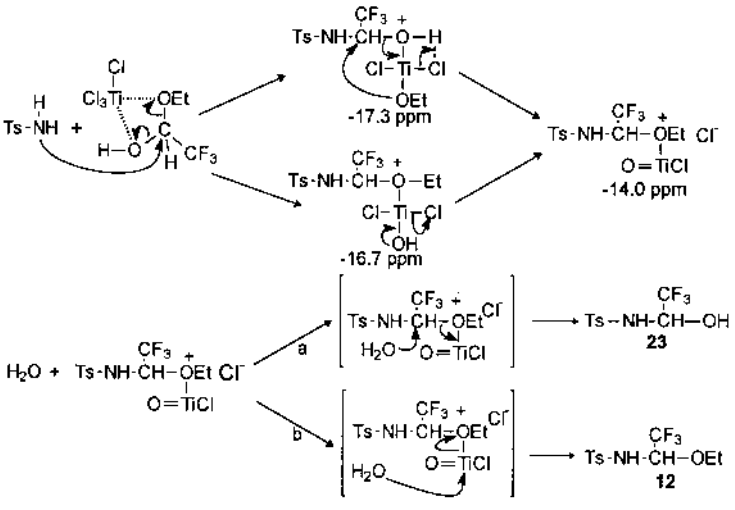


Chart 7

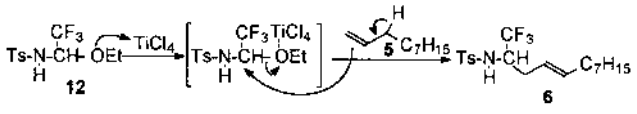


Chart 8

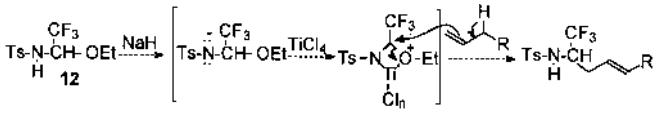


Chart 9

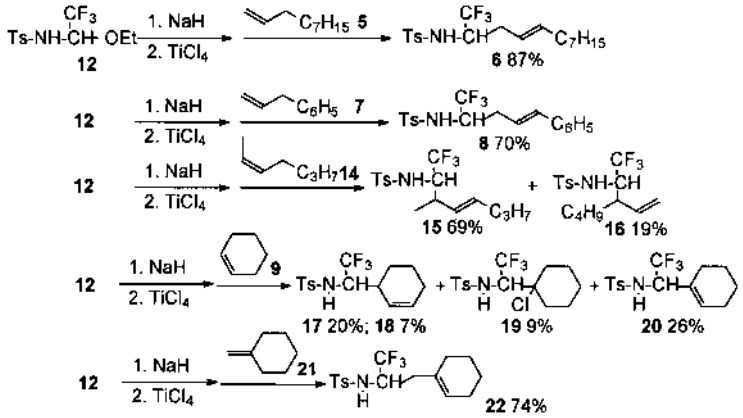


Chart 10

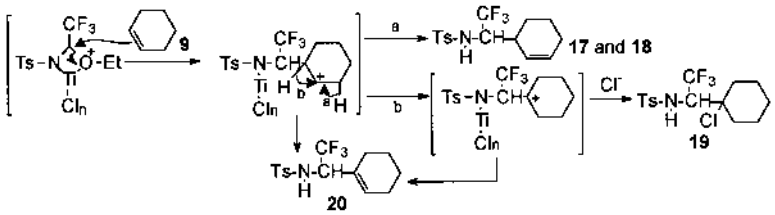
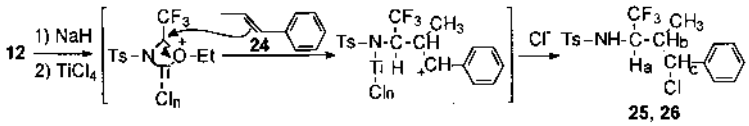


Chart 11



	25	26
$-CH_3$	0.66 (d, J = 7.0 Hz)	1.31 (d, J = 6.7 Hz)
$-\dot{C}-H_a$	4.80 (ddq, J = 1.2, 10.4, 7.3 Hz)	3.76 (ddq, J = 2.1, 10.4, 7.3 Hz)
$-\dot{C}-H_b$	2.58 (ddq, J = 1.2, 10.7, 7.0 Hz)	2.68 (ddq, J = 2.1, 9.8, 6.7 Hz)
$-\dot{C}-H_c$	4.44 (d, J = 10.7 Hz)	4.90 (d, J = 9.8 Hz)
NH	5.11 (d, J = 10.4 Hz)	4.94 (d, J = 10.4 Hz)

Chart 12

tic points are explained.

