Fluorinated Phenylcyclopropylamines. 1. Synthesis and Effect of Fluorine Substitution at the Cyclopropane Ring on Inhibition of Microbial Tyramine Oxidase

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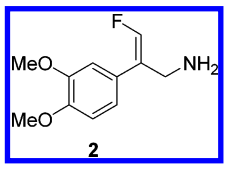
Two series of diastereopure phenylcyclopropylamine analogues, 2-fluoro-2-phenylcyclopropylamines and 2-fluoro-2-phenylcyclopropylalkylamines, as well as 2-fluoro-1-phenylcyclopropylamines and 2-fluoro-1-phenylcyclopropylmethylamines, were synthesized in order to study the effects of fluorine substitution on monoamine oxidase inhibition. Inhibitory activity was assayed using commercially available microbial tyramine oxidase. Characterization of tyramine oxidase, carried out prior to the inhibition experiments, confirmed earlier suggestions that this enzyme is a semicarbazide-sensitive copper-containing monoamine oxidase. The most potent competitive inhibitor was *trans*-2-fluoro-2-phenylcyclopropylamine, which had an IC_{50} value 10 times lower than that of the nonfluorinated compound, tranylcypromine. 2-Fluoro-1-phenylcyclopropylmethylamine was found to be a weak noncompetitive inhibitor of tyramine oxidase. The presence of a free amino group, directly bonded to the cyclopropane ring, and a fluorine atom in a relationship cis to the amino group were structural features that increased tyramine oxidase inhibition.

Introduction

The copper- (EC, 1.4.3.6) and flavin-containing amine oxidases (EC, 1.4.3.4) make up two general classes of the widely distributed monoamine oxidases (MAO).[1] Copper-containing amine oxidases (CAO) are strongly inhibited by semicarbazide, and this property distinguishes them from flavin-containing monoamine oxidases, which are selectively inhibited by acetylenic inhibitors such as clorgyline and deprenyl. Monoamine oxidases catalyze oxidation of a wide range of amine substrates, a requirement being the presence of an α-hydrogen. Flavin-linked mitochondrial monoamine oxidases are present in two catalytically distinguishable A and B subtypes (MAO A and MAO B) that have different substrate selectivities. These play very important physiologic roles related to regulation of amine levels.[2] CAOs have important and diverse functions in prokaryotes, including roles in nutrient metabolism. More recently, an increasing number of important roles of CAOs in eukaryotes have been identified and studied.[3] For example, a CAO has been found to be associated with the GLUT-4 glucose transporter and involved in the signaling of glucose uptake in adipocytes.[4] In another recent report the suggestion was made that CAO expression is a source of oxidative stress in the blood vessel walls in Alzheimer's disease.[5]

Indicative of the importance of MAO inhibitors as pharmacological and medicinal agents, in particular as mood elevating agents, hundreds of inhibitors of these enzymes have been developed. Many irreversible inhibitors are acetylenic compounds, such as the MAO A selective clorgyline and the MAO B selective L-deprenyl. Other irreversible inhibitors have been based on cyclopropylamines. An example is tranylcypromine (**1a**), used to treat certain depressive illnesses, an irreversible inhibitor that shows no selectivity for MAO A or B. A proposed mechanism involves initial one-electron oxidation of the amino group that leads to ring opening and covalent attachment to an active-site SH group (Scheme 1).[6] Tranylcypromine also inhibits CAO but in a reversible manner.[7]

A search for MAO B selective inhibitors that would be free of the well-documented "cheese effect" (inhibition of MAO A mediated oxidation of tyramine present in many foods, leading to blood pressure elevation) produced a series of potent 3-haloallylamines.[6] For example, 2-(3,4-dimethoxyphenyl)-3-fluoroallylamine (**2**) showed a B/A selectivity of about 100.



