Study on the Isomerization of 1-Acylazetidine. A Comparative Study with the Case of 1-Acylaziridine

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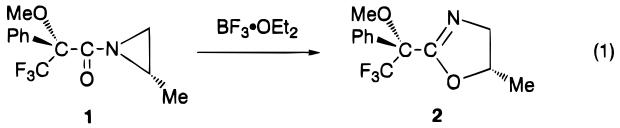
Azetidine has often been compared with aziridine, probably because it is also a small cyclic amine and the molecule is also strained. A number of physical and spectroscopic measurements have been done to inspect if there is some resemblance between the two cyclic amines. These results are collectively reviewed by Moore and Ayers.[1] In the review, it is mentioned as a general remark that azetidine has certain behavioral similarities to aziridine that stem from the small ring size and the ring strain. However, the physical properties that reflect the orbital hybridization closely resemble those of pyrrolidine, and thus, azetidine has few of the special characteristics exhibited by aziridine.

In a previous work,[2] we have shown that 1-(*R*)-(α-methoxy-α-trifluoromethylphenylacetyl)-(*S*)-2-methylaziridine (**1**) isomerizes to 2-(*R*)-(α-methoxy-α-trifluoromethyl)-benzyl-(*S*)-5-methyl-1,3-oxazoline-2 (**2**) with complete retention of the configuration at C-2 in the aziridine ring when **1** is heated in benzene with BF_3·OEt_2 for a short period. Molecular orbital calculations using 1-formyl-

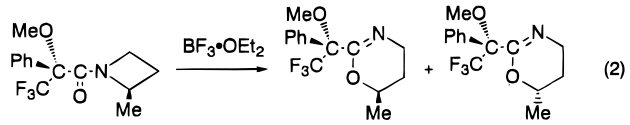


(1)

aziridine (**1a**) as a model compound have shown that the reaction is most likely to proceed by the S_Ni mechanism. This result prompted us to investigate the isomerization of an azetidine derivative to the corresponding oxazine to see if an S_Ni-like process is also possible.

Results and Discussion

Experimental Results. 1-(*R*)-[α-Methoxy-α-(trifluoromethyl)phenylacetyl]-(*R*)-2-methylazetidine (**3**) was prepared from (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*S*)-MTPA chloride] and (*R*)-2-methylazetidine and recrystallized from hexane to give an optically pure sample (100% ee). To a solution of 58 mg (0.2 mmol) of **3** was added 0.24 mL of a solution of BF_3·OEt_2 in benzene (1 mmol/1 mL), and the solution was heated at 70 °C. After every 2 h (at 2, 4, and 6 h), a part of the reaction mixture was removed and monitored. The ^{19}F NMR spectrum of each sample showed that it was a mixture of residual **3**, two diastereomeric oxazines, 2-[(*R*)-(α-methoxy-α-trifluoromethyl)benzyl]-[(*R*) or (*S*)]-6-methyl-5,6-dihydro-4*H*-1,3-oxazine [(*R*)(*R*)-**4**] and [(*R*)(*S*)-**4**], and a substance **5a** that would have formed from **4** by the reaction with BF_3·OEt_2. In every sample, the ratio of (*R*)-(*R*)-**4**:(*R*)(*S*)-**4** was found to be 80:20. Results are shown in Table 1.



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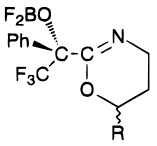
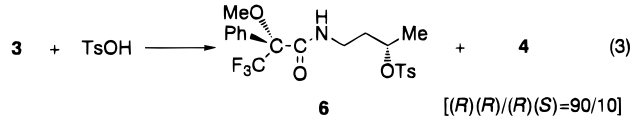


5a R=Me
5b R=H

Reaction of **3** with *p*-toluenesulfonic acid (TsOH) was carried out in a similar way as above, and the reaction mixture was inspected by ^{19}F NMR spectroscopy. When 1.2 molar equiv of TsOH was used, the composition after 1 h of heating was found to be 7% **3**, 39% ring-opened addition product *N*-[(*S*)-3-tosyloxybutyl]-(*R*)-MTPA amide (**6**), and 54% diastereomeric mixture of **4**, of which 89% was (*R*)(*R*) and 11% was (*R*)(*S*). Prolonged heating (4 h)



(3)

did not change the composition. On using 2.4 molar equiv of TsOH, the reaction was practically complete in 1 h, giving a mixture of 6% **6** and 94% **4** [90% (*R*)(*R*) and 10% (*R*)(*S*)]. Results are summarized in Table 2. In a separate experiment, **6** was heated in benzene in the presence of TsOH at 70 °C. After 1 h, 87% of **6** was converted to **4**, and the ratio of (*R*)(*R*)- to (*R*)(*S*)-**4** was found to be 93:7 (Table 3).