Allylbenzene (**7**) reacted similarly to give **8** in 70% yield. Thus, terminal olefins gave good results. When one equivalent of *cis*-2-heptene (**14**), a non-terminal olefin, was treated in the same condition as above, two ene products (**15** and **16**) were obtained in 59% and 19% yields. This is the first example which gave practical yields of ene type products from non-terminal olefins. When three equivalents of **14** to **12** was used, the yields were improved to 69% and 19%, respectively, but the regioselectivity was not changed remarkably. To improve this regioselectivity, reaction was carried out at 0 °C. Now, the starting material was recovered in 34%, but regioselectivity was unchanged. At −50 °C, all the starting materials were recovered. One difference of this reaction from the ene reaction of trifluoroacetaldehyde was that the latter gave only one regioisomer of type **15**. This suggests that the reaction proceeded through a much less stereo-demanding cationic intermediate than the four-membered complex in Chart 9. Another characteristic point is that only one diastereomer **15** or **16** was observed. We did not determine the stereochemistries, but speculated them to be (*R**,*R**) from the stereochemistry of the ene reaction of trifluoroacetaldehyde.[6] The same reaction using three equivalents of cyclohexene (**9**) gave two ene-type products (**17** and **18**) in 20 and 7% yields, respectively, with its double bond isomer (**20**) and an apparent HCl adduct (**19**) of this compound. The same reaction of methylenecyclohexane (**21**) gave a good yield of the ene-type product (**22**). Formation of these products were rationalized by cationic intermediates formed from the postulated four-membered complex, as illustrated for the reaction of **9** in Chart 11.

This speculation was supported by the reaction of β-methylstyrene (**24**). Thus, **24** was added to the mixture of **12**, sodium hydride and $TiCl_4$, followed by treatment of the mixture with ice-water to give *N*-[3-chloro-2-methyl-3-phenyl-1-(trifluoromethyl)propyl]tosylamide (**25** and **26**, a 1 : 3 mixture of diastereomers) in 66% yield. The diastereomers were hard to separate, but their structures were assigned by ^{1}H- and ^{19}F-NMR spectra. Formation of **25** and **26** was rationalized by a stable benzylic cationic intermediate shown in Chart 12.

A good enophile, hexafluoroacetone, did not react with **24** at all. This supports that this reaction of **12** is not a concerted ene reaction but a stepwise reaction.

In conclusion, *N*-tosyltrifluoroacetaldehyde imine (**4**) was found to react as an enophile, but its reaction is limited to ene compounds with a terminal double bond. Further, the yield of the reaction was unsatisfactorily low, probably due to the high sensitivity of **4** to moisture. Another difficulty of the reaction **4** is that it must be formed from trifluoroacetaldehyde (**2**), which is a gas at room temperature and needs a special apparatus. Some of these difficulties were solved by the reaction of trifluoroacetaldehyde ethyl hemiacetal (**1**) and tosylamide (**3**) with ene compounds in the presence of $TiCl_4$. This method eliminated some troubles using gaseous **2** and improved the yields a little, but ene compounds with substituents at both carbons of the double bond did not give practically useful yields of products. In the last reaction, *N*-(2,2,2-trifluoro-1-ethoxyethyl)tosylamide (**12**) was isolated as a by-product. The reaction of **12** with sodium hydride then $TiCl_4$, followed by addition of ene compounds, was found to give the ene-type products in good yields. Treatment of **1** and **3** with $TiCl_4$, followed by treatment of the mixture with ethanol, gave **12** in a good yield. Further, ene compounds of non-terminal olefins gave the ene type products in moderate yields. From consideration of the by-products, this reaction is speculated not to be a concerted ene reaction, but to be a stepwise cationic reaction. Though this is not a concerted ene reaction, it gives the ene type products in good yields and is useful for synthesis of the trifluoromethyl compounds.

Experimentals

General Procedures ^{1}H-NMR were recorded on JEOL-FX90Q and JNM-GX400 Spectrometer. Tetramethylsilane was used as an internal standard. ^{19}F-NMR were recorded on Hitachi FT-NMR R-1500 and JEOL-FX90Q Spectrometer. Benzotrifluoride was used as an internal standard. Mass spectra were obtained by JEOL JMS-DX-300. IR spectra were recorded on Hitachi 270-30 Infrared Spectrophotometer. Melting point was measured on an Ishii Shoten Melting Point Apparatus.

