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Synthetic Studies on the Key Component of the New Generation of Quinolonecarboxylic Acid, DU-6859. 1. Synthesis of (1*R*,2*S*)-2-Fluorocyclopropylamine by the Use of Optical Resolution

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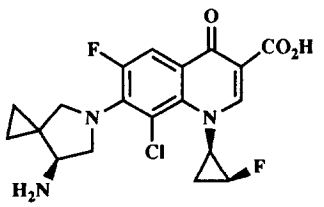
Abstract: *The title synthesis was achieved by employing highly cis-selective cyclopropanation of N-benzyl-N-vinylcarbamates with zinc-monofluorocarbenoid, deprotection of the formed N-benzyl-N-(cis-2-fluorocyclopropyl)carbamates, and optical resolution of the resulting dl-cis-2-fluorocyclopropylamine by the use of l-menthyl chloroformate as a resolving agent. The cis-selectivity observed for the key cyclopropanation could be explained by the bent transition state model.*

Antibacterial quinolonecarboxylic acids (new quinolones) are clinically important and widely used for therapy of various infections. Therefore, extensive studies have been made with an aim to explore novel quinolonecarboxylic acids exhibiting more excellent therapeutic indexes.[4] Quite recently, DU-6859 (**1**) was found as the new generation of quinolonecarboxylic acids, which shows prominent antibacterial activity with little



DU-6859 (**1**)

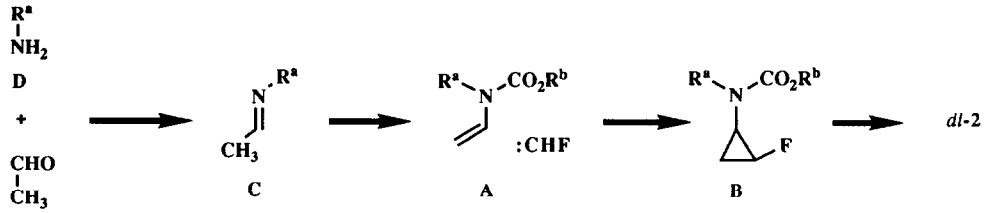
(1*R*,2*S*)-**2**

side effects.[5] One of the key structural features involved in **1** is its possession of the *cis*-oriented (1*R*,2*S*)-2-fluorocyclopropylamine [(1*R*,2*S*)-**2**][5c] moiety, the absolute stereochemistry of which has been definitely disclosed to be indispensable for its promising characteristics.

The structural simplicity of (1*R*,2*S*)-**2** notwithstanding, its synthesis meets with severe difficulty arising from stereoselective introduction of a fluorine atom into the cyclopropylamine skeleton with thermodynamically unfavorable *cis*-orientation. In the original synthesis of **1**,[5] the preparation of (1*R*,2*S*)-**2** commenced with the cyclopropanation of butadiene with bromofluorocarbene, producing a mixture of *cis*- and *trans*-1-bromo-1-fluoro-2-vinylcyclopropane[6] with undesired *trans*-selectivity.[7] The diastereomeric mixture was derived to (1*R*,2*S*)-**2** by sequential oxidation of the double bond by potassium permanganate, esterification, debromination by tri-*n*-butyltin hydride, seperation of the desired *cis*-2-fluorocyclopropanecarboxylate, optical resolution with (*R*)-1-phenylethylamine, and Curtius rearrangement with diphenylphosphoryl azide (DPPA). However, this synthetic route seems not to be applicable to an industrial preparation of (1*R*,2*S*)-**2** due to low stereoselectivity and uses of toxic and expensive reagents such as tri-*n*-butyltin hydride and DPPA. In order to make a large scale preparation of (1*R*,2*S*)-**2** possible, a novel preparation method was sought which could afford (1*R*,2*S*)-**2** more effectively than initially reported. With this objective in mind, we devoted our efforts on exploration of expeditious synthetic route to *dl-cis*-2-fluorocyclopropylamine (*dl*-**2**) and efficient optical resolution of *dl*-**2** to produce (1*R*,2*S*)-**2**.

One of the most direct approaches to *dl*-**2** is obviously the cyclopropanation of an enamine system with electrophilic monofluorocarbene species,[8] which requires no debromination and Curtius rearrangement. Based on this idea, a novel method for preparing *dl*-**2** was designed as depicted in **Scheme 1**. Taking into account stability of possible synthetic intermediates, vinylcarbamate (**A**) was selected as a suitable enamine system. It was anticipated that **A** has enough reactivity to the cyclopropanation and the stereoselectivity of cyclopropanation can be improved by suitable choice of the substituents (R^a and R^b). Possible fragmentation of the corresponding adduct (**B**) which may result from participation of the lone pair of nitrogen atom, was envisioned to be prohibited by the presence of alkoxycarbonyl group.[9] Deprotection of **B** can be achieved under acidic conditions, furnishing *dl*-**2** in a form of its salt. The vinylcarbamate (**A**) is accessible by alkoxycarbonylation of imine (**C**), which in turn is readily prepared from acetaldehyde and amine (**D**).

Scheme 1



We have now found that **A** cleanly reacts with zinc-monofluorocarbenoid in a highly *cis*-selective manner to afford *N*-protected-*N*-(*cis*-2-fluorocyclopropyl)carbamate (**B**) as a major product, from which *dl*-**2** can be readily elaborated. It has been also disclosed that optical resolution of *dl*-**2** can be achieved by employing *l*-menthyl chloroformate as a resolving agent. This report details a novel and efficient synthesis of *dl*-**2** and

subsequent successful optical resolution of *dl*-**2** to afford (1*R*,2*S*)-**2**.[10] Another novel synthesis of (1*R*,2*S*)-**2** featuring asymmetric synthesis is the subject of accompanying paper.[11]

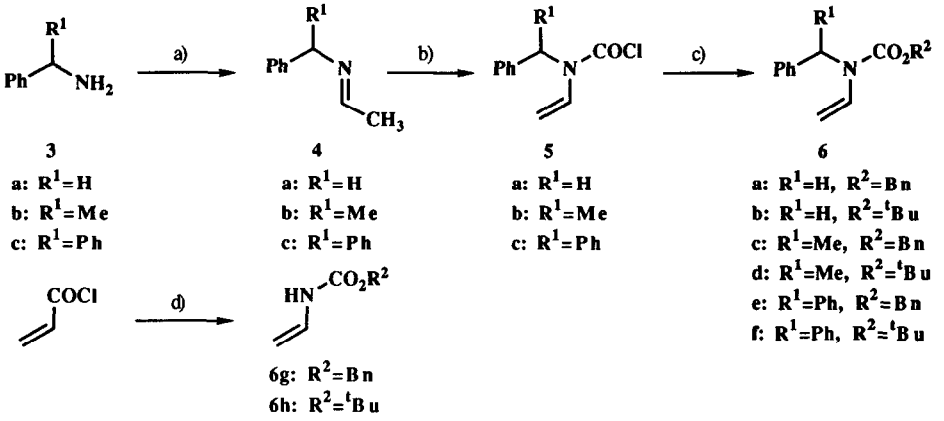
Results and Discussion

1. Synthesis of *N*-vinylcarbamates (6a-h), the substrates for cyclopropanation with zinc-monofluorocarbenoid.

Although several methods are known for preparing *N*-vinylcarbamates,[12] they seem not to be applicable for a large scale synthesis of *dl*-**2** due to the lack of operational simplicity. Accordingly, more facile and flexible preparation method of *N*-vinylcarbamates was required. Based on these considerations, *N*-benzyl-*N*-vinylcarbamoyl chlorides (**5**) were chosen as synthetic intermediates of *N*-vinylcarbamates as shown in **Scheme 2**. It was expected that different substituents (R^2) can be introduced into the carbamate portions by substituting the same carbamoyl chloride with different sodium alkoxides and that *N*-benzyl groups can be readily removed by hydrogenolysis under acidic conditions (*vide infra*).

Condensation of benzylamine (**3a**), *dl*-1-phenylethylamine (**3b**), and benzhydrylamine (**3c**) with acetaldehyde followed by treatment of the resulting imines (**4a-c**) with trichloromethyl chloroformate in the presence of triethylamine gave **5a-c**. Three sorts of the chlorides (**5a-c**) were treated with sodium benzyloxide or sodium *t*-butoxide, affording benzyl *N*-benzyl-*N*-vinylcarbamates (**6a,c,e**) and *t*-butyl *N*-benzyl-*N*-vinylcarbamates (**6b,d,f**), respectively. Related *N*-vinylcarbamates lacking *N*-benzyl groups (**6g**[13] and **6h**[14]) were also prepared from acryloyl chloride by the reported methods. Preparation of **6g,h** were carried out in order to explore the effects of *N*-benzyl groups on the cyclopropanation with zinc-monofluorocarbenoid.

Scheme 2



a) CH_3CHO, $MgSO_4$, Et_2O, 100 % b) $ClCO_2CCl_3$, Et_3N, toluene; **5a**, 58%; **5b**, 78%; **5c**, 53% (from **3a-c**) c) R^2OH, NaH, THF; **6a**, 79%; **6b**, 63%; **6c**, 100%; **6d**, 92%; **6e**, 82%; **6f**, 28% d) ref. 13. for **6g** and ref. 14. for **6h**

2. Cyclopropanation of 6 with zinc-monofluorocarbenoid.

With six types of *N*-benzyl-*N*-vinylcarbamates (**6a-f**) in hand, cyclopropanation of **6a-f** with zinc-monofluorocarbenoid[8b] generated from fluorodiiodomethane and diethylzinc was next attempted. As shown in **Table 1** (runs 1-11), the effects of solvents and temperatures on the cyclopropanation were examined using **6a**

as a substrate. In all cases, the desired *cis*-adduct (**7a**) was obtained as a major product with moderate *cis*-selectivity. The reactions in hydrocarbon solvents such as hexane, cyclohexane, and toluene (runs 1-3) gave heterogeneous mixtures with reaction progress. This may be due to poor solubility of organozinc compounds resulting from diethylzinc and fluorodiiodomethane in the solvents. No reaction took place in tetrahydrofuran (THF) at room temperature probably due to the decrease of electrophilicity of the zinc-monofluorocarbenoid caused by coordination of THF as a strong Lewis base (run 4).[15] The reactions in diethyl ether and chlorinated solvents (runs 5-8) proceeded in a homogeneous state and gave similar results to that for the reaction in hexane.[15] Considering the chemical yield and *cis*-selectivity as well as the short reaction time, dichloromethane (run 8) seemed to be the best solvent of choice. While the reactions at lower temperature gave a little improved *cis*-selectivity (runs 8-11), the best temperature was anticipated as -40°C, taking into account the chemical yield and short reaction time in addition to *cis*-selectivity (run 9).

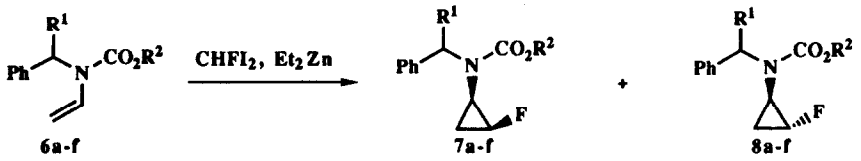


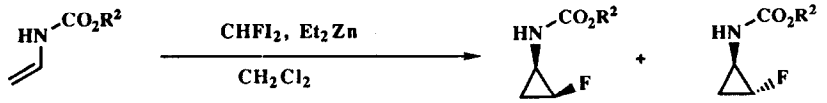
Table 1. Cycloaddition of *N*-benzyl-*N*-vinylcarbamates (**6a-f**) with zinc-monofluorocarbenoid.