To obtain some clue as to the possible site of coordination of BF_3 (ring nitrogen or carbonyl oxygen), 1-acetylazetidine (**7**) was prepared, and the change in the ^1H NMR spectra was observed on addition of BF_3·OEt_2. On addition of 1.2 molar equiv of BF_3·OEt_2, the triplets at 4.03 and 4.14 that were originally observed in the spectrum of **7** disappeared, and two triplets at 4.33 and 4.43 appeared.

Discussion

In the isomerization reaction of **3** with BF_3·OEt_2, the first step should be the coordination of BF_3 to **3**, because the azetidine ring never opens without acids under the

(1) Moore, J. A.; Ayers, R. S. In *Heterocyclic Compounds, Small Ring Heterocyles-Part-2*; Hassner, A., Ed; Binghamton, New York, l983; p 4.

(2) Hori, K.; Nishiguchi, T.; Nabeya, A. *J. Org. Chem.* **1998**, *62*, 3081.

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Table 1. Reaction of (*R*)(*R*)-3 with BF_3·OEt_2

	composition of reaction mixture (%)		
reaction time (h)	(*R*)(*R*)-**3**	**4** [(*R*)(*R*)/(*R*)(*S*)]	**5a** [(*R*)(*R*)/(*R*)(*S*)]
2	46	49 [82/18]	5 [80/20]
4	22	70 [83/17]	8 [80/20]
6	1	91 [81/19]	8 [81/19]

Table 2. Reaction of (*R*)(*R*)-3 with TsOH

mole ratio TsOH/**3**	reaction time (h)	composition of reaction mixture (%)		
		(*R*)(*R*)-**3**	**6**	**4** [(*R*)(*R*)/(*R*)(*S*)]
1.2	1	7	39	54 [89/11]
1.2	2	6	34	60 [89/11]
1.2	4	3	30	67 [90/10]
2.4	1	0	6	94 [90/10]
2.4	2	0	3	97 [89/11]

Table 3. Heating of 6 in Benzene with TsOH

	composition of reaction mixture (%)	
reaction time (h)	**6**	**4** [(*R*)(*R*)/(*R*)(*S*)]
1	13	87 [93/7]
2	8	92 [92/8]

reaction conditions mentioned above. There are two possible sites for BF_3 to coordinate: the ring nitrogen and the carbonyl oxygen. Thus far, no report on the coordination site of BF_3 to amides has been found. A number of works have investigated the protonation site for amides since the 1950s, and ^{1}H NMR spectroscopic inspection showed evidence for the O-protonation. As one of the most prominent examples, Gillespie and Birchall[3] showed the signal of an O−H bond in the ^{1}H NMR spectra of various amides taken in FSO_3H at low temperatures (−80 to −98 °C). Another example by Fraenkel and Niemann[4] showed that the unequivalency of the two methyl groups of DMF (for example) in the ^{1}H NMR spectrum was preserved in strongly acidic media (such as H_2SO_4). In *N*,*N*-dimethylamides (such as DMF or *N*,*N*-dimethylacetamide), the ^{1}H NMR spectra in neutral media show two peaks for the two *N*-methyl groups, demonstrating that the two methyl groups are in different environments. This phenomenon has been explained by the double bond character of the C−N bond of the amide. Thus, they concluded that the preservation of the unequivalency in acidic media should be strong evidence for the O-protonation, because the N-protonation should lead to the free rotation around the C−N bond and therefore should give a single peak for the protons for the two methyl groups.

In the ^{1}H NMR spectra of all of the 1-acylazetidines tested (1-aroyl and 1-acetylazetidine, **7**), there were always two peaks (two protons each) observed assignable to 2- and 4-CH_2 of the azetidine ring, in contrast to the case in 1-methyl and 1-tosylazetidine, in which only one triplet (four protons) was found. This means that in 1-acylazetidines also, the C−N bond is restricted from free rotation as a result of the double bond character of the C−N bond as in typical amides. Amide **7** was chosen as a sample to see the change in the ^{1}H NMR spectra on addition of BF_3·OEt_2. When 1.2 molar equiv of BF_3·OEt_2 was added, the two triplets (of 2- and 4-CH_2) appeared at lower positions than before. The reappearance of the two triplets for 2- and 4-CH_2 is in good accord with the coordination at the carbonyl oxygen.