Preparation of *N*-Tosyltrifluoroacetaldehyde Imine (4) $CF_3CH(OH)$-OEt (**1**, 3 ml) was added to concentrated H_2SO_4 (10 ml) at 80 °C, and CF_3CHO (**2**) was collected in a trap cooled at −78 °C. After **2** was introduced to a solution of *p*-toluenesulfonamide (**3**, 2.00 g, 11.7 mmol) in anhydrous THF (10 ml) containing pyridine (45 μl, 5 mol%), this mixture was allowed to stand in a sealed tube at room temperature for 2 d. The content was transferred to a round-bottom flask, and the tube was rinsed with C_6H_6 (5 ml). The combined mixture was concentrated using a vacuum-line. The residue was refluxed with thionyl chloride (2 ml) in C_6H_6 (5 ml) for 5 h, and the mixture was concentrated using a vacuum line. The residue, *N*-tosyltrifluoroacetaldehyde imine (**4**), was used for the ene reaction.

Ene Reaction of 4

Reaction with 1-Decene (5) 1-Decene (**5**, 1.35 ml, 7.1 mmol)) and xylene (10 ml) was added to **4** obtained as above, and the mixture was refluxed for 16 h. The mixture was poured into ice-water, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water and dried over $MgSO_4$. After solvent was evaporated under vacuum, the residue was separated by column chromatography (SiO_2, hexane–CH_2Cl_2, 7 : 3) to give *N*-[1-(trifluoromethyl)-3-undecenyl]tosylamide (**6**, 0.992 g, 34%). **6**: Colorless crystals. mp 46—47 °C. Mass spectrum (MS) *m/z*: 391 (M^+). HRMS Calcd for $C_{19}H_{28}F_3NO_2S$: 391.179. Found: 391.179. IR (KBr) cm^{-1}: 3292 (N–H), 1338, 1180 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.7 Hz), 1.13 (10H, m), 1.91 (2H, dt, J=6.7, 6.7 Hz), 2.27 (1H, ddd, J=7.3, 7.3, 14.7 Hz), 2.35 (1H, ddd, J=5.2, 7.3, 14.7 Hz), 2.43 (3H, s), 3.91 (1H, m, ddq on treatment with D_2O (J=5.2, 7.3, 7.3 Hz)), 5.04 (1H, d, J=9.2 Hz, disappeared on treatment with D_2O), 5.10 (1H, ddd, J=7.6, 7.6, 15.2 Hz), 5.47 (1H, dtt, J=15.2, 6.7, 1.2 Hz), 7.30 (2H, d, J=8.2 Hz), 7.73 (2H, d, J=8.2 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −11.2 (3F, d, J=7.3 Hz).

Reaction with Allylbenzene (7) A solution of the imine (**4**) and allylbenzene (**7**, 910 μl, 6.9 mmol) was refluxed for 16 h, and the mixture was treated as in the case of **5**. The residue was separated by column chromatography (SiO_2, hexane–CH_2Cl_2, 1 : 1) to give *N*-[4-phenyl-1-(trifluoromethyl)-3-butenyl]tosylamide (**8**, 0.493 g, 19%). **8**: Colorless crystals. mp 117—118 °C. MS *m/z*: 369 (M^+). HRMS Calcd for $C_{18}H_{18}F_3NO_2S$: 369.101. Found: 369.100. IR (KBr) cm^{-1}: 3280 (N–H), 1338, 1180 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s), 2.47 (1H, m), 2.60 (1H, m), 4.02 (1H, m), 4.87 (1H, d, J=9.5 Hz, disappeared on treatment with D_2O), 5.83 (1H, dt, J=15.8, 7.3 Hz), 6.39 (1H, d, J=15.8 Hz), 7.17 (2H, d, J=8.1 Hz), 7.24 (5H, s), 7.70 (2H, d, J=8.1 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −11.4 (3F, d, J=6.6 Hz).

Reaction with Cyclohexene (9) Cyclohexene (**9**, 700 μl, 6.9 mmol) was added to a solution of **4**, formed as above, in xylene (10 ml), and the mixture was refluxed for 16 h. The mixture was worked up as above, and the CH_2Cl_2 layer was concentrated. The residue was analyzed by ^{19}F-NMR, but no new fluorine compounds were detected.

Reaction with 2-Octene (10) A solution of 2-octene (**10**, 1.00 ml, 6.4 mmol) and **4** in toluene (10 ml) was refluxed for 13 h. The mixture was worked up as above and analyzed with ^{19}F-NMR, but no new fluorine compounds were detected.