Runs	Substrates	R^1	R^2	Conditions	Yield (%)[a]	Ratio (7:8)[b]
1	**6a**	H	Bn	hexane, -20 °C, 1 h	79	65 : 35
2				cyclohexane, -20 °C,1.5 h	63	65 : 35
3				toluene, -20 °C, 3.5 h	64	66 : 34
4				THF, -20 °C, 1.5 h, then rt, 1 h	-[c]	-[c]
5				Et_2O, -20 °C, then 0 °C, 1 h	73	63 : 37
6				CCl_4, -20 °C, 1.5h	75	60 : 40
7				$CHCl_3$, -20 °C, 0.5 h	81	63 : 37
8				CH_2Cl_2, -20 °C, 0.5 h	79	69 : 31
9				CH_2Cl_2, -40 °C, 0.5 h	78	71 : 29
10				CH_2Cl_2, -78 °C, 0.5 h	14	74 : 26
11				CH_2Cl_2, -78 °C, 15 h	68	76 : 24
12	**6b**	H	^{t}Bu	hexane, -20 °C, 1 h	69	62 : 38
13	**6c**	Me	Bn	CH_2Cl_2, -40 °C, 0.5 h	97	89 : 11[d,e]
14	**6d**	Me	^{t}Bu	CH_2Cl_2, -40 °C, 1 h	67	91 : 9[e]
15	**6e**	Ph	Bn	CH_2Cl_2, -40 °C, 0.5 h	90	93 : 7
16	**6f**	Ph	^{t}Bu	CH_2Cl_2, -40 °C, 0.5 h	87	93 : 7

a) Isolated yields. b) Determined by the weights of separated **7** and **8**. c) No reaction occurred. d) Determined by the integration of ^{19}F-NMR spectrum. e) Each of products (**7** and **8**) was a mixture of diastereomers. **7c** (1:1), **8c** (3:2), **7d** (1:1), **8d** (3:2).

Next, the cyclopropanation of various *N*-benzyl-*N*-vinylcarbamates (**6b-f**) other than **6a** was studied to explore the effects of substituents (R^1 and R^2). The results (runs 1, 9, and 12-16) deserve some comments. Thus, the bulkiness of alkoxy group (R^2) gave no obvious influence on the stereoselectivity (runs 1, 13, 15 vs runs 12, 14, 16). In contrast, increase of the bulkiness of *N*-benzyl groups, that is, R^1 groups resulted in enhancement of the *cis*-selectivity (runs 1, 9, 12 vs runs 13-16). The chirality involved in 1-phenylethyl groups of **6c,d** showed almost no diastereoface-selectivity [see, foot note e) in **Table 1**]. The best chemical yield (97%) and *cis*-selectivity (93:7) could be realized for the reactions employing **6c** and **6e,f**, respectively. Taking into account the chemical yield and *cis*-selectivity, the reaction with **6c** is anticipated to be most practical. Stereochemistries of **7a-f** and **8a-f** were tentatively assigned by their ^{1}H-NMR spectra (see **Experimental**) and confirmed by the successful synthesis of *dl*-**2** from **7a-f** and that of *dl-trans*-2-fluorocyclopropylamine (*dl*-**11**) from **8a** (*vide infra*).

On the other hand, **6g,h** bearing no *N*-benzyl groups underwent no clean reaction with zinc-monofluorocarbenoid (**Table 2**). Thus, the reaction with **6g** under the conditions similar to those employed for **6a-f** gave a very low yield of the adducts (**9g** and **10g**) along with a lot of polar products (run 1). This is probably due to instability of **6g** and/or **9g** and **10g** under the reaction conditions. Although the yields of the reactions employing **6g,h** could be slightly improved in the presence of molecular sieves 4A (MS4A) and dimethoxyethane (DME) as additives,[11] the *cis*-selectivities were found to be almost identical with those obtained for **6a,b** (runs 2,3). These results cleanly disclosed that **6a-f** bearing *N*-benzyl groups are much better substrates for cyclopropanation in light of the yield and *cis*-selectivity. The structure of **9g** was confirmed by comparing its ^{1}H-NMR spectrum with that of **9h**, and its successful transformation to *dl*-**2** (*vide infra*). On the other hand, the stereochemistry of **9h** was established by comparison of its ^{1}H-NMR spectrum with that of an authentic sample.[5b] The structures of **10g,h** were assigned based on their ^{1}H-NMR spectra (*vide infra*).



6g,h **9g,h** **10g,h**

Table 2. Cycloaddition of *N*-vinylcarbamates (**6g,h**) with zinc-monofluorocarbenoid.

Runs	Substraes	R^2	Conditions	Yield (%)[a]	Ratio (**9**:**10**)
1	**6g**	Bn	-40 °C, then rt	<10	-[b]
2	**6g**	Bn	MS4A, DME, rt, 1 h	25	64 : 36[c]
3	**6h**	^{t}Bu	MS4A, DME, 0 °C, 0.5 h	30	60 : 40[d]

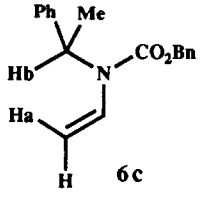
a) Isolated yields. b) Not determined. c) Determined by the weights of separated **9g** and **10g**. d) Determined by the integration of ^{19}F-NMR spectrum.

3. Mechanistic consideration of cyclopropanation of 6 with zinc-monofluorocarbenoid

As mentioned above, the steric bulkiness of the alkyl group (R^1) involved in the *N*-benzyl moiety of **6** gives a remarkable influence on the stereoselectivity, while that of the alkyl group (R^2) present in the alkoxycarbonyl moiety does not. This observation let us assume that the vinyl group, the reaction site of **6**,

should occupy the position closer to R^1 than to R^2. In fact, NOE measurements in the ^{1}H-NMR spectrum of **6c** showed clear NOEs between Ha and Hb, the methyl group, and the phenyl group, respectively, as shown in **Fig 1**. These NOEs definitely indicates that the vinyl group of **6c** is located close to the 1-phenylethyl group. Accordingly, the conformational flexibility of 1-phenylethyl group should be the reason why high asymmetric induction was not realized for the reactions with **6c,d**.

Fig 1

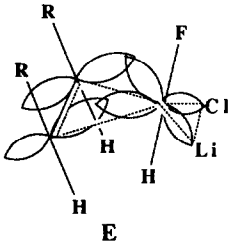


6c

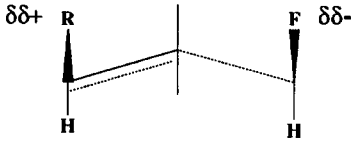
NOE (irr. Ha)	
Hb	4.3%
Me	1.7%
Ph	2.1%

Schlosser and Heinz reported that the cyclopropanation of cyclohexene with lithium-monofluorocarbenoid gave the *cis*- and *trans*-adducts (*cis*:*trans* = 2.3:1) in a very low yield.[8a] As shown in **Scheme 3**, they proposed two types of the transition state models to explain the observed *cis*-selectivity. One of the propositions was the "bent" model (**E**), and the other one was the dipolar model (**F**) in which electrostatic attraction between the electronegative fluorine atom and the positively charged substituent (R) is seriously taken into consideration. If

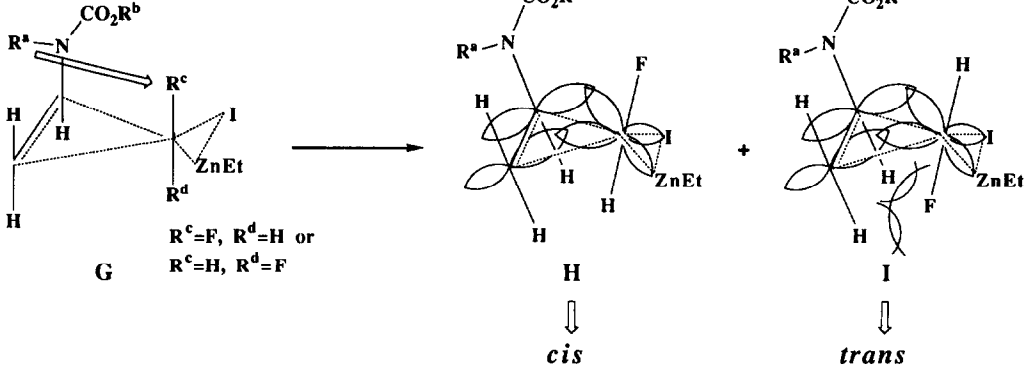
Scheme 3



E



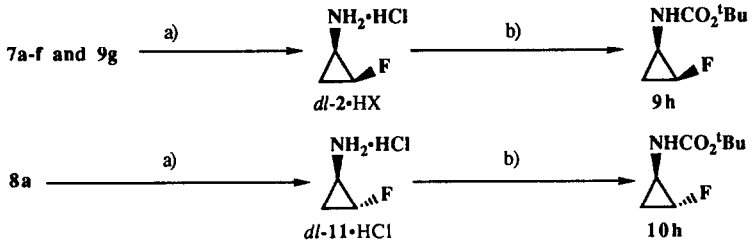
F



electrostatic effect constituted an important factor in the reactions of **6** with zinc-monofluorocarbenoid as depicted in **F**, the reaction of **6a,b** carrying less bulky R^a groups would give better *cis*-selectivity because of the reduced steric interaction between R and F. In contrast, **6c-f** bearing more bulky R^a afforded higher *cis*-selectivity. Accordingly, it appeared that the steric factor plays more important role on the stereoselectivity than the electrostatic effect. The bulky substituent (R^a) present in the vicinity of the vinyl group would make the transition state (**G**) "bent" by the steric interaction between R^a group and hydrogen or fluorine atom on the zinc-monofluorocarbenoid approaching to **6**, furnishing the "bent" transition state (**H**) or (**I**). It is obvious that the steric interaction is more released in **H** than in **I** since a fluorine atom is conceivably larger than a hydrogen atom.[16] *N*-Benzyl-*N*-vinylcarbamates (**6c-f**) bearing sterically more bulky R^a group cause severe steric interaction between R^a and R^c in **G**. Accordingly, **6c-f** are anticipated to undergo highly *cis*-selective cyclopropanation by way of **H**. It is also reported that, in the reaction of cyclohexene with zinc-carbenoids, the reaction with more bulky carbenoid bearing a phenyl group gives much better *cis*-selectivity than that with less bulky carbenoid.[17] This observation might be similarly rationalized by the "bent" model.

4. Synthesis of *dl-cis*-2-fluorocyclopropylamine (*dl*-2)

As highly *cis*-selective cyclopropanation of the **6a-f** with zinc-monofluorocarbenoid was established, deprotection of **7** and **8** was next studied to produce *dl*-**2** and *dl*-**11**, respectively. Since *dl*-**2** was found to be



a) For *dl*-**2**•HX, see, **Table 3**; for *dl*-**11**•HCl, H_2, 10 % Pd-C, AcOH; HCl-MeOH b) $(Boc)_2O$, Et_3N, CH_2Cl_2

Table 3. Deprotection of **7a-f** and **9g** to *dl*-**2**•HX.