The next step will be the attack of the cabonyl oxygen on the ring carbon adjacent to the nitrogen. The coordination of BF_3 at the carbonyl oxygen should make the nucleophilic attack easy. The coordination should induce a positive charge on the nitrogen, and therefore, the carbons adjacent to the nitrogen should also be positively charged to some extent. The experimental results showed that the ring opened exclusively at the N−CH(CH_3) bond and that the configuration at the carbon atom was partially retained. If the isomerization took place by the S_Ni mechanism as in **1**, the configuration at the attacked carbon should be completely retained. Therefore, the S_Ni mechanism is ruled out. Because no nucleophiles that might participate in the ring-opening reaction are present in the reaction system, the S_N1 mechanism is the only possible one. It has been known that in many of the S_N1 reactions starting from optically pure material the product is a mixture of the inverted compound and the racemic modification. The predominance of the inversion over the retention in these cases has been attributed to the shielding of the frontside of the carbonium ion by the leaving group, which should lead to the preference of the backside attack of the nucleophile to give the inverted product.[5] The reverse is the case with **3**, where the frontside attack should be more favored than the backside attack owing to the particular conformation, in which the attacking carbonyl oxygen is favorably situated to approach the carbonium ion from the same side as the departing nitrogen. If the carbonyl oxygen attaches itself to the carbonium ion before such a conformation collapses, the retention of the configuration should result.

Thus far, it has been shown that, unlike the isomerization of **1** to **2**, the isomerization of **3** to **4** proceeds by an S_N1 mechanism. This difference seems to stem from the difference of the substrate coordination site of BF_3. In 1-acetylazetidine, the coordination of BF_3 at the carbonyl oxygen was shown to be likely by the ^{1}H NMR analysis. In the case with 1-acylaziridines, however, MO calculations have shown that the protonation at the ring nitrogen is slightly more stable (1.8 kcal mol^{-1}, calculated using 1-formylaziridine as a model compound and proton) than the protonation at the carbonyl oxygen.[2] In the ^{1}H NMR spectra of 1-acylaziridines, the unequivalency has never been observed between the protons or the substituents on the 2- and 3-carbon atom. For example, 1-toluoyl-*cis*-2,3-dimethylaziridine gave only one doublet (of CHCH_3, six protons) and one doublet-quartet (of CH−CH_3, two protons) in the ^{1}H NMR spectrum, indicating that the rotation of the C−N bond is fairly fast. This means that the double bond character of the C−N bond is not so pronounced as in typical amides. It follows that the ring nitrogen should be more basic than that in ordinary amides, and therefore, the coordination of acids at the nitrogen is likely. It was shown in our previous paper[2] that such an initial state of N-coordination is very suitable for the reaction to go by the S_Ni mechanism. In the case of **3**, the lack of such anomaly will lead to the coordination at the carbonyl oxygen and thus adversely affect the S_Ni process because (1) the nucleophilic reactivity of the carbonyl oxygen is reduced by the coordination and (2) the O−CH(CH_3) distance is lengthened.

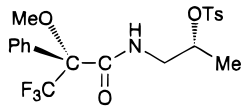
In the reaction of (*R*)(*R*)-**3** with TsOH, two routes are possible that would give rise to **4**: (1) via **6** by addition−

(3) Gillespie, R. J.; Birchall, T. *Can. J. Chem.* **1963**, *41*, 148.
(4) (a) Katritzky, A. R.; Phil, M. A. D.; Jones, R. A. Y. *Chem. Ind.* **1961**, 722. (b) Fraenkel, G.; Niemann, C. *Proc. Natl. Acad. Sci. U.S.A.* **1958**, *44*, 688.

(5) Morrison, R. T.; Boyd, R. N. *Organic Chemistry*, 6th ed.; Prentice Hall: New Jersey, 1992; p 194.

elimination mechanism and (2) proton-catalyzed direct isomerization as in the case of BF_3·OEt_2. If the reaction goes exclusively by mechanism 2, the high ee value for **4** (80%) cannot be explained, becauase the ee value was only 60% in BF_3-catalyzed isomerization (Table 1). Therefore, mechanism 2 does not seem to be important, though it may not be excluded. If oxazine **4** is formed via **6** followed by ring closure (mechanism 1), the ring-closing step should be accompanied by partial racemization, because the ring-opening addition reaction of (*R*)(*R*)-**3** and TsOH proceeded with complete inversion of the configuration to give a single diastereomer, **6**. Heating of **6** with TsOH in benzene revealed that partial racemization (∼15%) actually took place in the ring-closing process (Table 3). The fact that the percentage of racemization at the ring-closing step is very close to that observed in the reaction of (*R*)(*R*)-**3** and TsOH (∼20%, Table 2) suggests that mechanism 1 is very likely.