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Irreversible inhibition of the enzyme resulted from covalent bonding that involved interactions of an enzyme-associated nucleophile with a reactive intermediate derived from the 3-haloallylamine moiety.[6] The 3-haloallylamines are also effective irreversible inhibitors of CAO.[8]

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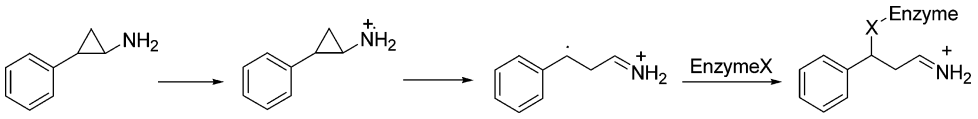
Scheme 1. Proposed Mechanism for Inactivation of MAO by Cyclopropylamines[6]



The above brief survey reveals the frequent use of either a cyclopropyl ring or a halogen substituent as a potentially reactive site on the amine side chain. In the present study, we have combined the dual features of the cyclopropyl ring and fluorine in a series of tranylcypromine analogues and have investigated their inhibitory activities toward amine oxidases. It is well documented that fluorine substitution alters the physiological behavior of bioactive compounds[9] and has pronounced effects on chemical properties of molecules. Relevant to this study, substitution of fluorine increases the strain energy of the cyclopropane ring,[10] and involvement of mechanisms based on cyclopropyl ring opening (Scheme 1) could be favored by this substitution. In addition, the effects of fluorine substitution on interaction with the active site through steric or electronic effects are of interest.

We have synthesized two series, 2-fluoro-2-phenylcyclopropylamines (analogues of tranylcypromine) and (2-fluoro-2-phenylcyclopropyl)alkylamines, as well as 2-fluoro-1-phenylcyclopropylamine and (2-fluoro-1-phenylcyclopropyl)methylamines, and report herein their activities as inhibitors of tyramine oxidase, a copper-containing monoamine oxidase. The influence of para substituents and the different activity of enantiomers of "fluorotranylcypromine" will be reported in a following paper. The activities of these compounds as inhibitors of MAO A and B are currently under investigation and will be reported later.

Chemistry

Two different methods of cyclopropanation of fluorinated precursors were used that produced either 2-fluoro-2-phenyl or 2-fluoro-1-phenyl-substituted cyclopropylcarboxylic esters. The ester group was converted either to the amino group or homologous amines by straightforward reactions to give the two series of title compounds that were investigated (Figure 1).

2-Fluoro-2-phenylcyclopropylamines and (2-Fluoro-2-phenylcyclopropyl)alkylamines. We have previously reported the facile addition of ethyl diazoacetate to 1-fluorostyrene to give a 1:1 diastereomeric mixture of ethyl 2-fluoro-2-phenylcyclopropylcarboxylates **10a** and **10b**.[11a] In our earlier reports we also reported the application of the esters to the preparation of variously substituted cyclopropanes, including aminocyclopropanes. We have used this approach in the present work and describe in detail the preparation and structure elucidation of 2-fluoro-2-phenylcyclopropylamines and 2-fluoro-2-(phenylcyclopropyl)alkylamines. Thus, the adducts **10a** and **10b** can be separated either chromatographically or, after saponification, by recrystallization of the corresponding carboxylic acids **11a** and **11b**. Curtius degradation to the Boc-protected amines **12a** and **12b** and deprotection with HCl produced the fluorinated analogues of tranylcypromine as hydrochlorides **6a** and **6b** (Scheme 2).[11]

Esters **10a** and **10b** also served as starting materials for the preparation of the homologous fluorinated amines **7** and **8**. After saponification, the carboxylic acids **11a** and **11b** were transformed to the primary carboxamides **9a** and **9b** via in situ formation of the acid chlorides and treatment with concentrated aqueous ammonia. Reduction of the carboxamides with borane and precipitation with HCl gave the amine hydrochlorides **7a** and **7b** (Scheme 3). In contrast, reaction of the cis-configured carboxamide **9b** with $LiAlH_4$ in diethyl ether occurred with simultaneous reduction of the carboxamide and fluorine moiety to give the nonfluorinated cyclopropylmethylamine, which was isolated as the hydrochloride **7c**. The identities of the carboxamides **9a** and **9b** have been proved by X-ray structural analyses.[11b] The X-ray structure of compound **7a** is given in the Supporting Information.