Runs	Substrates	R^1	R^2	Methods[a)]	Yield (%)[b)]	HX
1	**7a**	H	Bn	A	94	HCl
2	**7b**	H	^{t}Bu	B	75	HCl
3	**7c**	Me	Bn	A	77	HCl
4	**7c**	Me	Bn	C[c)]	52	TsOH
5	**7d**	Me	^{t}Bu	B	81	HCl
6	**7e**	Ph	Bn	A	73	HCl
7	**7e**	Ph	Bn	D	83	TsOH
8	**7f**	Ph	^{t}Bu	B	66	HCl
9	**9g**	-	Bn	D	87	TsOH

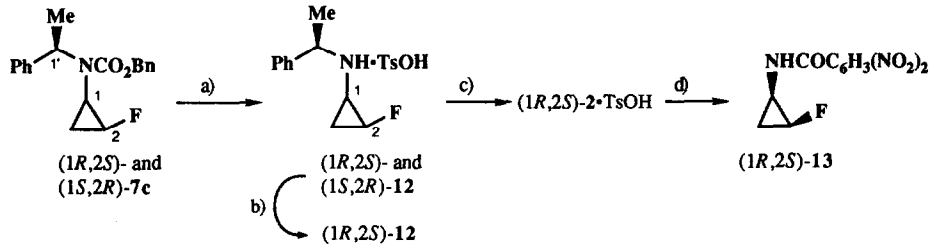
a) Method A: H_2, 10% Pd-C, AcOH; HCl-MeOH. Method B: CF_3CO_2H, CH_2Cl_2; H_2, 10% Pd-C, AcOH; HCl-MeOH. Method C: H_2, 10% Pd-C, AcOH; TsOH, MeOH. Method D: H_2, 10% Pd-C, TsOH, MeOH.
b) Isolated yield by trituration with ether or chloroform. c) A mixture of **7c** and **8c** (91:9) was used as the substrate.

unstable under basic conditions, transformation of **7a-f** to *dl*-**2** was attempted under acidic conditions as shown in **Table 3**. Thus, in the cases of **7a,c,e** carrying benzyloxycarbonyl (Cbz) group, simultaneous removals of the *N*-benzyl and the Cbz groups were effected by hydrogenolysis in the presence of 10% palladium on charcoal in acetic acid, affording the hydrochloride of *dl*-**2** (*dl*-**2**•HCl) (runs 1,3,6) after treatment with methanolic hydrogen chloride. The *p*-toluenesulfonate of *dl*-**2** (*dl*-**2**•TsOH) was also produced by hydrogenolysis of **7c** in acetic acid followed by treatment with 1 molar equivalent of *p*-toluenesulfonic acid (run 4), or by hydrogenolysis of **7e** in the presence of 1 molar equivalent of TsOH in methanol (run 7). The adduct (**9g**) lacking *N*-benzyl group was also converted to *dl*-**2**•TsOH by the same conditions as employed for **7e**. In the cases of **7b,d,f** bearing *t*-butoxycarbonyl (Boc) groups, acidic removal of the Boc groups with trifluoroacetic acid followed by hydrogenolysis of the *N*-benzyl groups and treatment with methanolic hydrogen chloride furnished *dl*-**2**•HCl (runs 2,5,8). It is worth noting that even the mixture of **7c** and **8c** (91 : 9) can afford pure *dl*-**2**•TsOH due to its excellent crystallization ability (run 4). Treatment of *dl*-**2**•HCl with di-*t*-butyl dicarbonate in the presence of triethylamine gave rise to **9h**, whose ^{1}H-NMR and IR spectra were identical with those of an authentic sample.[5b] Hydrogenolysis of **8a** followed by treatment with methanolic hydrogen chloride also gave *dl*-**11**•HCl in 83% yield. This was similarly protected with a Boc group to afford **10h**. In the ^{1}H-NMR spectra of *dl*-**2**•HCl, **9h**, *dl*-**11**•HCl, and **10h**, the coupling constants between the C_1- and C_2-protons are as follows: *dl*-**2**•HCl, 5.5 Hz; **9h**, 6.0 Hz; *dl*-**11**•HCl, 1.3 Hz; **8h**, 0.8 Hz. These spectral characteristics are well compatible with the fact that *dl*-**2**•HCl, **9h** and *dl*-**11**•HCl, **10h** bear *cis*- and *trans*-stereochemistries, respectively.

5. Synthesis of (1*R*,2*S*)-2-fluorocyclopropylamine [(1*R*,2*S*)-**2**]

With completion of the efficient synthetic route to *dl*-**2**, the preparation of highly optically active (1*R*,2*S*)-**2** was next studied. As mentioned above, the reaction of *dl*-benzyl *N*-(1-phenylethyl)-*N*-vinylcarbamate (**6c**) with zinc-monofluorocarbenoid afforded a high yield of **7c** without diastereoface-selectivity (**Table 1**, run 13). Employing this reaction, the preparation of (1*R*,2*S*)-**2** from the mixture of optically active (1*R*,2*S*)- and (1*S*,2*R*)-**7c** was first examined as shown in **Scheme 4**. Since almost a 1:1 diastereomeric mixture of (1*R*,2*S*)- and (1*S*,2*R*)-**7c** produced from (*R*)-1-phenylethylamine following the same procedure as for **7c** was found to be an oily substance, partial hydrogenolysis of the diastereomeric mixture was performed in the presence of TsOH by employing 5% palladium on charcoal, affording a mixture of the *p*-toluenesulfonates of (1*R*,2*S*)- and (1*S*,2*R*)-*N*-

Scheme 4

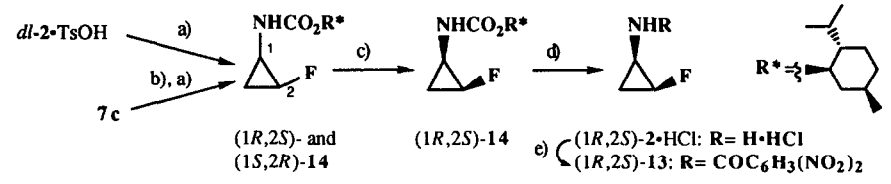


a) H_2, 5% Pd-C, TsOH, MeOH, 89% b) Two recrystallizations from toluene, 9% [based on (1*R*,2*S*)- and (1*S*,2*R*)-**12**] or 18% [based on (1*R*,2*S*)-**12**] c) H_2, 10% Pd-C, AcOH, 100% d) 3,5-$(NO_2)_2C_6H_3COCl$, Et_3N, THF

[(*R*)-1-phenylethyl]-2-fluorocyclopropylamine [(1*R*,2*S*)- and (1*S*,2*R*)-**12**•TsOH] as a crystalline solid. Two recrystallizations of this mixture from toluene gave desired (1*R*,2*S*)-**12**•TsOH, mp 134-135.5 °C and $[\alpha]_D^{20}$ +22.9° (*c* 0.498, MeOH), (94% de by ^{19}F-NMR spectrum), in 9% yield based on the total amount of (1*R*,2*S*)- and (1*S*,2*R*)-**12**•TsOH [18% yield based on (1*R*,2*S*)-**12**•TsOH]. Subsequent hydrogenolysis of (1*R*,2*S*)-**12**•TsOH furnished (1*R*,2*S*)-**2**•TsOH, mp 168.5-170.5 °C (decomp.) and $[\alpha]_D^{20}$ -8.9° (*c* 0.699, MeOH), in a quantitative yield. Chiral HPLC analysis of the 3,5-dinitrobenzamide [(1*R*,2*S*)-**13**] derived from (1*R*,2*S*)-**2**•TsOH obviously established the absolute configuration and optical purity (94% ee) of (1*R*,2*S*)-**2**•TsOH.[18]

Although desired (1*R*,2*S*)-**2** with high optical purity could be prepared from the diastereomeric mixture of (1*R*,2*S*)- and (1*S*,2*R*)-**7c**, the overall process seemed to be less practical due to the low yield of fractional recrystallization. Accordingly, optical resolution of *dl*-**2** was next examined as the second preparation method of (1*R*,2*S*)-**2**. After numerous unsuccessful experiments using *d*-camphorsulfonic acid and *l*-di-*O*-benzoyltartaric acid as resolution agents, the optical resolution of *dl*-**2** was found to be effectively achieved by employing *l*-menthyl chloroformate as shown in **Scheme 5**. Thus, *dl*-**2**•TsOH was acylated with *l*-menthyl chloroformate to give a 1:1 diastereomeric mixture of the *l*-menthyl carbamates [(1*R*,2*S*)- and (1*S*,2*R*)-**14**] as a crystalline solid in 95% yield. Since the 1-phenylethyl group of **7c** was found to be cleanly cleaved under strongly acidic conditions (see **Experimental**),[19] simultaneous removals of the 1-phenylethyl and Cbz groups of **7c** followed by carbamate formation of resulting crude *dl*-**2**•HCl with *l*-menthyl chloroformate directly produced a mixture of (1*R*,2*S*)- and (1*S*,2*R*)-**14** in 69% yield based on **7c**. The latter process is obviously more practical than the former stepwise method especially in a large scale preparation due to no use of hydrogenolysis over expensive palladium on charcoal. Four repeated recrystallizations of the mixture of (1*R*,2*S*)- and (1*S*,2*R*)-**14** from hexane-ethyl acetate afforded pure (1*R*,2*S*)-**14**, mp 119.5-120.5 °C and $[\alpha]_D^{20}$ -45.9° (*c* 1.05, MeOH)(94% de by ^{19}F-NMR spectrum), in 26% yield based on the total amount of (1*R*,2*S*)- and (1*S*,2*R*)-**14** [52% yield based on (1*R*,2*S*)-**14**)]. Acidic hydrolysis of (1*R*,2*S*)-**14** under usual conditions furnished (1*R*,2*S*)-**2** in 88% yield as its hydrochloride [(1*R*,2*S*)-**2**•HCl], mp 153-157 °C (decomp.) and $[\alpha]_D^{20}$ -19.0° (*c* 0.738, EtOH) [*lit.*[5c] mp 96-100 °C and $[\alpha]_D$ -18.99° (*c* 1.011, EtOH)].[20] The optical purity of this sample was similarly determined as 96% ee by chiral HPLC analysis[18] of derived (1*R*,2*S*)-**13**.

Scheme 5



a) *l*-menthyl chloroformate, CH_2Cl_2, $NaHCO_3$aq, 95% from *dl*-**2**•TsOH, 69% from **7c** (two steps) b) conc. HCl, MeOH, sealed tube, 100 °C c) Four recrystallizations from hexane-AcOEt, 26% [52% based on (1*R*,2*S*)-**14**] d) conc. HCl, MeOH, reflux, 88% e) 3,5-$(NO_2)_2C_6H_3COCl$, Et_3N, THF

Conclusion

As mentioned above, we have succeeded in developing a highly *cis*-selective synthetic route to *dl*-**2** by employing the cyclopropanation of *N*-benzyl-*N*-vinylcarbamates with zinc-monofluorocarbenoid, and an efficient optical resolution method of *dl*-**2** providing highly optically active (1*R*,2*S*)-**2**.

Experimental

General. All melting points were determined with a Yanagimoto MP-21 melting point apparatus and were uncorrected. Optical rotations were measured with a Horiba SEPA-200 auto digital polarimeter. Infrared (IR) spectra were recorded on a JASCO A-202 spectrometer. ^{1}H-NMR spectra were measured with a Hitachi R-90H (90 MHz), a Brucker AM 200 (200 MHz), and a Brucker AM 400 (400 MHz) spectrometer. The chemical shifts are expressed in ppm downfield from tetramethylsilane, using tetramethylsilane (δ = 0) and/or residual chloroform (δ = 7.25) as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. ^{19}F-NMR spectra were measured with a Brucker AM 200 (188 MHz) spectrometer. The chemical shifts are expressed in ppm downfield from trichlorofluoromethane, using trichlorofluoromethane (δ = 0) as an internal standard. Mass spectra were taken with a Hitachi RMU-6MG mass spectrometer. Unless otherwise noted, all experiments were carried out under an atmosphere of dry argon using anhydrous solvents. Especially, tetrahydrofuran and ethyl ether were distilled from sodium benzophenone ketyl. For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F254, 0.25 mm, Art 5715) were used. The following abbreviations were used for solvents: tetrahydrofuran (THF), diethyl ether (Et_2O), ethyl acetate (AcOEt), methanol (MeOH), and dichloromethane (CH_2Cl_2). Fluorodiiodomethane ($CHFI_2$) was prepared by the reported method.[21]

***N*-Benzyl-*N*-vinylcarbamoyl Chloride (5a)** To a stirred suspension of **3a** (3.08 g, 28 mmol) and anhydrous $MgSO_4$ (4.0 g) in Et_2O (30 ml) was added acetaldehyde (1.9 ml, 34 mmol) at 0 °C. After stirring for 1 h at the same temperature, the mixture was filtered, and the filtrate was concentrated *in vacuo* to afford crude **4a** as a pale yellow oil (3.87 g, quantitative yield). This compound was immediately used for the next step without further purification. ^{1}H-NMR ($CDCl_3$): 2.01 (d, 3H, J = 4.8 Hz, Me), 4.55 (brs, 2H, CH_2Ph), 7.28 (s, 5H, Ph), 7.80 (q, 1H, N=C*H*Me). To a solution of **4a** (3.87 g, 28 mmol) in benzene (50 ml) was successively added Et_3N (4.3 ml, 31 mmol) and trichloromethyl chloroformate (1.8 ml, 15 mmol) at room temperature. After stirring for 2 h at the same temperature, the mixture was filtered. The filtrate was concentrated *in vacuo* to give crude *N*-benzyl-*N*-(1-chloroethyl)carbamoyl chloride as a reddish oil (7.19 g). This compound was directly used for the next operation without purification. ^{1}H-NMR (C_6D_6): 1.00 (d, 3H, J = 6.6 Hz, Me), 4.11 (d, 1H, J = 17.0 Hz, NC*H*HPh), 4.55 (d, 1H, J = 17.0 Hz, NCH*H*Ph), 6.20 (q, 1H, J = 6.6 Hz, C*H*Me), 6.8-7.1 (m, 5H, Ph). MS (m/z): 235, 233, 231 (M^+), 196 (M^+-Cl), 132, 91. Distillation of the crude chloride (7.19 g) by Kugelrohr oven gave **5a** as a pale yellow oil (3.19 g, 58% from **3a**). bp 100-150 °C (1.0 mmHg, bath temp.). IR (neat): 3080, 3050, 1735, 1632, 1498, 1450, 1178 cm^{-1}. ^{1}H-NMR (C_6D_6): 4.02 (br d, 1H, J = 8.5 Hz, *E*-C*H*=), 4.15 (dd, 1H, J = 1.6 and 15.7 Hz, *Z*-C*H*=), 4.84 (s, 2H, CH_2Ph), 7.04 (br s, 6H, Ph and NCH=). MS (m/z): 197, 195 (M^+), 126, 91.