Ene Type Reaction of Trifluoroacetaldehyde Ethyl Hemiacetal (1) and Tosylamide (3) in the Presence of a Lewis Acid

Reaction with 1-Decene (5): In the Presence of $AlCl_3$ In a stream of Ar, **1** (66 μl, 0.55 mmol) was added to solution of **3** (0.171 g, 1.0 mmol) and $AlCl_3$ (133 mg, 1.0 mmol) in benzene (2 ml), and the mixture was stirred at 80 °C for 16 h. After **5** (190 μl, 1.0 mmol) was added, the mixture was refluxed for 12 h. The mixture was poured into ice-water, and extracted with Et_2O. The Et_2O layer was dried over $MgSO_4$, and the solvent was evaporated under vacuum. The residue was separated by column chromatography (SiO_2, hexane–CH_2Cl_2–AcOEt, 7 : 2 : 1) to give *N*-(2,2,2-trifluoro-1-phenylethyl)tosylamide (**11**, 0.213 g, 65%), but **6** was not obtained. **11**: Colorless crystals. mp 159—161 °C. MS *m/z*: 329 (M^+). HRMS Calcd for $C_{15}H_{14}F_3NO_2S$: 329.070. Found: 329.069. IR (KBr) cm^{-1}: 3264 (N–H), 1334, 1170 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s), 4.92 (1H, dq, J=9.2, 7.3 Hz (q, J=7.3 Hz) on treatment with D_2O), 5.46 (1H, d, J=9.2 Hz, disappeared on treatment with D_2O), 7.16 (2H, d, J=8.5 Hz), 7.17—7.33 (5H, m), 7.61 (2H, d, J=8.5 Hz). ^{19}F-NMR ($CDCl_3$) δ: −10.4 (3F, d, J=7.3 Hz).

Reaction with 1-Decene (5): In the Presence of $TiCl_4$ In an atmosphere of Ar, **1** (132 μl, 1.1 mmol) and $TiCl_4$ (218 μl, 2.0 mmol) was added to a solution of **3** (0.171 g, 1.0 mmol) in CH_2Cl_2 (2 ml), and the mixture was stirred at room temperature for 4 h. After **5** (380 μl, 2.0 mmol) was added, the mixture was stirred for 6 h in a closed vessel. The mixture was poured into ice-water, then extracted with Et_2O. The Et_2O layer was dried over $MgSO_4$. After the solvent was evaporated under vacuum, the residue was separated by column chromatography (SiO_2, hexane–CH_2Cl_2–AcOEt, 7 : 2 : 1) to give **6** (0.256 g, 66%) and *N*-(2,2,2-trifluoro-1-ethoxyethyl)tosylamide (**12**, 0.055 g, 18%). **12**: Colorless crystals. mp 81—82 °C. MS *m/z*: 297 (M^+). HRMS Calcd for $C_{11}H_{14}F_3NO_3S$: 297.065. Found: 297.064. IR (KBr) cm^{-1}: 3828 (N–H), 1344, 1160 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, t, J=6.8 Hz), 2.48 (3H, s), 3.63 (1H, dq, J=9.3, 6.8 Hz), 3.78 (1H, J=9.3, 6.8 Hz), 4.98 (1H, dq, J=10.1, 4.4 Hz), 5.45 (1H, d, J=10.1 Hz, disappeared on treatment with D_2O), 7.42 (2H, d, J=8.3 Hz), 7.92 (1H, d, J=8.3 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −16.8 (3F, d, J=4.4 Hz).

Reaction with Allylbenzene (7) in the Presence of $TiCl_4$ In an atmosphere of Ar, **1** (132 μl, 1.1 mmol) and $TiCl_4$ (218 μl, 2.0 mmol) was added to a solution of **3** (0.171 g, 1.0 mmol) in CH_2Cl_2 (2 ml), then the mixture was stirred at room temperature for 4 h. After **7** (300 μl, 2.3 mmol) was added, the mixture was stirred for 6 h in a sealed vessel. The mixture was poured into ice-water, and extracted with Et_2O. The Et_2O layer was dried over $MgSO_4$, and the solvent was evaporated under vacuum. The residue was separated by column chromatography (SiO_2, hexane–AcOEt–Et_2O, 8 : 1 : 1) to give **8** (124 mg, 34%) and **12** (74 mg, 25%).

Reaction with Allylbenzene (7) in the Presence of $AlCl_3$ In an atmosphere of Ar, **1** (198 μl, 1.5 mmol) was added to a solution of **3** (0.514 g, 3.0 mmol) and $AlCl_3$ (0.809 g, 6.1 mmol) in benzene (5 ml), and the mixture was stirred at 90 °C for 16 h. After **7** (400 μl, 3.0 mmol) was added to the mixture, it was stirred for 12 h. The mixture was worked up as above and the product was purified by column chromatography (SiO_2, hexane–CH_2Cl_2, 8 : 2) to give **8** (0.176 g, 31%).