The next higher homologues were prepared by reduction of the ethyl carboxylates **10a** and **10b**, subsequent tosylation of the alcohols **13a** and **13b** to form **14a** and **14b**, and nucleophilic substitution of the tosyl group by cyanide to form **15a** and **15b**. Reduction of the cyano

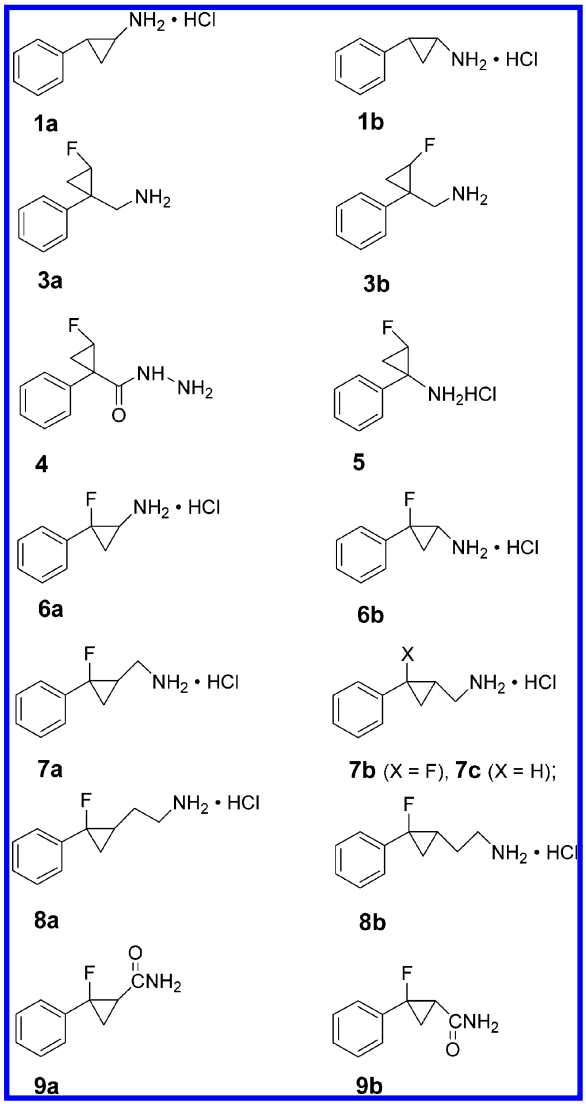
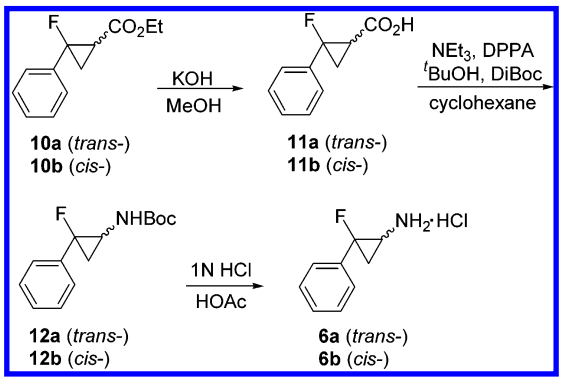
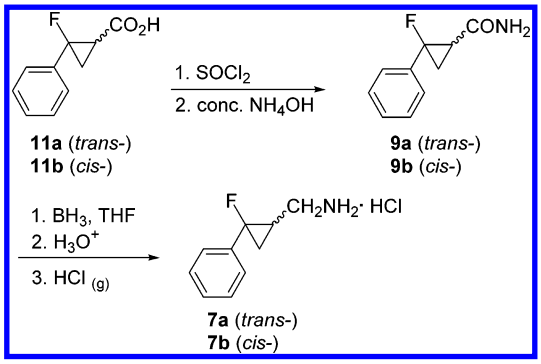


Figure 1. Compounds under investigation.