***dl*-*N*-(1-Phenylethyl)-*N*-vinylcarbamoyl Chloride (5b)** To a stirred suspension of **3b** (10.0 g, 83 mmol) and anhydrous $MgSO_4$ (10 g) in Et_2O (50 ml) was added acetaldehyde (5.5 ml, 99 mmol) at 0 °C. After stirring for 1.5 h at the same temperature, the mixture was filtered. The filtrate was concentrated *in vacuo* to give crude **4b** as an oil (12.0 g, quantitative yield). This compound was immediately used for the next step without further purification. IR ($CHCl_3$): 2960, 2860, 1605, 1495, 1445, 1370, 1085 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.48 (d, 3H, J = 6.8 Hz, *Me*CHPh , 1.97 (d, 3H, J = 4.8 Hz, *Me*CH=N), 4.27 (q, 1H, J = 6.8 Hz, CH_3C*H*Ph), 7.1-7.5 (m, 5H, Ph), 7.79 (q, 1H, J = 4.8 Hz, CH_3C*H*=N). MS (m/z): 147 (M^+), 132, (M^+-CH_3), 105 (M^+-CH_3CH=N, base peak). To a stirred solution of crude **4b** (12.0 g, 83 mmol) in toluene (100 ml) was successively added Et_3N (13.7 ml, 91 mmol) and trichloromethyl chloroformate (5.5 ml, 45 mmol) at room temperature. After stirring for 2 h at the same temperature, the mixture was heated at 80 °C for 2 h. After cooling to room temperature, the mixture was filtered. The filtrate was concentrated *in vacuo*, affording an oily residue, which was distilled under a reduced pressure to give **5b** as an oil (13.4 g, 77 % from **3b**), bp 122-124 °C (4 mmHg). IR ($CHCl_3$): 1730, 1630, 1385, 1255, 855, 695 cm^{-1}. ^{1}H-NMR (C_6D_6): 1.28 (d, 3H, J = 7.0 Hz, *Me*), 4.30 (dd, 1H, J = 1.1 and 9.2 Hz, *E*-C*H*=), 4.48 (br d, 1H, J = 16.3 Hz, *Z*-C*H*=), 5.41 (q, 1H, J = 7.0 Hz, MeC*H*), 6.38 (dd, 1H, J = 9.2 and 16.3 Hz, NC*H*=), 7.05 (s, 5H, Ph). MS (m/z): 209 (M^+), 130, 105.

***N*-Diphenylmethyl-*N*-vinylcarbamoyl Chloride (5c)** To a stirred suspension of **3c** (2.73 g, 15 mmol) and anhydrous $MgSO_4$ (2.0 g) in Et_2O (10 ml) was added acetaldehyde (1.0 ml, 18 mmol) at 0 °C. After stirring for 12 h at the same temperature, the mixture was filtered. The filtrate was concentrated *in vacuo* to give crude **4c** as an oil (3.31 g, quantitative yield). This compound was immediately used for the next reaction without further purification. ^{1}H-NMR ($CDCl_3$): 2.05 (d, 3H, J = 4.8 Hz, *Me*CH), 5.36 (s, 1H, Ph_2C*H*), 7.1-7.5 (m, 10H, Phx2), 7.90 (q, 1H, J = 4.8 Hz, N=CH). MS (m/z): 209 (M^+), 183, 167 (base peak), 106. To a stirred solution of **4c** (3.13 g, 15 mmol) in benzene (30 ml) was successively added Et_3N (2.29 ml, 16 mmol) and trichloromethyl chloroformate (0.98 ml, 8.2 mmol) at room temperature. After stirring for 3 h at the same temperature, the mixture was filtered. The filtrate was concentrated *in vacuo* to afford *N*-(1-chloroethyl)-*N*-diphenylmethylcarbamoyl chloride as an oil (4.88 g). IR (neat): 1750, 1255, 1220 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.72 (d, 3H, J = 6.4 Hz, Me), 6.28 (s, 1H, Ph_2C*H*), 6.2-6.6 (m, 1H, C*H*Me), 7.2-7.5 (m, 10H, Phx2). MS (m/z): 271 (M^+-HCl), 244, 209, 167 (base peak). This crude chloride was distilled under a reduced pressure to give **5c** as an oil (1.88 g, 53%, from **3c**), bp 120-125 °C (1-2 mmHg, bath temp.). IR (neat): 1740, 1630, 1495, 1450, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 4.75 (br d, 1H, J = 9.0 Hz, *E*-C*H*=), 4.93 (br d, 1H, J = 16.3 Hz, *Z*-C*H*=), 6.65 (dd, 1H, J = 9.0 and 16.3 Hz, NCH=), 6.77 (s, 1H, Ph_2C*H*), 7.0-7.5 (m, 10H, Phx2). MS (m/z): 271 (M^+), 209, 167.

Benzyl *N*-Benzyl-*N*-vinylcarbamate (6a) To a stirred suspension of NaH (60% oily dispersion, 7.0 mg, 0.18 mmol) in THF (0.5 ml) was added benzyl alcohol (25 µl, 0.24 mmol) at 0 °C. After stirring for 20 min, a solution of **5a** (22.7 mg, 0.17 mmol) in THF (0.5 ml) was added dropwise to the mixture at the same temperature. After the stirring was continued for 20 min, the reaction was quenched with a saturated solution of NH_4Cl, and the mixture was extracted with Et_2O. The organic extracts were combined, washed with brine, dried ($MgSO_4$), filtered, then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane, then hexane-AcOEt, 20:1) to afford **6a** as colorless crystals (24.6 mg, 79%), mp 45-45.5 °C (recrystallized from hexane).

IR (KBr): 3050, 2980, 2940, 1716, 1628, 1392, 1342, 1208 cm^{-1}. ^{1}H-NMR (C_6D_6): 4.07 (d, 1H, J = 9.2 Hz, *E*-C*H*=), 4.16 (d, 1H, J = 15.8 Hz, Z-C*H*=), 4.4-4.8 (br s, 2H, NCH_2Ph), 5.05 (s, 2H, OCH_2Ph), 7.0-7.6 (br s, 11H, Phx2 and NCH=). MS (m/z): 267 (M^+), 222, 176, 132, 91. *Anal.* Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.34; H, 6.35; N, 5.03.

***t*-Butyl *N*-Benzyl-*N*-vinylcarbamate (6b)** Treatment of **5a** (121 mg, 0.62 mmol) with *t*-butanol (115 μl, 1.2 mmol) and NaH (60% oily dispersion, 37.0 mg, 0.93 mmol) in THF (5 ml) under the same conditions as described for the preparation of **6a** gave crude **6b** after concentration of the combined organic extracts *in vacuo*. Purification of crude **6b** by column chromatography on silica gel (hexane, then hexane-AcOEt, 20:1) gave **6b** as a colorless oil (90.4 mg, 63%). IR ($CHCl_3$): 2980, 1700, 1625, 1372 cm^{-1}. ^{1}H-NMR (C_6D_6): 1.34 (s, 9H, *t*-Bu), 4.10 (d, 1H, J = 9.3 Hz, *E*-C*H*=), 4.17 (d, 1H, J = 16.3 Hz, Z-C*H*=), 4.59 (br s, 2H, NCH_2Ph), 7.10 (br, 5H, Ph), 7.50 (br, 1H, NCH=). MS (m/z): 233 (M^+), 177 (M^+-CH_2=CMe_2), 132, 105, 91, 57.

Benzyl *N*-(1-Phenylethyl)-*N*-vinylcarbamate (6c) The same treatments of **5b** (10.5 g, 50 mmol) with benzyl alcohol (5.61 g, 52 mmol) and NaH (60% oily dispersion, 3.0 g, 75 mmol) (washed with hexane before use) in THF (15 ml) as described for the preparation of **6a** gave almost pure **6c** as a colorless oil (14.1 g, quantitative yield) after concentration of combined organic extracts *in vacuo*. Since this sample was found to be almost pure by the ^{1}H-NMR spectrum, it was immediately used for the next step without further purification. IR ($CHCl_3$): 1705, 1635, 1395, 700 cm^{-1}. ^{1}H-NMR (C_6D_6): 1.40 (d, 3H, J=7.0 Hz, *Me*CH, spin saturation at δ = 4.25, NOE: 1.7%), 4.08 (dd, 1H, J = 0.7 and 9.7 Hz, *E*-C*H*=), 4.25 (br d, 1H, J = 16.2 Hz, Z-C*H*=), 4.92 (s, 2H, CH_2Ph), 5.36 (q, 1H, J = 7.0 Hz, MeC*H*, spin saturation at δ = 4.25, NOE: 4.3%), 6.9-7.2 (m, 11H, NCH=, Phx2, spin saturation at δ = 4.25, NOE: 2.1%). MS (m/z): 281 (M^+), 190 (M^+-C_7H_7), 146 (M^+-CO_2CH_2Ph), 105, 91 ($C_7H_7^+$, base peak).

***t*-Butyl *N*-(1-Phenylethyl)-*N*-vinylcarbamate (6d)** Treatments of **5b** (3.93 g, 19 mmol) with *t*-butanol (3.46 ml, 37 mmol) and NaH (60% oily dispersion, 1.49 g, 37 mmol) (washed with hexane before use) in THF (16 ml) under the same conditions as described for the preparation of **6a** gave almost pure **6d** as a colorless oil (4.28 g, 92%) after concentration of combined organic extracts *in vacuo*. This compound was pure enough for the next step by the ^{1}H-NMR spectrum. IR ($CHCl_3$): 3000, 1700, 1630, 1330, 860 cm^{-1}. ^{1}H-NMR (C_6D_6): 1.25 (s, 9H, *t*-Bu), 1.52 (d, 3H, J = 7.0 Hz, *Me*CH), 4.16 (br d, 1H, J = 9.7 Hz, *E*-C*H*=), 4.30 (br d, 1H, J = 14.7 Hz, Z-C*H*=), 5.34 (q, 1H, J = 7.0 Hz, MeC*H*), 7.0-7.5 (m, 6H, NCH=, Ph). MS m/z: 247 (M^+), 191 (M^+-CH_2=CMe_2), 147 (M^+-CH_2=CMe_2, -CO_2), 105.