Reaction of *cis*-2-Heptene (14) in the Presence of $TiCl_4$ In an atmosphere of Ar, **1** (132 μl, 1.1 mmol) and $TiCl_4$ (218 μl, 2.0 mmol) was added to a solution of **3** (0.171 g, 1.0 mmol) in CH_2Cl_2 (2 ml), and the mixture was stirred at room temperature for 4 h. After *cis*-2-heptene (**14**, 280 μl, 2.0 mmol) was added to the mixture, it was stirred for 6 h in a closed vessel. The mixture was poured into ice-water, and extracted with Et_2O. The Et_2O layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was analyzed by ^{1}H-NMR (400 MHz) to contain **12** (76%, based on 1,4-dioxane (5 μl)), but no ene products were detected. When **14** (420 μl, 3.0 mmol) was

used, formation of *N*-[2-methyl-1-(trifluoromethyl)-3-heptenyl]tosylamide (**15**) and *N*-[1-(trifluoromethyl)-2-vinylhexyl]tosylamide (**16**) was confirmed in a total yieid of 11% by NMR. The spectral data for these products will be presented in a latter part of this report.

Reaction of Cyclohexene (9) In an atmosphere of Ar, **1** (132 μl, 1.1 mmol) and $TiCl_4$ (218 μl, 2 mmol) was added to a solution of **3** (0.171 g, 1 mmol) in CH_2Cl_2 (2 ml), and the mixture was stirred for 4 h. After **9** (220 μl, 2 mmol) was added, the mixture was stirred at room temperature for 48 h. The mixture was worked up as above, and the residue was separated by column chromatography (SiO_2, hexane–CH_2Cl_2, 7 : 3 and hexane–CH_2Cl_2–Et_2O, 5 : 5 : 1) to give a mixture of *N*-[1-(1-chlorocyclohexyl)-2,2,2-trifluoroethyl]tosylamide (**19**) and *N*-[1-(3-cyclohexenyl)-2,2,2-trifluoroethyl]tosylamide (**17**) (22 mg, **17**=11%, **19**=2%), and a mixture of *N*-[1-(3-cyclohexenyl)-2,2,2-trifluoroethyl]tosylamide (**18**) and *N*-[1-(1-cyclohexenyl)-2,2,2-trifluoroethyl]tosylamide (**20**) (3 mg), and **12** (0.107 g, 72%). Structures of **17** to **20** were determined by comparison of spectra with those obtained in the latter part of this report.

Reaction Using *N*-(2,2,2-Trifluoro-1-ethoxyethyl)tosylamide (12)

Prepartion of 12 In an atmosphere of Ar, **1** (1.32 ml, 11 mmol) and $TiCl_4$ (2.18 ml, 20 mmol) was added slowly to a solution of **3** (1.71 g, 10 mmol) in CH_2Cl_2 (20 ml), and the mixture was stirred for 14 h. After EtOH (3.50 ml, 60 mmol) was added to the mixture, and stirred for further 1 h. The mixture was poured into ice-water, and extracted with Et_2O. The Et_2O layer was washed with H_2O and dried over $MgSO_4$. After solvent was evaporated under vacuum, the residue was purified by column chromatography (SiO_2, hexane–CH_2Cl_2–AcOEt, 7 : 2 : 1) to give **12** (2.49 g, 84%).

Reaction with 5 in the Presence of $TiCl_4$ In an atmosphere of Ar, $TiCl_4$ (218 μl, 2.0 mmol) was added to a solution of **12** (0.300 g, 1.0 mmol) in CH_2Cl_2 (2 ml) and the mixture was stirred at room temperature for 3 h in a closed vessel. After **5** (190 μl, 1.0 mmol) was added, the mixture was stirred at room temperature for 20 h. The mixture was poured into ice water, then extracted with Et_2O. The Et_2O layer was dried over $MgSO_4$. After the solvent was evaporated under vacuum, the residue was separated by column chromatography (SiO_2, hexane–CH_2Cl_2–AcOEt, 7 : 2 : 1) to give **6** (0.112 g, 29%).

For the analysis of the mechanism, the reaction was carried out in an NMR tube using $CDCl_3$ as the solvent.

Reaction of 1-Decene (5) with 12 in the Presence of NaH and $TiCl_4$ In an atmosphere of Ar, a solution of **12** (0.300 g, 1.0 mmol) in CH_2Cl_2 (0.50 ml) was added slowly to a suspension of 60% NaH (50 mg) in CH_2Cl_2 (1.50 ml), and the mixture was stirred at room temperature for 1.5 h. After $TiCl_4$ (218 ml, 2.0 mmol) and **5** (190 μl, 1.0 mmol) were added to this mixture at 0 °C, it was stirred for a further 4 h at room temperature, then poured into ice-water and extracted with Et_2O. The Et_2O layer was dried over $MgSO_4$, and the solvent was evaporated under vacuum. The residue was separated by column chromatography (SiO_2, hexane–CH_2Cl_2–AcOEt, 7 : 2 : 1) to give **6** (0.339 g, 87%).