It is noted that the ring-closing step of **6** to **4** was accompanied by partial racemization. This result makes a marked contrast to the ring closure of the addition



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product of **1** and TsOH, **8** to **2**,[2] where complete inversion of the configuration took place to give **2** of 100% ee. (The result was confirmed recently. See the Experimental Section). This means that although the conversion of **8** to **2** proceeds completely by the S_N2 mechanism, the conversion of **6** to **4** does not go by the S_N2 mechanism exclusively under similar reaction conditions. The reason for the difference has not been elucidated so far.

Molecular Orbital Calculations

The ab initio MO calculations were performed by using the GAUSSIAN94 program[6] to obtain stable structures of the bases and their protonated species and also the structures of the transition states (TS) and the intermediates. The 6-31G* basis sets[7] were used to optimize these geometries. Vibrational frequency calculations were performed for all of the geometries optimized in the present study.

It was ascertained in a previous paper[2] that 1-acylaziridines isomerize to oxazolines by the S_Ni mechanism. In contrast, the experimental results mentioned above suggest that the isomerization of 1-acylazetidines to oxazines does not proceed by the S_Ni mechanism but by an S_N1 mechanism under similar reaction conditions as in **1**. Here, mention is made of the elucidation of the isomerization mechanism from the theoretical point of view, forcusing our attention on the comparison of the result with that obtained in 1-formylaziridine, **1a**.

1-Formyl-2-methylazetidine (**3b**) was used as a model compound for **3** instead of 1-formylazetidine (**3a**). In the acid-catalyzed isomerization of 1-acyl-2-methylaziridines, 5-methyloxazolines resulting from the cleavage of the N−CH(CH_3) bond are the only[2] or main (∼90%)[8] product, and we confirmed in the previous study[2] that the consideration of the substituent effect was essential in the theoretical elucidation of the reaction mechanism. Furthermore, it was found in the present study that 6-methyloxazine (from the N−CH(CH_3) bond cleavage) was the only product of isomerization, and no trace of 4-methyloxazine (from the N−CH_2 bond cleavage) was detected by ^1H and ^{19}F NMR spectroscopy. Therefore, **3b** should be more appropriate than **3a** as the model of the present study. As mentioned previously,[2] calculations at the MP2/6-31G**//RHF/6-31G* level of theory, using **1a** as a model compound, showed that the protonation at the N-atom is 1.8 kcal mol^{-1} more favored than the protonation at the carbonyl oxygen. In the case of 1-formyl-2-methylazetidine (**3b**), however, the O-protonated form was found to be more stable than the N-protonated one by 10.4 kcal mol^{-1} at the MP2 level. This suggests that the predominance of **3**(OH^+) can be expected in nonpolar solvents such as benzene.

Ab initio MO calculations[9] optimized an open-chain carbocationic intermediate, **3b**(OH^+,open). This makes a marked contrast to the case in **1a**, where no stable cation was obtained. The energy level of the intermediate was shown to be 42.0 kcal mol^{-1} above the level of **3b**(OH^+).[10] Then, we found two TSs successively. One was the TS for the ring-opening process of the four-membered ring, **3b**(OH^+,3TS), with an imaginary frequency of 90.0 i cm^{-1}, and the other was that for the ring-closing process to form **4b**(OH^+), **3b**(OH^+,4TS), with an imaginary frequency 158.9i cm^{-1}. The TS structure[11] of **3b**(OH^+,3TS) was estimated to be 49.5 kcal mol^{-1} higher in energy than **3b**(OH^+), and that of **3b**(OH^+,4TS) was 43.3 kcal mol^{-1} higher than the same level, respectively. Results are shown in Figure 2.