Benzyl *N*-Diphenylmethyl-*N*-vinylcarbamate (6e) The same treatments of **5c** (160 mg, 0.59 mmol) with benzyl alcohol (114 mg, 1.1 mmol) and NaH (60% oily dispersion, 47 mg, 1.2 mmol) in THF (4 ml) as described for the preparation of **6a** gave crude **6e** after concentration of organic extracts *in vacuo*. Purification of crude **6e** by column chromatography on silica gel (hexane-AcOEt, 10:1) gave pure **6e** as a pale yellow oil (166 mg, 82%). IR (neat): 1710, 1630, 1400, 1300, 1270 cm^{-1}. ^{1}H-NMR (C_6D_6): 3.76 (br d, 1H, J = 10.3 Hz, *E*-C*H*=), 4.10 (br d, 1H, J = 16.0 Hz, Z-CH_2=), 4.51 (s, 2H, CH_2Ph), 6.29 (s, 1H, Ph_2CH), 6.5-6.9 (m, 16H, NCH=, Phx3). MS (m/z): 343 (M^+), 252, 208, 167, (base peak).

***t*-Butyl *N*-Diphenylmethyl-*N*-vinylcarbamate (6f)** Treatments of **5c** (517 mg, 1.9 mmol) with *t*-butanol (422 mg, 5.7 mmol) and NaH (60% oily dispersion, 228 mg, 5.7 mmol) in THF (6 ml) under the same conditions as described for the preparation of **6a** gave crude **6f** after concentration of the organic extracts *in vacuo*. Purification of crude **6f** by column chromatography on silica gel (hexane-CH_2Cl_2, 1:1) gave pure **6f** as a pale yellow oil (164 mg, 28%). IR (neat): 1705, 1625, 1400, 1320, 1155 cm^{-1}. ^{1}H-NMR (C_6D_6): 1.22 (s, 9H, *t*-Bu), 4.21 (br d, 1H, J = 9.2 Hz, *E*-C*H*=), 4.54 (br d, 1H, J = 16.0 Hz, Z-C*H*=), 6.59 (s, 1H, Ph_2CH), 7.0-7.5 (m, 11H, NCH=, Phx2). MS (m/z): 309 (M^+), 253, 208, 167 (base peak).

Benzyl *N*-Vinylcarbamate (6g) This was prepared according to the reported procedure,[13] mp 42-43 °C (*lit.*[13] mp 43-44 °C).

***t*-Butyl *N*-Vinylcarbamate (6h)** This was prepared according to the reported procedure,[14] mp 67-68 °C (*lit.*[14] mp 66 °C).

Benzyl *N*-Benzyl-*N*-[(1*R,2*S**)-2-Fluorocyclopropyl]carbamate (7a) and Its (1*R**,2*R**)-isomer (8a) (Table 1, run 9)** To a stirred solution of **6a** (98.4 mg, 0.37 mmol) in dry CH_2Cl_2 (1.8 ml) was added Et_2Zn (0.98 M hexane solution, 0.75 ml, 0.74 mmol) and $CHFI_2$ (211 mg, 0.74 mmol) in CH_2Cl_2 (3.6 ml) at -40 °C. After stirring for 20 min at the same temperature, Et_2O and a saturated solution of NH_4Cl were added to the reaction mixture, and the aqueous phase separated was extracted with Et_2O. The organic extracts were combined, washed with brine, dried ($MgSO_4$), filtered, then concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane-Et_2O, 6:1, then 5:1) to afford more polar **7a** as a colorless oil (60.3 mg, 55%) and less polar **8a** as colorless crystals (25.4 mg, 23%). **7a**: IR (neat): 3080, 3050, 1710, 1408, 1122 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.9-1.3 (m, 2H, CH_2CHF), 2.50 (br, 1H, CHF), 4.4-4.9 (m, 3H, NCH_2Ph and CHF), 5.20 (s, 2H, OCH_2Ph), 7.1-7.5 (m, 10H, Phx2). MS (m/z): 300 (M^++1), 208 (M^+-C_7H_7), 164, 91. **8a**: mp 42.5-43 °C (recrystallized from hexane-AcOEt). IR (KBr): 3100, 3060, 3040, 3000, 2945, 1700, 1405, 1280, 1118 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 1.02 (m, 1H, C*H*HCHF), 1.31 (m, 1H, CH*H*CHF), 2.89 (ddd, 1H, J = 5.8, 9.2, and 15.5 Hz, NC*H*CH_2), 4.28 (d, 1H, J = 15.1 Hz, C*H*HPh), 4.57 (d, 1H, J = 15.1 Hz, CH*H*Ph), 4.60 (br ddd, 1H, J = 2.8, 6.6, and 61.7 Hz, CHF), 7.2-7.4 (m, 10H, Phx2). MS m/z: 300 (M^++1), 208, 164, 91. *Anal.* Calcd. for $C_{18}H_{18}NO_2F$•0.2 H_2O: C, 71.36; H, 6.12; N, 4.62. Found: C, 71.39; H, 5.90; N, 4.60.

***t*-Butyl *N*-Benzyl-*N*-[(1*R**,2*S**)-2-fluorocyclopropyl]carbamate (7b) and Its (1*R**,2*R**)-isomer (8b) (Table 1, run 12)** Treatments of **6b** (75.3 mg, 0.32 mmol) with Et_2Zn (0.98 M hexane solution, 0.66 ml, 0.65 mmol) and $CHFI_2$ (192 mg, 0.67 mmol) in hexane (1.5 ml) at -20 °C by the same procedure as described for the preparation of **7a** and **8a** gave a crude mixture of **7b** and **8b** after extractive isolation. This was subjected to column chromatography on silica gel (hexane, then hexane-

AcOEt, 20:1) to give more polar **7b** (37.0 mg, 43%) and less polar **8b** (22.3 mg, 26%) both as an oil. **7b**: IR (neat): 2980, 2940, 1700, 1385, 1162, 1124 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.9-1.2 (br, 2H, C*H*$_2$CHF), 1.48 (s, 9H, *t*-Bu), 2.40 (br, 1H, NC*H*CH$_2$), 4.3-4.8 (m, 3H, PhC*H*$_2$ and CHF), 7.22-7.35 (m, 5H, Ph). MS (m/z): 209 (M^+-CH_2=CMe_2), 132, 91, 57. **8b**: IR (neat): 2980, 2940, 1700, 1385, 1162, 1124 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.97 (m, 1H, C*H*HCHF), 1.27 (m, 1H, CH*H*CHF), 1.48 (s, 9H, *t*-Bu), 4.20 (d, 1H, J = 15.4 Hz, C*H*HPh), 4.53 (d, 1H, J = 15.4 Hz, CH*H*Ph), 4.56 (br ddd, 1H, J = 3.0, 6.4, and 62.2 Hz, CHF), 7.2-7.36 (m, 5H, Ph). MS (m/z): 209 (M^+-CH_2=CMe_2), 132, 91, 57.

Benzyl *N*-[(1*R,2*S**)-2-Fluorocyclopropyl]-*N*-(1-phenylethyl)carbamate (7c) and Its (1*R**,2*R**)-Isomer (8c) (Table 1, run 13)** The same treatments of **6c** (7.13 g, 25 mmol) with Et_2Zn in hexane (1.0 M hexane solution, 51 ml, 51 mmol) and $CHFI_2$ (51 mmol) in CH_2Cl_2 (100 ml) as described for the preparation of **7a** and **8b** gave a crude mixture of **7c** and **8c** after extractive isolation. ^{19}F-NMR: -223.6 (44/100 F, **7c**), -223.3 (45/100 F, **7c**), -210.4 (7/100 F, **8c**), -210.3 (4/100 F, **8c**). This mixture was subjected to column chromatography on silica gel (hexane-AcOEt, 7:1) to give more polar **7c** as a 1:1 diastereomeric mixture (6.87 g, 87%) and less polar **8c** as a 3:2 diastereomeric mixture (880 mg, 10%). Both **7c** and **8c** were obtained as a colorless oil. Another lot of the mixture of **7c** and **8c** (5.11 g, 90 %, **7c** : **8c** = 91 : 9) was also prepared from **6c** (5.13 g, 18 mmol), Et_2Zn (1.0 M hexane solution, 27.3 ml, 27 mmol), and $CHFI_2$ (7.80 g, 27 mmol) in CH_2Cl_2 (150 ml) after extractive isolation and purification by column chromatography on a short silica gel column (26 g, hexane-AcOEt, 7:1). This was immediately used for the next step without further purification. **7c**: IR ($CHCl_3$): 1695, 1410, 1305, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.75-1.05 (m, 2Hx1/2 + 1/2H, C*H*$_2$CHF + C*H*HCHF), 1.1-1.3 (m, 1/2H, CH*H*CHF), 1.69 (d, 3Hx1/2, J = 7.1 Hz, *Me*CH), 1.70 (d, 3Hx1/2, J = 7.2 Hz, *Me*CH), 2.35-2.50 (m, 1H, NC*H*CHF), 4.45 (dm, 1/2H, J = 64 Hz, CHF), 4.52 (dm, 1/2H, J = 64 Hz, CHF), 5.0-5.15 (br, 1/2H, MeC*H*), 5.12 (s, 2Hx1/2, C*H*$_2$Ph), 5.17 (s, 2Hx1/2, C*H*$_2$Ph), 5.35-5.45 (br, 1/2H, MeC*H*), 7.1-7.5 (m, 10H, Phx2). MS (m/z): 313 (M^+), 222 (M^+-C_7H_7), 178 (M^+-CO_2CH_2Ph), 105, 91. **8c**: IR ($CHCl_3$): 1695, 1410, 1300, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.65-0.75 (m, 3/5H, C*H*HCHF), 0.93-1.40 (m, 2Hx2/5 + 3/5H, C*H*$_2$CHF + CH*H*CHF), 1.67 (d, 3H, J = 7.2 Hz, *Me*CH), 2.7-2.85 (m, 1H, NC*H*CHF), 4.22 (dddd, 2/5H, J = 1.2, 3.4, 6.8, and 62.1 Hz, CHF), 4.54 (dddd, 3/5H, J = 0.9, 3.5, 6.9, and 62.3 Hz, CHF), 5.17 (s, 2Hx2/5, C*H*$_2$Ph), 5.18 (d, 3/5H, J = 12.5 Hz, C*H*HPh), 5.22 (d, 3/5H, J = 12.5 Hz, CH*H*Ph), 5.3-5.41 (m, 1H, MeC*H*), 7.2-7.5 (m, 10H, Phx2). MS (m/z): 313 (M^+), 222 (M^+-C_7H_7), 178 (M^+-CO_2CH_2Ph), 105, 91.

***t*-Butyl *N*-[(1*R**,2*S**)-2-Fluorocyclopropyl]-N-(1-phenylethyl)carbamate (7d) and Its (1*R**,2*R**)-Isomer (8d) (Table 1, run 14)** Treatments of **6d** (3.99 g, 16 mmol) with Et_2Zn (1.0 M hexane solution, 32.3 ml, 32 mmol) and $CHFI_2$ (9.22 g, 32 mmol) in CH_2Cl_2 (66 ml) by the same procedure as described for the preparation of **7a** and **8a** gave a crude mixture of **7d** and **8d** after extractive isolation. This mixture was subjected to column chromatography on silica gel (hexane-AcOEt, 10:1) to give more polar **7d** as a 1:1 diastereomeric mixture (2.73 g, 61%) and less polar **8d** as a 3:2 diastereomeric mixture (261 mg, 6%). Both of **7d** and **8d** were obtained as a colorless oil. **7d**: IR ($CHCl_3$): 3000, 1690, 1390, 1370,1320, 860 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.7-1.05 (m, 2Hx1/2 + 1/2H, C*H*$_2$CHF + C*H*HCHF), 1.08-1.23 (m, 1/2H, CH*H*CHF), 1.36 (s, 9Hx1/2, *t*-Bu), 1.44 (s, 9Hx1/2, *t*-Bu), 1.67 (d, 3Hx1/2, J = 7.1 Hz, *Me*CH), 1.68 (d, 3Hx1/2, J=7.2 Hz, *Me*CH), 2.3-2.45 (m, 1H, NC*H*CHF), 4.44 (dm, 1/2H, J = 62.1 Hz, CHF), 4.51 (dm, 1/2H, J = 63.9 Hz, CHF), 4.95-5.1 (br, 1/2H, MeC*H*), 5.20-5.40 (br, 1/2H, MeC*H*), 7.16-7.5 (m, 5H, Ph). MS (m/z): 223 (M^+-CH_2=CMe_2), 178 (M^+-$CO_2{}^t$Bu), 105. **8d**: IR ($CHCl_3$): 3000, 1690, 1395, 1300, 960 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.6-0.72 (m, 2/5H, C*H*HCHF), 0.9-1.04 (m, 2/5H, CH*H*CHF), 1.05-1.20 (m, 3/5H, C*H*HCHF), 1.20-1.35 (m, 3/5H, CH*H*CHF), 1.45 (s, 9Hx2/5, *t*-Bu), 1.46 (s, 9Hx3/5H, *t*-Bu), 1.64 (d, 3Hx2/5, J = 7.2 Hz, *Me*CH), 1.65 (d, 3Hx3/5, J = 7.2 Hz, *Me*CH), 2.65-2.8 (m, 1H, NC*H*CHF), 4.24 (dddd, 2/5H, J = 1.1, 3.3, 6.7, and 62.2 Hz, CHF), 4.49 (dddd, 3/5H, J = 1.0, 3.5, 6.8, and 62.5 Hz, CHF), 5.24 (q, 3/5H, J = 7.2 Hz, MeC*H*), 5.25 (q, 2/5H, J = 7.2 Hz, MeC*H*), 7.2-7.35 (m, 5H, Ph). MS (m/z): 223 (M^+-CH_2=CMe_2), 178 (M^+-$CO_2{}^t$Bu), 105.