Reaction of Allybenzene (7) with 12 in the Presence of NaH and $TiCl_4$ In an atmosphere of Ar, a solution of **12** (0.300 g, 1.0 mmol) in CH_2Cl_2 (0.50 ml) was added slowly to a suspension of 60% NaH (50 mg) in CH_2Cl_2 (1.50 ml), and the mixture was stirred at room temperature for 1.5 h. After $TiCl_4$ (218 μl, 2.0 mmol) and **7** (200 μl, 1.5 mmol) were added to this mixture at 0 °C, it was stirred for a further 4 h. After the mixture was worked up as above, the residue was purified by column chromatography (SiO_2, hexane–Et_2O–AcOEt, 8 : 1 : 1) to give **8** (0.258 g, 70%).

Reaction of *cis*-2-Heptene (14) with 12 in the Presence of NaH and $TiCl_4$ In an atmosphere of Ar, a solution of **12** (0.300 g, 1.0 mmol) in CH_2Cl_2 (0.50 ml) was added slowly to a suspension of 60% NaH (50 mg) in CH_2Cl_2 (1.50 ml), and the mixture was stirred at room temperature for 1.5 h. After $TiCl_4$ (218 μl, 2.0 mmol) and **14** (140 μl, 1.0 mmol) was added to this mixture at 0 °C, it was stirred for a further 4 h. After the mixture was worked up as above, the residue was purified by column chromatography (SiO_2, hexane–CH_2Cl_2–Et_2O, 6 : 3 : 1) to give **15** (0.206 g, 59%) and **16** (0.066 g, 19%). **15**: Colorless crystals. mp 77—78 °C. MS *m/z*: 349 (M^+). HRMS Calcd for $C_{16}H_{22}F_3NO_2S$: 349.132. Found: 349.132. IR (KBr) cm^{-1}: 3296 (N–H), 1328, 1164 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J*=7.3 Hz), 1.09 (3H, d, *J*=7.0 Hz), 1.37 (2H, tq, *J*=7.6, 7.0 Hz), 1.98 (2H, dt, *J*=7.0, 7.3 Hz), 2.42 (3H, s), 2.72 (1H, m), 3.86 (1H, ddq, *J*=9.5, 3.5, 8.0 Hz), 4.77 (1H, d, *J*=9.5 Hz), 5.29 (1H, dddd, *J*=1.2, 1.2, 5.8, 15.6 Hz), 5.55 (1H, ddt, *J*=1.2, 7.0, 15.6 Hz), 7.29 (2H, d, *J*=8.2 Hz), 7.74 (2H, d, *J*=8.2 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −8.78 (3F, d, *J*=8.0 Hz). **16**: Colorless crystals. MS *m/z*: 349 (M^+). HRMS Calcd for $C_{16}H_{22}F_3NO_2S$: 349.132. Found: 349.132. IR (KBr) cm^{-1}: 3292 (N–H), 1330, 1166 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J*=7.3 Hz), 1.26 (4H, m), 1.42 (2H, m), 2.42 (3H, s), 2.52 (1H, m), 3.97 (1H, ddq, *J*=2.8, 12.5, 8.0 Hz), 4.71 (1H, d, *J*=12.5 Hz), 5.16 (1H, ddd, *J*=0.9, 1.2, 17.1 Hz), 5.27 (1H, dd, *J*=1.2, 10.7 Hz), 5.62 (1H, dddq, *J*=8.2, 10.7, 17.1, 0.9 Hz), 7.29 (2H, d, *J*=8.2 Hz), 7.74 (2H, d, *J*=8.2 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −8.78 (3F, d, *J*=8.0 Hz). The same reaction using **14** (420 μl, 3.0 mmol) at room temperature for 24 h gave a mixture of **15** and **16** (0.303 g, 87%, ratio 3.5 : 1 based on NMR). The same reaction at −50 °C resulted in recovery of the starting materials.