Conclusion

The MO calculations using **3b** as the model for **3** and proton showed that O-protonation is much more favorable than N-protonation. This might give support for the O-coordination of BF_3 from the energetic viewpoint. The lengthening of the O−CH(CH_3) distance on going from the initial state to the transition state was shown to be as follows: 2.902 Å for **3b**(OH^+) and 3.094 Å for **3b**(OH^+, 3TS), as shown in Figure 1. In contrast, the O−CH(CH_3) length was shown to be shortened in the case with **1a**, from 2.876 Å in **1a**(NH^+) to 2.629 Å in **1a**(NH^+,TS).[2] These results give support for the discussion on the adverse effects of the O-coordination toward the S_Ni process.

(6) GAUSSIAN94; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A., Gaussian Inc., Pittsburgh, PA, 1995.

(7) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257.

(8) Nishiguchi, T.; Tochio, H.; Nabeya, A.; Iwakura, Y. *J. Am. Chem. Soc.* **1969**, *91*, 5841.

(9) Prior to ab initio MO calculations, we performed semiempirical MO calculations (PM3, MOPAC Ver. 93; Stewart, J. J. P. Fujitsu Ltd.: Tokyo, Japan, 1993) in search of the intermediate and the TSs and used them as the initial geometries for the ab initio MO calculations.

(10) For estimating free energy differences in the gas phase at 298 K, 1 atm, we used energies at the MP2/6-31G**//RHF/6-31G* level of theory and those from the vibration frequency of the RHF/6-31G* calculations without scale factor.

(11) Calculations using TSs obtained gave few geometries along the IRC [(a) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363. (b) Head-Gordon, M.; Pople, J. A. *J. Chem. Phys.* **1988**, *89*, 5777.], probably because the potential surfaces around these TSs are very flat.

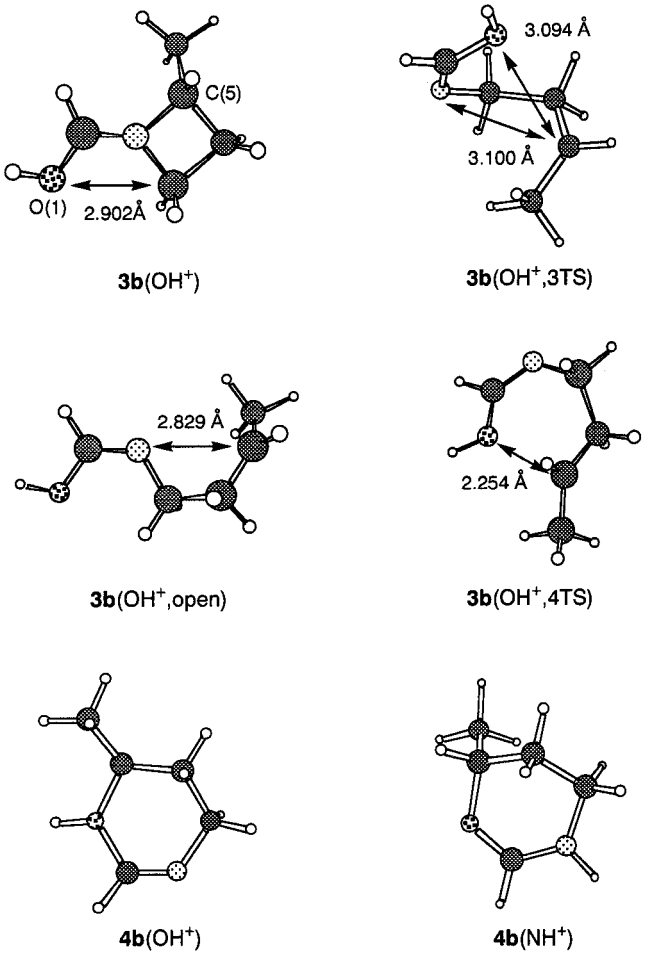

Figure 1.

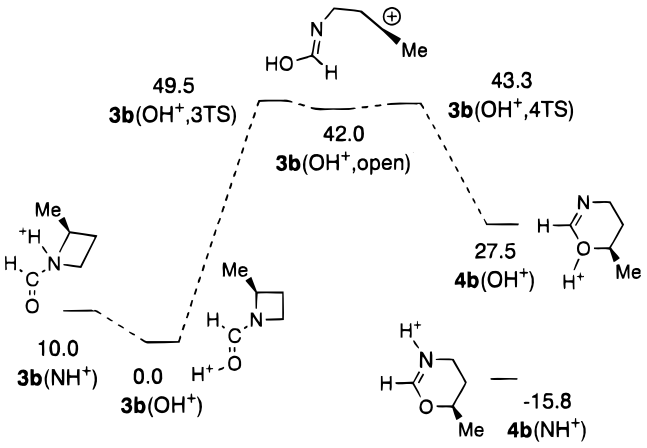

Figure 2. The energy relation diagram in kcal mol^{-1} units among the reactant, the transition states, and the intermediate. Values in kcal mol^{-1} units are free energy differences at 298 K, 1 atm.