Benzyl *N*-Diphenylmethyl-*N*-[(1*R,2*S**)-2-fluorocyclopropyl]carbamate (7e) and Its (1*R**,2*R**)-Isomer (8e) (Table 1, run 15)** The same treatments of **6e** (28 mg, 0.082 mmol) with Et_2Zn (1.0 M hexane solution, 0.16 ml, 0.16 mmol) and $CHFI_2$ (46 mg, 0.16 mmol) in CH_2Cl_2 (1.25 ml) as described for the preparation of **7a** and **8a** gave a crude mixture of **7e** and **8e** after extractive isolation. This crude mixture was subjected to column chromatography on silica gel (hexane-AcOEt, 8:1) to give more polar **7e** (25.5 mg, 83%) and less polar **8e** (2 mg, 7%) both as a colorless oil. **7e**: IR ($CHCl_3$): 1700, 1405, 1300 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.7-0.9 (m, 1H, C*H*HCHF), 1.1-1.2 (m, 1H, CH*H*CHF), 2.2-2.3 (m, 1H, NC*H*CHF), 4.48 (dtd, 1H, J = 3.3, 6.3, and 63.4 Hz, CHF), 5.14 (s, 2H, PhC*H*$_2$), 6.43 (s, 1H, Ph$_2$C*H*), 7.1-7.5 (m, 15H, Phx3). MS m/z: 375 (M^+), 240, 167 (base peak). **8e**: IR ($CHCl_3$): 1700, 1540, 1400, 1295 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.95-1.05 (m, 1H, C*H*HCHF), 1.1-1.3 (m, 1H, CH*H*CHF), 2.68 (dddd, 1H, J = 1.2, 5.8, 9.6, and 16.7 Hz, NC*H*CHF), 4.48 (dddd, 1H, J = 1.2, 3.5, 6.8, and 61.8 Hz, CHF), 5.16 (s, 2H, PhC*H*$_2$), 6.43 (s, 1H, Ph$_2$C*H*), 7.1-7.5 (m, 15H, Phx3). MS (m/z): 375 (M^+), 285, 240, 167 (base peak).

***t*-Butyl *N*-Diphenylmethyl-*N*-[(1*R**,2*S**)-2-fluorocyclopropyl]carbamate (7f) and Its (1*R**,2*R**)-Isomer (8f) (Table 1, run 16)** Treatments of **6f** (39.5 mg, 0.13 mmol) with Et_2Zn in (1.0 M hexane solution, 0.25 ml, 0.25 mmol) and $CHFI_2$ (72.0 mg, 0.25 mmol) in CH_2Cl_2 (1.5 ml) by the same procedure as described for the preparation of **7a** and **8a** gave a crude mixture of **7f** and **8f** after extractive isolation. This crude mixture was subjected to column chromatography on silica gel (hexane-AcOEt, 10:1) to give more polar **7f** (35.2 mg, 81%) and less polar **8f** (2.8 mg, 6%) both as a colorless oil. **7f**: IR ($CHCl_3$): 1695, 1380, 1300 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.6-0.8 (m, 1H, C*H*HCHF), 1.0-1.15 (m, 1H, CH*H*CHF), 1.38 (s, 9H, *t*-Bu), 2.15-2.35 (m, 1H, NC*H*CHF), 4.46 (dm, 1H, J = 63.7 Hz, CHF), 6.32 (br s, 1H, Ph$_2$C*H*), 7.2-7.4 (m, 10H, Phx2). MS (m/z): 285 (M^+-CH_2=CMe_2), 240, 167 (base peak). **8f**: IR ($CHCl_3$): 1695, 1380, 1300 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.8-1.0 (m, 1H, C*H*HCHF), 1.1-1.25 (m, 1H, CH*H*CHF), 1.39 (s, 9H, *t*-Bu), 2.65 (br ddd, 1H, J = 6.0, 9.6, and 16.9 Hz, NC*H*CHF), 4.46 (dddd, 1H, J = 1.3, 3.5, 6.8, and 62.1 Hz, CHF), 6.30 (s, 1H, Ph$_2$C*H*), 7.15-7.4 (m, 10H, Phx2). MS (m/z): 285 (M^+-CH_2=CMe_2), 240, 167.

Benzyl *N*-[(1*R,2*S**)-2-Fluorocyclopropyl]carbamate (9g) and Its (1*R**,2*R**)-Isomer (10g) (Table 2, run 2)** To a stirred suspension of **6g** (58.5 mg, 0.33 mmol), $CHFI_2$ (284 mg, 1.0 mmol), 1,2-dimethoxyethane (DME, 100 μl), and molecular sieves 4A (MS4A, 60 mg) in CH_2Cl_2 (1 ml) was added $ZnEt_2$ (1.0 M hexane solution, 1.0 ml, 1.0 mmol) at room temperature. After stirring for 1 h at the same temperature, the mixture was diluted with a saturated solution of NH_4Cl and CH_2Cl_2. The aqueous phase separated was extracted with CH_2Cl_2. The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2) to give a mixture of **7g** and **8g** (17.2 mg, 25%) as a colorless oil. ^{19}F-NMR: -218.0 (64/100F, **7g**), -210.9 (36/100F, **8g**). The mixture was subjected to column chromatography on silica gel (hexane-AcOEt, 4:1) to afford more polar **7g** and less polar **8g** both as a colorless solid. **7g**: mp 71-72 °C (recrystallized from hexane). IR ($CHCl_3$): 3470, 1725, 1510, 1405 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.7-1.3 (m, 2H, C*H*$_2$CHF), 2.68 (m, 1H, NCH), 4.62 (dtd, 1H, J = 3.5, 6.0, and 62.0 Hz, CHF), 5.00 (br, 1H, NH), 5.13 (s, 2H, C*H*$_2$Ph), 7.35 (br s, 5H, Ph). *Anal.* Calcd for $C_{11}H_{12}FNO_2$: C, 63.15; H, 5.78; N, 6.69. Found: C, 63.00; H, 5.88; N, 6.51. **8g**: mp 64.5-66 °C (recrystallized from hexane). IR ($CHCl_3$): 3460, 1730, 1505, 1455, 1405 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.85-1.05 (m, 1H, C*H*HCHF), 1.25-1.45 (m, 1H, CH*H*CHF), 2.95 (ddddd, 1H, J = 1.0, 1.6, 5.6, 9.4, and 15.3 Hz, NCH), 4.54 (br ddd, 1H, J = 2.6, 6.2, 61.9 Hz, CHF), 4.81 (br, 1H, NH), 5.11 (br s, 2H, C*H*$_2$Ph), 7.35 (m, 5H, Ph). *Anal.* Calcd for $C_{11}H_{12}FNO_2$: C, 63.15; H, 5.78; N, 6.69. Found: C, 63.00; H, 5.88; N, 6.50.

***t*-Butyl *N*-[(1*R**,2*S**)-2-Fluorocyclopropyl]carbamate (9h) and Its (1*R**,2*R**)-Isomer (10h) (Table 2, run 3)** a) Preparation of **9h** and **10h** from **6h**: Treatments of **6h** (102 mg, 0.71 mmol) with $CHFI_2$ (611 mg, 2.1 mmol), Et_2Zn (1.0 M hexane solution, 2.1 ml, 2.1 mmol), DME (0.22 ml), and MS4A (100 mg) in CH_2Cl_2 (2 ml) in the same manner as described for the preparation of **9g** and **10g**, gave a crude mixture of **9h** and **10h**. The mixture was subjected to column chromatography on silica gel (hexane-Et_2O, 2:1) to afford more polar **9h** (22.5 mg, 18%) and less polar **10h** (15.2 mg, 12%) both as a colorless solid. **9h**: mp 64-65.5 °C (recrystallized from hexane). IR (KBr): 3360, 3000, 1705, 1688, 1516, 1275, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.6-1.3 (m, 2H, C*H*$_2$CHF), 1.46 (s, 9H, *t*-Bu), 2.5-2.76 (m, 1H, NCH), 4.62 (dtd, 1H, J = 3, 6, and 65 Hz, CHF), 4.5-5.0 (br, 1H, NH). This ^{1}H-NMR spectrum was identical with that reported for (1*R*,2*S*)-**9h**.[5b] *Anal.* Calcd for $C_8H_{14}FNO_2$: C, 54.84; H, 8.05; N, 7.99. Found: C, 54.86; H, 8.04; N, 7.95. **10h**: mp 46-48 °C (recrystallized from hexane). IR (KBr): 3400, 3000, 1686, 1516, 1368, 1280, 1168, 1060 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.6-1.5 (m, 2H, C*H*$_2$CHF), 1.45 (s, 9H, *t*-Bu), 2.7-3.1 (m, 1H, NCH), 4.54 (dddd, 1H, J = 1, 3.3, 6.6, 62 Hz, CHF), 4.5-4.8 (br, 1H, NH). *Anal.* Calcd for $C_8H_{14}FNO_2$: C, 54.84; H, 8.05; N, 7.99. Found: C, 54.64; H, 8.20; N, 7.90.

b) Preparation of **9h** from *dl*-**2**•HCl: To a stirred mixture of *dl*-**2**•HCl (24.4 mg, 0.22 mmol) and di-*t*-butyl dicarbonate (106 mg, 0.49 mmol) in CH_2Cl_2 (1 ml) was added Et_3N (61 μl, 0.438 mmol) at 0 °C. After stirring for 2 h at the same temperature, the mixture was diluted with water and Et_2O, and the aqueous phase separated was extracted with Et_2O. The organic extracts were combined, washed with brine, dried ($MgSO_4$), filtered, then concentrated *in vacuo*, to give a residue which was subjected to column chromatography on silica gel (hexane-Et_2O, 4:1) to afford **9h** as colorless crystals (27.9 mg, 78%), mp 65.5-66 °C (recrystallized from hexane). All the spectral data of this sample were identical with those described in a).

c) Preparation of **10h** from *dl*-**11**•HCl: The same treatments of *dl*-**11**•HCl (9.2 mg, 0.083 mmol) with di-*t*-butyl dicarbonate (36 mg, 0.17 mmol) and Et_3N (25 μl, 0.18 mmol) as described in b) gave **10h** as a colorless solid (4.0 mg, 28%) after extractive isolation and purification by column chromatography, mp 48-48.5°C (recrystallized from hexane). All the spectral data of this sample were identical with those described in a).