Reaction of Cyclohexene (9) with 12 in the Presence of NaH and $TiCl_4$ In an atmosphere of Ar, a solution of **12** (0.300 g, 1.0 mmol) in CH_2Cl_2 (0.50 ml) was added slowly to a suspension of 60% NaH (50 mg) in CH_2Cl_2 (1.50 ml), and the mixture was stirred at room temperature for 1.5 h. After $TiCl_4$ (218 μl, 2.0 mmol) and **9** (300 μl, 3.0 mmol) was added to this mixture at 0 °C, it was stirred for a further 6 h. After the mixture was worked up as above, the residue was purified by column chromatography (SiO_2, hexane–CH_2Cl_2–Et_2O, 6 : 3 : 1) to give **20** (32 mg, 9%), **17** (66 mg, 20%), **18** (22 mg, 7%) and **19** (85 mg, 26%). **17**: Colorless crystals. MS *m/z*: 333 (M^+). HRMS Calcd for $C_{15}H_{18}F_3NO_2S$: 333.101. Found: 333.101. IR (KBr) cm^{-1}: 3292 (N–H), 1334, 1172 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.55 (2H, m), 1.80 (2H, m), 2.00 (2H, m), 2.42 (3H, s), 2.75 (1H, m), 3.89 (1H, ddq, *J*=2.4, 9.1, 8.1 Hz), 4.70 (1H, d, *J*=9.1 Hz, disappeared on treatment with D_2O), 5.52 (1H, m), 6.03 (1H, ddt, *J*=3.2, 10.4, 3.7 Hz), 7.28 (2H, d, *J*=8.5 Hz), 7.73 (2H, d, *J*=8.5 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −8.88 (3F, d, *J*=8.1 Hz). **18**: Colorless crystals. mp 131—133 °C. MS *m/z*: 333 (M^+). HRMS Calcd for $C_{15}H_{18}F_3NO_2S$: 333.101. Found: 333.101. IR (KBr) cm^{-1}: 3292 (N–H), 1328, 1164 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.32 (1H, m), 1.52 (1H, m), 1.79 (2H, m), 19.7 (2H, m), 2.42 (3H, s), 2.65 (1H, m), 4.00 (1H, ddq, *J*=4.9, 9.2, 8.0 Hz), 4.72 (1H, d, *J*=9.2 Hz, disappeared on treatment with D_2O), 5.37 (1H, m), 5.79 (1H, ddt, *J*=2.8, 10.1, 4.0 Hz), 7.28 (2H, d, *J*=7.9 Hz), 7.73 (2H, d, *J*=7.9 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −8.01 (3F, d, *J*=8.0 Hz). **19**: Colorless crystals. mp 181—183 °C. MS *m/z*: 371 (M+2), 369 (M^+). HRMS Calcd for $C_{15}H_{19}ClF_3NO_2S$: 369.078. Found: 369.078. IR (KBr) cm^{-1}: 3288 (N–H), 1330, 1176 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.72 (8H, m), 2.19 (2H, m), 2.42 (3H, s), 4.14 (1H, dq, *J*=9.8, 7.3 Hz), 5.19 (1H, d, *J*=9.8 Hz, disappeared on treatment with D_2O), 7.30 (2H, d, *J*=8.2 Hz), 7.74 (2H, d, *J*=8.2 z). ^{19}F-NMR ($CDCl_3$) ppm: −3.74 (3F, d, *J*=7.3 Hz). **20**: Colorless crystals. MS *m/z*: 333 (M^+). HRMS Calcd for $C_{15}H_{18}F_3NO_2S$: 333.101. Found: 333.100. IR (KBr) cm^{-1}: 3280 (N–H), 1334, 1170 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.30 (1H, m), 1.39 (2H, m), 1.52 (1H, m), 1.70—1.88 (3H, m), 1.93 (1H, m), 2.42 (3H, s), 4.27 (1H, dq, *J*=9.5, 8.0 Hz), 5.14 (1H, d, *J*=9.5 Hz, disappeared on treatment with D_2O), 5.66 (1H, m) , 7.29 (2H, d, *J*=8.5 Hz), 7.71 (2H, d, *J*=8.5 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −9.67 (3F, d, *J*=8.0 Hz).