Finally, the presence of an open-chain carbocationic intermediate, **3b**(OH^+,open) would explain the partial racemization that took place during the isomerization, and the small energy difference between the intermediate and the second TS, **3b**(OH^+,4TS) might explain the overwhelming predominance of the retention observed in the experiment.

Experimental Section

General Information. Elemental analyses were performed by the Institute of Physical and Chemical Research, Wako, Saitama. (*S*)-MTPA chloride was purchased from Aldrich Chemical Co. (Milwaukee, WI). NMR spectra (^1H, ^{19}F, and ^{13}C) were recorded (270 MHz for ^1H, 254 MHz for ^{19}F, and 67.80 MHz for ^{13}C) using TFA as a standard for ^{19}F NMR.

Preparation of (*R*)-2-Methylazetidine. (*S*)-4-Amino-2-butanol was prepared from (*S*)-1,2-propanediol through four steps in overall yield of 16%, bp 85−87 °C (19 mmHg). The optical purity of the amino alcohol was found to be 100% ee from the ^{19}F spectrum of its MTPA amide. From the amino alcohol, (*R*)-2-methylazetidine was prepared according to the method reported by Vaughan et al.[12] in overall yield of 14%, bp 72−73 °C; $[\alpha]^{20}_D$ −15.6 (*c* = 4.90, hexane).[13] The optical purity of the azetidine was determined by the ^{19}F NMR spectroscopy of **3** before recrystallization to be 90% ee.

1-[(*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetyl]-(*R*)-2-methylazetidine [(*R*)(*R*)-3]. Into an ice-cooled solution of 80 mg (1.1 mmol) of (*R*)-2-methylazetidine and 110 mg (1.1 mmol) of Et_3N in ether was added dropwise a solution of 253 mg (1.0 mmol) of (*S*)-MTPA chloride in ether. After 2 h of stirring, the precipitated Et_3NHCl was removed by filtration, and the filtrate was washed with brine, dried (Na_2SO_4), and concentrated on a rotary evaporator to give **3** (90% ee) in quantitative yield. Recrystallization from hexane gave an optically pure sample of (*R*)(*R*)-**3**: mp 103−105 °C; ^1H NMR (C_6D_6) δ ∼0.94 (m, 1H), 1.29 (d, 3H, *J* = 6.2 Hz), ∼1.6 (m, 1H), ∼2.95 (dt, 1H, *J* = 6.6, 9.7 Hz), 3.38, 3.39 (s, 3H), ∼3.43 (dt, 1H, *J* = 5.9, 9.7 Hz), ∼4.25 (m, 1H), ∼7.1 (m, 3H), 7.71 (d, 2H); ^{19}F NMR (C_6D_6) δ 5.62 [(*R*)-(*S*)-**3** had a signal at 6.05]. Anal. Calcd for $C_{14}H_{16}NO_2F_3$: C, 58.33; H, 5.61; N, 4.88. Found: C, 58.34; H, 5.50; N, 4.90.

Reaction of (*R*)(*R*)-3 with BF_3·OEt_2. Into a solution of 58 mg (0.2 mmol) of (*R*)(*R*)-**3** in 1 mL of benzene (dried over CaH_2) was added 0.24 mL of a solution of BF_3·OEt_2 in benzene (1 mmol/1 mL), and the reaction mixture was heated at 70 °C with stirring. After 2 h of heating, 0.3 mL of the reaction mixture was removed and taken up in benzene. The benzene solution was washed with 1 N NaOH and brine, dried (Na_2SO_4), and concentrated to give a sample for ^1H and ^{19}F NMR spectroscopy. These spectra showed that the sample consisted of unreacted **3**, oxazines (*R*)(*R*)-**4** and (*R*)(*S*)-**4**, and another substance **5a**, 2-[(*R*)-α-difluoroboryloxy-α-trifluoromethyl]-[(*R*) or (*S*)]-6-methyl-5,6-dihydro-4*H*-1,3-oxazine. In a similar manner, a part of the reaction mixture was removed and analyzed after 4 and 6 h. Results are summarized in Table 1.