(1*R,2*S**)-2-Fluorocyclopropylamine Hydrochloride (*dl*-2•HCl)** a) Preparation from **7a,c,e**: To a solution of **7a** (80.4 mg, 0.27 mmol) in AcOH (0.8 ml) was added 10% Pd-C (16 mg), and the mixture was stirred for 3.5 h at room temperature under a hydrogen atmosphere (1 atmospheric pressure). The mixture was filtered, and a methanolic solution of hydrogen chloride (5 M solution, 3 ml) was added to the filtrate. The mixture was concentrated *in vacuo* to afford *dl*-**2**•HCl as a crystalline solid. This was recrystallized from MeOH-Et_2O to give pure *dl*-**2**•HCl as colorless crystals (28.2 mg, 94%), mp 118-120 °C (decomp.). IR (KBr): 3600-2400 (br), 2920, 1990, 1605, 1520, 1436, 1332, 1216, 1060, 798, 758 cm^{-1}. ^{1}H-NMR (CD_3OD, CD_2HOD = 3.35 as an internal standard): 1.05-1.5 (m, 2H, CH_2), 2.6-2.9 (m, 1H, CHN), 4.87 (dtd, 1H, J = 3.7, 5.5, and 64.0 Hz, CHF). *Anal.* Calcd. for C_3H_7ClFN: C, 32.30; H, 6.33; N, 12.56. Found: C, 32.46; H, 6.24; N, 12.28. Hydrogenolysis of **7c** (75 mg, 0.24 mmol) over 10% Pd-C (45 mg) in AcOH (1 ml) under a hydrogen atmosphere (pressure of 3.5 kg/cm^2) at room temperature for 4 h, followed by treatment with a methanolic solution of hydrogen chloride (8 M solution), concentration *in vacuo*, and recrystallization, gave *dl*-**2**•HCl as colorless crystals (20 mg, 77%). The hydrochloride (*dl*-**2**•HCl) (4.8 mg, 73%) was also obtained by hydrogenolysis of **7e** (21.9 mg, 0.058 mmol) over 10% Pd-C (15 mg) in AcOH (0.5 ml) under a hydrogen atmosphere (pressure of 3 kg/cm^2) at room temperature for 3 h, followed by treatment with a methanolic solution of hydrogen chloride (5 M solution), concentration *in vacuo*, and recrystallization. The ^{1}H-NMR spectra of *dl*-**2**•HCl obtained from **7c,e** were identical with those of the sample prepared from **7a**.

b) Preparation from **7b,d,f**: To a stirred solution of **7b** (13.6 mg, 0.051 mmol) in CH_2Cl_2 (0.2 ml) was added trifluoroacetic acid (60 μl, 0.78 mmol) at room temperature. After stirring for 1 h at the same temperature, the mixture was concentrated *in vacuo*. To the residue was added AcOH (0.3 ml) and 10% Pd-C (4 mg), and the mixture was stirred for 4 h at room temperature under a hydrogen atmosphere (1 atmospheric pressure). The mixture was treated in the same manner as described for the preparation of *dl*-**2**•HCl from **7a**, affording *dl*-**2**•HCl as colorless crystals (4.3 mg, 75%) after recrystallizing from MeOH-Et_2O. Treatments of **7d** (148 mg, 0.52 mmol) with trifluoroacetic acid (1.5 ml) in CH_2Cl_2 (1.5 ml) followed by hydrogenolysis over 10% Pd-C (80 mg) in AcOH (3 ml) under a hydrogen atmosphere (pressure of 3.5 kg/cm^2) gave *dl*-**2**•HCl (47 mg, 81%) after treatment with a methanolic solution of hydrogen chloride (8 M solution), concentration *in vacuo*, and recrystallization. Treatments of **7f** (29.9 mg, 0.097 mmol) with trifluoroacetic acid (0.5 ml) in CH_2Cl_2 (1 ml) followed by hydrogenolysis over 10% Pd-C (15 mg) in AcOH (0.5 ml) under a

hydrogen atmosphere (pressure of 3 kg/cm^2) gave *dl*-**2**•HCl (7.1 mg, 66%) after treatment with a methanolic solution of hydrogen chloride (8 M solution), concentration *in vacuo*, and recrystallization. The ^{1}H-NMR spectra of these three lots of *dl*-**2**•HCl were identical with that described in a).

(1*R,2*S**)-2-Fluorocyclopropylammonium *p*-Toluenesulfonate (*dl*-2•TsOH)** Preparation from **7c,e,g**: A mixture of **7c** and **8c** (91 : 9) (205 mg, 0.65 mmol) was added to a mixture of TsOH (110 mg, 0.64 mmol) and 10% Pd-C (40 mg) in AcOH (2 ml), and the whole was stirred for 15 h under a hydrogen atmosphere (pressure of 4.2 kg/cm^2). The mixture was filtered, and the filtrate was concentrated *in vacuo* to give a residue, which was stirred in $CHCl_3$ (4 ml) to afford *dl*-**2**•TsOH as colorless crystals (84.8 mg, 52%). An analytical sample was prepared by recrystallization from toluene-EtOH, mp 180-181 °C (decomp.). IR (KBr): 3200-2900 (br), 1605, 1520, 1450, 1330, 1200, 1170, 1125, 1070, 1035, 1010 cm^{-1}. ^{1}H-NMR (CD_3OD, CD_2HOD = 3.35 as an internal standard): 1.16-1.30 (m, 2H, CH_2), 2.37 (s, 3H, *Me*$C_6H_4SO_3$), 2.64-2.71 (m, 1H, CHN), 4.85 (dtd, 1H, J = 4.0, 5.3, and 63.6 Hz, CHF). *Anal.* Calcd. for $C_{10}H_{14}FNO_3S$: C, 48.57; H, 5.71; N, 5.66. Found: C, 48.55; H, 5.65; N, 5.87.
Hydrogenolysis of **7e** (1.40 g, 3.7 mmol) was performed over 10% Pd-C (200 mg) in MeOH (20 ml) in the presence of TsOH (640 mg, 3.8 mmol) under a hydrogen atmosphere (1 atmospheric pressure) for 11 h. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was washed with Et_2O to give *dl*-**2**•TsOH (758 mg, 83%) as colorless crystals. To a solution of **7g** (5.3 mg, 0.025 mmol) in MeOH (0.25 ml) was added 5% Pd-C (5 mg) and a methanolic solution of TsOH in MeOH (0.094 M solution, 0.27 ml, 0.025 mmol), and the mixture was stirred for 1.5 h at room temperature under a hydrogen atmosphere (1 atmospheric pressure). The mixture was filtered, and the filtrate was concentrated *in vacuo* to give *dl*-**2**•TsOH (5.5 mg, 87%). The ^{1}H-NMR spectra of these two lots of *dl*-**2**•TsOH were identical with that of the sample prepared from the mixture of **7c** and **8c**.

(1*R,2*R**)-2-Fluorocyclopropylamine Hydrochloride (*dl*-11•HCl)** Hydrogenolysis of **8a** (64.8 mg, 0.22 mmol) over 10% Pd-C (12 mg) in AcOH (0.6 ml) under the same conditions as described for the preparation of *dl*-**2**•HCl from **7a** gave *dl*-**11**•HCl as colorless crystals (20.1 mg, 83%) after recrystallization from MeOH-Et_2O, mp 99-102.5 °C (decomp). IR (KBr): 2400-3600, 2900, 1590, 1145, 1065, 1006, 932, 780 cm^{-1}. ^{1}H-NMR (CD_3OD, CD_2HOD = 3.35 as an internal standard): 1.21 (m, 1H, C*H*HCHF), 1.54 (m, 1H, CH*H*CHF), 3.05 (ddd, 1H, J = 5.9, 10.2, and 15.6 Hz, CHN), 4.87 (ddd, 1H, J = 3.4, 7.4, and 61.0 Hz, CHF). *Anal.* Calcd. for C_3H_7ClFN•0.1 MeOH: C, 34.44; H, 6.50; N, 12.21. Found: C, 32.17; H, 6.40; N; 11.94.

***N*-[(*R*)-1-Phenylethyl]-*N*-vinylcarbamoyl Chloride [(*R*)-5b]** Treatments of (*R*)-**3b** (5.0 g, 41 mmol) with acetaldehyde (2.75 ml, 49 mmol) and anhydrous $MgSO_4$ (5 g) in Et_2O (25 ml) by the same procedure as described for the preparation of **4b** gave (*R*)-**4b** as an oil (6.07 g, quantitative yield) after concentration *in vacuo*. The ^{1}H-NMR spectrum of (*R*)-**4b** was identical with that of **4b**. This was immediately used for the next step without further purification. The imine [(*R*)-**4b**] (6.07 g, 41.3 mmol) obtained was treated with trichloromethyl chloroformate (2.72 ml, 23 mmol) and Et_3N (6.3 ml, 45 mmol) in toluene (100 ml) by the same procedure as described for the preparation of **5b**, giving (*R*)-**5b** as an oil (6.59 g, 76%) after distillation under reduced pressure, bp 120-122 °C (4 mmHg). The ^{1}H-NMR and IR spectra of (*R*)-**5b** were identical with those of **5b**.

Benzyl *N*-[(*R*)-1-Phenylethyl]-*N*-vinylcarbamate [(*R*)-6c] This compound [(*R*)-**6c**] (2.32 g, 64%) was prepared as an oil from (*R*)-**5b** (2.71 g, 13 mmol), NaH (60% oily dispersion, 776 mg, 18 mmol), and benzyl alcohol (2.7 ml, 26 mmol) in dry THF (40 ml) by the same procedure as described for the preparation of **6c**, $[\alpha]_D^{20}$ +60.2° (*c* 1.14, MeOH). The ^{1}H-NMR and IR spectra of (*R*)-**6c** were identical with those of **6c**.

Benzyl *N*-[(1*R,2*S**)-2-Fluorocyclopropyl]-*N*-[(*R*)-1-phenylethyl]carbamate [(1*R*,2*S*)- and (1*S*,2*R*)-7c] and Its (1*R**,2*R**)-Isomer [(1*R*,2*R*)- and (1*S*,2*S*)-8c]** A crude mixture of [(1*R*,2*S*)- and (1*S*,2*R*)-**7c**] and [(1*R*,2*R*)- and (1*S*,2*S*)-**8c**] were prepared from (*R*)-**6c** (100 mg, 0.36 mmol), Et_2Zn (1.0 M hexane solution, 1.0 ml, 1.0 mmol), and $CHFI_2$ (305 mg, 1.1 mmol) in CH_2Cl_2 (2 ml) by the same procedure as described for the preparation of the mixture of **7c** and **8c**. The mixture was subjected to column chromatography on silica gel (hexane-AcOEt, 20:1, then 10:1) to give a 1:1 mixture of (1*R*,2*S*)- and (1*S*,2*R*)-**7c** (98.5 mg, 88%) as a colorless oil and a 3:2 mixture of (1*R*,2*R*)- and (1*S*,2*S*)-**8c** (13 mg, 12%) as a colorless oil. All the spectral data of the mixture of (1*R*,2*S*)- and (1*S*,2*R*)-**7c** and that of (1*R*,2*R*)- and (1*S*,2*S*)-**8c** were identical with those of **7c** and **8c**, respectively.