Reaction of Methylenecyclohexane (21) with 12 in the Presence of NaH and $TiCl_4$ In an atmosphere of Ar, a solution of **12** (1.00 g, 3.4 mmol) in CH_2Cl_2 (1.50 ml) was added slowly to a suspension of 60% NaH (170 mg) in CH_2Cl_2 (4.50 ml), and the mixture was stirred at room temperature for 1 h. After $TiCl_4$ (660 μl, 6.1 mmol) and **21** (360 μl, 3.0 mmol) was added to this mixture at 0 °C, it was stirred for a further 12 h. After the mixture was worked up as above, the residue was purified by column chromatography (SiO_2, hexane–CH_2Cl_2–Et_2O, 7 : 2 : 1) to give **22** (0.774 g, 74%). **22**: Colorless crystals. mp 132—133 °C. MS *m/z*: 347 (M^+). HRMS Calcd for $C_{16}H_{20}F_3NO_2S$: 347.117. Found: 347.117. IR (KBr) cm^{-1}: 3280 (N–H), 1334, 1160 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.51 (1H, m), 1.52 (1H, m), 1.59 (2H, m), 1.82 (1H, m), 1.94 (1H, m), 1.98 (2H, m), 2.07 (1H, dd, *J*=10.4, 14.0 Hz), 2.42 (3H, s), 2.43 (1H, dd, *J*=4.3, 14.0 Hz), 4.06 (1H, dddq, *J*=4.3, 7.9, 10.4, 6.6 Hz), 4.45 (1H, d, *J*=7.9 Hz, disappeared on treatment with D_2O), 5.54 (1H, m), 7.28 (2H, d, *J*=8.2 Hz), 7.73 (2H, d, *J*=8.2 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −11.9 (3F, d, *J*=6.6 Hz). When the reaction mixture was treated not with ice-water, but with water, the HCl adduct of **22**, *N*-[2-(1-chloro-1-cyclohexyl)-1-(trifluoromethyl)ethyl]tosylamide (2.37 g, 31%) was obtained. Colorless crystals. mp 145—148 °C. MS *m/z*: 385 (M+2), 383 (M^+). HRMS Calcd for $C_{16}H_{21}ClF_3NO_2S$: 383.093. Found: 383.093. IR (KBr) cm^{-1}: 3292 (N–H), 1330, 1160 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.19 (1H, m), 1.48—1.61 (4H, m), 1.61—1.81 (3H, m), 1.93 (1H, m), 1.96 (1H, dd, *J*=9.5, 15.6 Hz), 2.05 (1H, m), 2.20 (1H, dd, *J*=2.1, 15.6 Hz), 2.42 (1H, s), 4.47 (1H, dddq, *J*=2.1, 8.6, 9.5, 6.6 Hz), 5.15 (1H, d, *J*=8.6 Hz, disappeared on treatment with D_2O), 7.28 (2H, d, *J*=8.2 Hz), 7.74 (2H, d, *J*=8.2 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −12.4 (3F, d, *J*=6.6 Hz).

Reaction of β-Methylstyrene (24) with 12 in the Presence of NaH and $TiCl_4$ In an atmosphere of Ar, a solution of **12** (0.300 g, 1.0 mmol) in CH_2Cl_2 (0.50 ml) was added slowly to a suspension of 60% NaH (50 mg) in CH_2Cl_2 (1.50 ml), and the mixture was stirred at room temperature for 1 h. After $TiCl_4$ (218 μl, 2.0 mmol) and **24** (120 μl, 1.0 mmol) was added to this mixture at 0 °C, it was stirred for a further 6 h. After the mixture was worked

up as above, the residue was purified by column chromatography (SiO_2, hexane–CH_2Cl_2–Et_2O, 7 : 1 : 1) to give a mixture of *N*-[3-chloro-2-methyl-3-phenyl-1-(trifluoromethyl)propyl]tosylamide (**25**, **26**, 0.268 g, 66%, ratio= 3 : 1 based on NMR). Colorless crystals. MS *m/z*: 407 (M+2), 405 (M^+). HRMS Calcd for $C_{18}H_{19}ClF_3NO_2S$: 405.078. Found: 405.078. IR (KBr) cm^{-1}: 3284 (N–H), 1340, 1168 (SO_2). **25**: ^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, d, J=7.0 Hz), 2.46 (3H, s), 2.58 (1H, ddq, J=1.2, 10.7, 7.0 Hz), 4.44 (1H, d, J=10.7 Hz), 4.80 (1H, ddq, J=1.2, 10.4, 7.3 Hz), 5.11 (1H, d, J=10.4 Hz, disappeared on treatment with D_2O), 7.22 (2H, d, J=8.2 Hz), 7.35 (5H, m), 7.86 (2H, d, J=8.2 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −9.13 (3F, d, J=7.3 Hz). **26**: ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6.7 Hz), 2.40 (3H, s), 2.68 (1H, ddq, J=2.1, 9.8, 6.7 Hz), 3.76 (1H, ddq, J=2.1, 10.4, 7.3 Hz), 4.90 (1H, d, J=9.8 Hz), 4.94 (1H, d, J=10.4 Hz, disappeared on treatment with D_2O), 7.21 (2H, d, J=8.2 Hz), 7.35 (5H, m), 7.62 (2H, d, J=8.2 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −9.13 (3F, d, J=7.3 Hz).

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References and Notes

1) A preliminary report of this work was accepted by *J. Fluorine Chem*.
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