Authentic Sample of N-[(*S*)-3-Tosyloxybutyl]-(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetamide (6). Starting from 126 mg (0.5 mmol) of (*S*)-MTPA chloride and (*S*)-3-amino-2-butanol, the crude amide was obtained. The crude amide was dissolved in 1 mL of pyridine, and to this solution was added 200 mg (1.0 mmol) of TsCl and 24 mg (0.2 mmol) of DMAP. After 2 days of stirring at room temperature, water was added, and the mixture was stirred for another 1 h. Then the mixture was taken up in benzene, and the benzene solution was washed successively with 1 N HCl, aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). Evaporation of the solvent (rotary) gave 110 mg of crude **6**. Column chromatography of the crude **6** (AcOEt/hexane 25:75) gave 70 mg (30% based on MTPA chloride) of analytical sample of **6**: oil; ^1H NMR (C_6D_6) δ 0.82 (d, 3H, *J* = 6.2 Hz), ∼1.34 (m, 1H), ∼1.6 (m, 1H), 1.84 (s, 3H), ∼3.0 (m, 1H), 3.21, 3.22 (s, 3H), ∼3.3 (m, 1H), ∼4.6 (m, 1H), 6.74 (d, 2H), ∼7.1 (m, 5H), 7.71 (d, 2H), 7.75 (d, 2H); ^{19}F NMR (C_6D_6) δ 6.63. Anal. Calcd for $C_{21}H_{24}NO_5F_3S$: C, 54.89; H, 5.26; N, 3.05. Found: C, 54.82, 55.08; H, 5.27, 5.37; N, 3.02, 2.93.

Authentic Sample of 2-[(*R*)-α-Methoxy-α-(trifluoromethyl)benzyl]-(*R*)-6-methyl-5,6-dihydro-4*H*-1,3-oxazine [(*R*)-(*R*)-4]. A solution of 50 mg (0.11 mmol) of **6** and 50 mg (0.9 mmol) of KOH in 1 mL of EtOH was stirred at room temperature for 2 h. After concentration of the solution (rotary), the residue was dissolved in benzene, and the benzene solution was washed with water and dried (Na_2SO_4). After evaporation of the solvent, the residue was recrystallized from hexane to give 25 mg (81%) of (*R*)(*R*)-**4**: mp 110−111 °C; ^1H NMR (C_6D_6) δ 0.75 (d, 3H, *J* = 6.2 Hz), ∼1.08 (m, 2H), ∼3.15 (ddd, 1H, *J* = 16.9, 5.3, 9.7 Hz),

(12) Vaughan, W. R.; Klonowski, R. S.; McElhinney, R. S.; Millward, B. B. *J. Org. Chem.* **1961**, *26*, 138.

(13) Reported value for (*S*)-2-methylazetidine: $[\alpha]^{20}_D$ +11.6 (*c* = 1.0, hexane). See Kostyanovsky, R. G.; Gella, I. M.; Markov, V. I.; Samojlova, Z. E. *Tetrahedron* **1974**, *30*, 39.

~3.33 (ddd, 1H, J = 3.5, 5.1 Hz), ~3.54 (m, 1H), 3.540, 3.545 (s, 3H), ~7.2 (m, 3H), 7.86 (d, 2H); ^{19}F NMR (C_6D_6) δ 5.065; ^{13}C NMR ($CDCl_3$) δ 20.99, 28.36, 42.18, 54.59, 54.62, 72.08, 83.80, 125.99, 127.32, 127.34, 127.99, 128.54, 128.88. Anal. Calcd for $C_{14}H_{16}NO_2F_3$: C, 58.33; H, 5.61; N, 4.88. Found: C, 58.51; H, 5.55; N, 4.88.

Useful NMR data for (*R*)(*S*)-**4**: ^{1}H NMR (C_6D_6) δ 0.70 (d, 3H, J = 6.2 Hz), 3.532, 3.537 (s, 3H); ^{19}F NMR (C_6D_6) δ 4.936.