***N*-[(1*R**,2*S**)-2-Fluorocyclopropyl]-*N*-[(*R*)-1-phenylethyl]ammonium *p*-Toluenesulfonate [(1*R*,2*S*)- and (1*S*, 2*R*)-12]** A suspension of the mixture of (1*R*,2*S*)- and (1*S*,2*R*)-**7c** (1.22 g, 3.9 mmol), TsOH (670 mg, 3.9 mmol), and 5% Pd-C (200 mg) in AcOEt (20 ml) were stirred at room temperature under a hydrogen atmosphere (1 atmospheric pressure) for 3 h. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give a crystalline solid, which was triturated with Et_2O to yield a 1:1 mixture of (1*R*,2*S*)- and (1*S*,2*R*)-**12**•TsOH as colorless crystals (1.21 g, 89%). IR (KBr): 3440, 3010, 1600, 1230, 1115 cm^{-1}. ^{19}F-NMR ($CDCl_3$): -226.92 (1/2F), -222.97 (1/2F). ^{1}H-NMR ($CDCl_3$): 0.85-1.02 (m, 1H, C*H*HCHF), 1.74-1.90 (m, 1H, CH*H*CHF), 1.80 (d, 3Hx1/2, J = 6.9 Hz, PhCH*Me*), 1.87 (d, 3Hx1/2, J = 6.9 Hz, PhCH*Me*), 2.06-2.12 (m, 1Hx1/2, NC*H*CH2), 2.22-2.29 (m, 1Hx1/2, NC*H*CH2), 2.37 (s, 3H, *Me*$C_6H_4SO_2$), 4.38 (q, 1Hx1/2, J = 6.9 Hz, PhC*H*Me), 4.39 (dtd, 1Hx1/2, J = 3.4, 5.3, and 59.0 Hz, CHF), 4.48 (dtd, 1Hx1/2, J = 3.2, 5.2, and 62.5 Hz, CHF), 4.50 (q, 1Hx1/2, J = 6.9 Hz, PhC*H*Me), 7.19 (d, 2H, J = 8.2 Hz, ArH), 7.31-7.37 (m, 3H, ArH), 7.48-7.55 (m, 2H, ArH), 7.77 (d, 2H, J = 8.2 Hz, ArH).
A part of the mixture of (1*R*,2*S*)- and (1*S*,2*R*)-**12**•TsOH (1.06 g, 3.0 mmol) was dissolved in hot toluene (10 ml). The toluene solution was kept at 40-44 °C for 2 days to give crystals, which were collected by filtration, and recrystallized once from hot toluene to give (1*R*,2*S*)-**12**•TsOH as colorless crystals (94 mg, 9%), mp 134-135.5 °C and $[\alpha]_D^{20}$ +22.9° (*c* 0.498, MeOH). The diastereomeric excess of this sample was estimated by its ^{19}F-NMR spectrum. IR (KBr): 3440, 3020, 2475, 1600, 1230, 1115 cm^{-1}. ^{19}F-NMR ($CDCl_3$): -226.92 (1Fx97/100), -222.97 (1Fx3/100). ^{1}H-NMR ($CDCl_3$): 0.91 (tdd, 1H, J = 6.2, 9.4, and 15.6 Hz, C*H*HCHF), 1.77-1.90 (m, 1H, CH*H*CHF), 1.81 (d, 3H, J = 6.9 Hz, PhCH*Me*), 2.11 (m, 1H, NC*H*CH_2), 2.37 (s, 3H,

Me$C_6H_4SO_2$), 4.40 (q, 1H, J = 6.9 Hz, PhC*H*Me), 4.50 (dddd, 1H, J = 3.4, 5.2, 6.2, 62.6 Hz, CHF), 7.20 (d, 2H, J = 7.9 Hz, ArH), 7.30 (m, 3H, ArH), 7.58 (m, 2H, ArH), 7.79 (d, 2H, J = 7.9 Hz, ArH). CIMS (m/z): 352 (M^++1), 272, 180, 105 (base peak), 57. *Anal.* Calcd for $C_{18}H_{22}FNO_3S$: C, 61.51; H, 6.31; N, 3.99. Found: C, 61.61; H, 6.40; N, 4.10.

(1*R*,2*S*)-2-Fluorocyclopropylammonium *p*-Toluenesulfonate [(1*R*,2*S*)-2•TsOH] A mixture of (1*R*,2*S*)-**12**•TsOH (50 mg, 0.14 mmol) and 10% Pd-C (10 mg) in AcOH (2 ml) was stirred at room temperature for 5 h under a hydrogen atmosphere (pressure of 4.2 kg/cm^2). The mixture was filtered, and the filtrate was concentrated *in vacuo* to give (1*R*,2*S*)-**2**•TsOH as colorless crystals (35 mg, quantitative yield), mp 168.5-170.5 °C (decomp.) (recrystallized from toluene) and $[\alpha]_D^{20}$ -8.9° (*c* 0.699, MeOH). The optical purity of this sample was estimated as 94% ee by HPLC analysis of the corresponding 3,5-dinitrobenzamide derivative [(1*R*,2*S*)-**13**] (*vide infra*). IR (KBr): 3440, 2950, 1620, 1210, 1115 cm^{-1}. ^{1}H-NMR (CD_3OD, CD_2HOD = 3.35 as an internal standard): 1.17-1.29 (m, 2H, NCHC*H*$_2$), 2.36 (s, 3H, *Me*$C_6H_4SO_2$), 2.64-2.69 (m, 1H, NC*H*CH_2), 4.84 (dtd, 1H, J = 3.9, 5.3, and 63.5 Hz, CHF), 7.23 (d, 2H, J = 8.0 Hz, ArH), 7.70 (d, 2H, J = 8.0 Hz, ArH). CIMS (m/z): 248 (M^++1), 199, 132, 93, 76 (base peak). The ^{1}H-NMR spectrum of this sample was identical with that of *dl*-**2**•TsOH. *Anal.* Calcd for $C_{10}H_{14}FNO_3S$: C, 48.57; H, 5.71; N, 5.66. Found: C, 48.70; H, 5.78; N; 5.40. In order to determine the optical purity of (1*R*,2*S*)-**2**•TsOH, (1*R*,2*S*)-**13** was prepared as follows. Thus, to a stirred mixture of (1*R*,2*S*)-**2**•TsOH (1 mg) and 3,5-dinitrobenzoyl chloride (3 mg) in THF (1 ml) was added Et_3N (3 μl) at room temperature. After stirring for 1 h at room temperature, a saturated solution of $NaHCO_3$ (0.3 ml) was added, and the mixture was stirred vigorously for 15 min. The mixture was diluted with CH_2Cl_2 (3 ml), dried ($MgSO_4$), and filtered through a pad of silica gel to give a dichloromethane solution of (1*R*,2*S*)-**13** usable for chiral HPLC analysis. The dichloromethane solution of *dl*-**13** was similarly prepared from *dl*-**2**•TsOH. The analysis conditions for HPLC were as follows: column, Sumipax OA-4600; mobile phase, hexane:1,2-dichloroethane:ethanol = 60:40:5; flow rate, 1.0 ml/min; detector, UV (254 nm). Retention time for *dl*-**13**: 10.9 min [50%, (1*R*,2*S*)-form], 14.9 min [50%, (1*S*,2*R*)-form]. Retention time for (1*R*,2*S*)-**13** prepared from (1*R*,2*S*)-**2**•TsOH: 10.6 min (97%), 14.9 min (3%), 94 % ee (*vide infra*).

(1*R*,2*S*,5*R*)]-5-Methyl-2-(1-methylethyl)cyclohexyl *N*-(1*R,2*S**)-2-Fluorocyclopropylcarbamate [(1*R*,2*S*)- and (1*S*,2*R*)-14]** To a stirred mixture of *dl*-**2**•TsOH (1.64 g, 6.6 mmol) and *l*-menthyl chloroformate (2.13 ml, 9.9 mmol) in CH_2Cl_2 (40 ml) was added a solution of $NaHCO_3$ (1.10 g, 13 mmol) in H_2O (40 ml). After stirring overnight at room temperature, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The all organic extracts were combined, washed with brine, dried ($MgSO_4$), then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane-Et_2O, 1:1) to afford a mixture of (1*R*,2*S*)- and (1*S*,2*R*)-**14** as colorless crystals (1.62 g, 95%), mp 78.5-80.5 °C. ^{19}F-NMR (acetone-d_6): -227.9 [1/2F, (1*R*,2*S*)-**14**], -228.2 [1/2F, (1*S*,2*R*)-**14**].

Another lot of a 1:1 mixture of (1*R*,2*S*)- and (1*S*,2*R*)-**14** was directly prepared from **7c**. A solution of **7c** (200 mg, 0.64 mmol) in MeOH-conc. HCl (1:5, 6 ml) was heated at 100 °C for 24 h in a sealed tube. After cooling, the mixture was washed with AcOEt. The aqueous phase was concentrated *in vacuo* to give crude *dl*-**2**•HCl as colorless crystals, which was suspended in CH_2Cl_2 (1 ml). To the suspension was added *l*-menthyl chloroformate (0.15 ml, 0.70 mmol) and a solution of $NaHCO_3$ (200 mg) in H_2O (4 ml) at 0 °C. After stirring for 2 h at the same temperature, the mixture was extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, dried (Na_2SO_4), filtered, then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane-Et_2O, 2:1) to afford a mixture of (1*R*,2*S*)- and (1*S*,2*R*)-**14** as colorless crystals (114 mg, 69%).

A mixture of (1*R*,2*S*)- and (1*S*,2*R*)-**14** (790 mg) was recrystallized twice from hexane-EtOAc (40:1) and twice from hexane-EtOAc (20:1) to yield (1*R*,2*S*)-**14** as colorless needles [207 mg, 26% based on the mixture of (1*R*,2*S*)- and (1*S*,2*R*)-**14**], mp 119.5-120.5 °C and $[\alpha]_D^{20}$ -45.9 ° (*c* 1.05, MeOH). ^{19}F-NMR (acetone-d_6): -227.9 [97/100 F, (1*R*,2*S*)-**14**], -228.2 [3/100 F, (1*S*,2*R*)-**14**]. IR (KBr): 3380, 2870, 1690, 1580, 1270 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.80 (d, 3H, J = 7.0 Hz, *Me*CH), 0.80-1.14 (m, 4H), 0.89 (d, 3H, J = 4.3 Hz, *Me*CH), 1.31 (br s, 1H), 1.43-1.54 (m, 1H), 1.63-1.71 (m, 2H), 1.92 (br s, 1H), 2.07 (br d, 1H, J = 12.1 Hz), 2.69 (br s, 1H, NCH), 4.58 (dt, 1H, J = 4.2, 11.1 Hz, NCO_2CH), 4.60 (br d, 1H, J = 63.2 Hz, CHF), 4.85 (br s, 1H, NH). MS (m/z): 257 (M^+), 139, 83 (base peak), 55. *Anal.* Calcd for $C_{14}H_{24}FNO_2$: C, 65.34; H, 9.40; N, 5.44. Found: C, 65.45; H, 9.42; N, 5.42. Isolation of (1*S*,2*R*)-**14** in a pure state was not attempted.

(1*R*, 2*S*)-2-Fluorocyclopropylamine Hydrochloride [(1*R*,2*S*)-2•HCl] To a solution of (1*R*,2*S*)-**14** (50 mg, 0.19 mmol) in MeOH (1 ml) was added conc. HCl (1 ml). The mixture was heated at 80 °C for 2 days. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give a crystalline residue, which was recrystallized from EtOH-Et_2O to afford (1*R*,2*S*)-**2**•HCl as colorless crystals (19.1 mg, 88%), mp 153-157 °C (decomp.) and $[\alpha]_D^{20}$ -19.0° (*c* 0.738, EtOH). [*lit.*[5c] mp 96-100°C, $[\alpha]_D$ -18.99° (*c* 1.011, EtOH)].[20] The optical purity of this sample was determined as 96% ee by chiral HPLC analysis of the corresponding 3,5-dinitrobenzamide [(1*R*,2*S*)-**13**] (*vide infra*). The ^{1}H-NMR spectrum of (1*R*,2*S*)-**2**•HCl was identical with that of *dl*-**2**•HCl. In order to estimate the optical purity of (1*R*,2*S*)-**2**, it was acylated with 3,5-dinitrobenzoyl chloride in a similar manner to that described for the preparation of (1*R*,2*S*)-**13** from (1*R*,2*S*)-**2**•TsOH. The analysis conditions for HPLC were as follows: column, Sumipax OA-4600; mobile phase, hexane:1,2-dichloroethane:ethanol = 60:40:5; flow rate, 1.0 ml/min; detector, UV (254 nm). Retention time for *dl*-**13**: 10.9 min [50%, (1*R*,2*S*)-form], 14.9 min [50%, (1*S*,2*R*)-form]. Retention time for (1*R*,2*S*)-**13** prepared from (1*R*,2*S*)-**2**•HCl: 10.6 min (98%), 14.9 min (2%), 96 % ee.

References and Notes

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