Authentic Sample of 2-[(*R*)-α-difluoroboryloxy-α-(trifluoromethyl)benzyl]-(*R*)-6-methyl-5,6-dihydro-4*H*-1,3-oxazine [(*R*)(*R*)-5a]. To a solution of 60 mg (0.21 mmol) of (*R*)-(*R*)-**4** in 0.5 mL of benzene, was added a solution of BF_3·OEt_2 in benzene (1 mmol/1 mL), and the mixture was heated at 70 °C for 14 h. After addition of benzene to the reaction mixture, the solution was washed with 2 N NaOH and brine, dried (Na_2SO_4), and concentrated. Column chromatography of the residue using ethyl acetate and hexane (AcOEt 30−50%) gave a solid material, which was recrystallized from benzene and hexane to provide 12 mg (19%) of (*R*)(*R*)-**5a**: mp 133−135 °C; ^{1}H NMR ($CDCl_3$) δ 1.59 (d, 3H, J = 6.4 Hz), ~1.8 (dddd, 1H, J = 15.0, 7.7, 9.5 Hz), ~2.25 (ddt, 1H, J = 14.7 Hz), 3.60 (q, 2H, J = 9.7 Hz), 4.84 (ddq, 1H, J = 2.9, 6.4 Hz), 7.43 (m, 3H), 7.86 (t, 2H); ^{19}F NMR (C_6D_6) δ −1.18 (CF_3); ^{13}C NMR ($CDCl_3$) δ 19.90 (C-CH_3), 25.90 (CH_2), 37.24 (CH_2), 79.09 (*C*H), 126.60, 126.63, 128.53, 129.89. Anal. Calcd for $C_{13}H_{13}NO_2BF_5$: C, 48.63; H, 4.08; N, 4.36. Found: C, 48.84, 48.89; H, 4.04, 4.09; N, 4.23, 4.24.

Useful NMR data for (*R*)(*S*)-**5a**: ^{1}H NMR ($CDCl_3$) δ 1.64 (d, 3H, J = 6.4 Hz); ^{19}F NMR (C_6D_6) δ −1.27 (CF_3).

To obtain more information about **5**, 2-[(*R*)-α-difluoroboryloxy-α-(trifluoromethyl)benzyl]-5,6-dihydro-4*H*-1,3-oxazine (**5b**) was prepared: mp 140−141 °C; IR (KBr) 1690 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO_2BF_5$: C, 46.95; H, 3.61; N, 4.56, F (of CF_3 only), 19.05. Found: C, 46.99; H, 3.57; N, 4.53; F, 18.92, 19.17. The ^{19}F NMR spectroscopy (−200 to +150 ppm) was performed by Shonan Analyses Center Inc., using TFA as external standard: ^{19}F NMR (470.40 MHz, $CDCl_3$) δ −1.32 (s, 3F), −71.76 (dd, 1F, J = 75.2, 28 Hz), −73.89 (dd, 1F, J = 75.2, 15 Hz).

Reaction of (*R*)(*R*)-3 with TsOH. Into a solution of 0.24 mmol of TsOH (46 mg of TsOH·H_2O was dehydrated under vacuum at 110 °C for 1 h) in 0.5 mL of benzene was added a solution of 58 mg (0.2 mmol) of (*R*)(*R*)-**3** in 0.5 mL of benzene at 70 °C, and the solution was heated at the same temperature. After 1, 2, and 4 h, 0.3 mL of the mixture was removed and dissolved in benzene. The solution was washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to afford a sample for ^{19}F NMR analyses. In another run, 2.4 molar equiv (vs **3**) of TsOH was used. A solution of 58 mg (0.2 mmol) of (*R*)-(*R*)-**3** and 0.48 mmol of TsOH (92 mg of monohydrate was dehydrated) in 2 mL of benzene was heated at 70 °C, and the composition of the reaction mixture was analyzed as above (Table 2).

Heating of 6 in Benzene in the Presence of TsOH. A solution of 46 mg (0.1 mmol) of **6** and 0.12 mmol of TsOH in 1 mL of benzene was heated at 70 °C, and the reaction mixture was analyzed after 1 and 2 h as in the preceding experiment. Results are summarized in Table 3.

Heating of 0.1 mmol of **8** and 0.12 mmol of TsOH in benzene at 70 °C for 1 h resulted in the conversion of 22% of **8** to (*R*)-(*S*)-**2**.

Changes in the ^{1}H NMR Spectra of 1-Acetylazetidine (7) on Addition of BF_3·OEt_2. Amide **7** was prepared from acetyl chloride, azetidine, and Et_3N: ^{1}H NMR ($CDCl_3$) δ 1.84 (s, 3H), 2.26 (q, 2H), 4.03 (t, 2H), 4.14 (t, 2H). On addition of 1.2 molar equiv of BF_3·OEt_2, the following peaks were observed: δ 2.23 (s, 3H), 2.49 (q, 2H), 4.32 (t, 2H), 4.42 (t, 2H).

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