Scheme 2

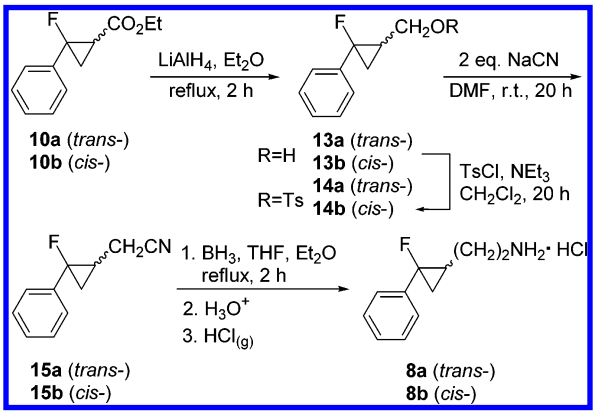


Scheme 3



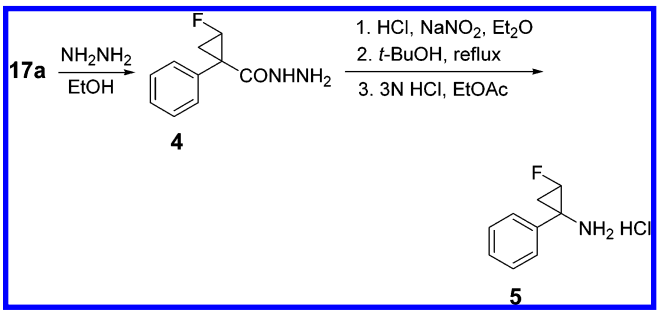
group with borane gave the amines **8a** and **8b**, which were isolated by precipitation of the hydrochlorides (Scheme 4). The configuration of **14b** was proved by X-ray structural analysis (cf. Supporting Information).

Scheme 4



2-Fluoro-1-phenylcyclopropylamine and (2-Fluoro-1-phenylcyclopropyl)methylamines. 2-Fluoro-1-phenylcyclopropylamine and (2-fluoro-1-phenylcyclopropyl)methylamines were available from ethyl 3-fluoro-2-phenylacrylates **16a** and **16b** according to our recent protocol by cyclopropanation with diazomethane.[12] Subsequent reduction of **17a** and **17b** to the corresponding

Scheme 6



cyclopropylmethanols **18a** and **18b**, mesylation to **19a** and **19b**, and nucleophilic displacement of the mesyl group by ammonia gave the desired methylamines **3a** and **3b** (Scheme 5).

The cyclopropylamine **5** was also prepared from the carboxylic ester **17a**. After conversion to the hydrazide **4**, the amine was obtained by Hoffmann degradation[12] (Scheme 6).

Tyramine Oxidase Characterization. Tyramine oxidase, purchased from Sigma, is sold as a flavin-containing amine oxidase (EC, 1.4.3.4). However, the properties of this enzyme are quite different from the properties of flavin-containing monoamine oxidases previously reported by many researchers. Wouters et al. suspected that the Sigma tyramine oxidase is a copper-containing amine oxidase on the basis of spectral characteristics, molecular weight, and inhibition profile.[13] We also confirmed the absence of inhibition of the enzyme by clorglyline and (*R*)-deprenyl. In contrast, the enzyme was strongly inhibited by semicarbazide (Figure 2). Activity of this enzyme is also decreased in the presence of diethyldithiocarbamate, which is a strong copper ion chelating agent (Figure 2). All of the results obtained in this study strongly suggest that this enzyme is a copper-containing amine oxidase (CAO).

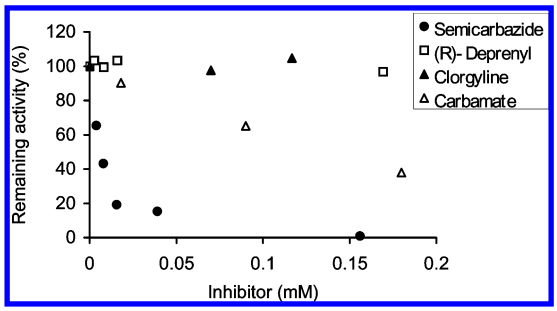
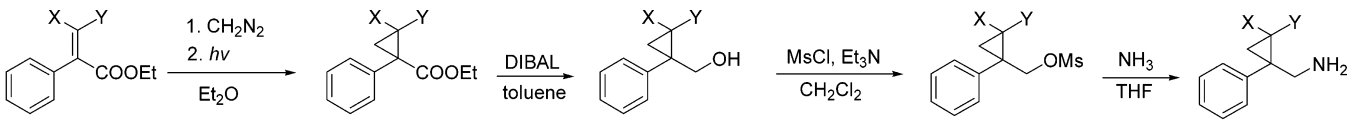


Figure 2. Concentration-dependent effect of different inhibitors on tyramine oxidase activity.

Previous investigations have shown that the CAO of bovine serum,[14] *Escherichia coli*,[15] *Arthrobacter globiformis*,[16] porcine plasma, porcine kidney, and pea seedlings[17] contains an organic cofactor, the quinone of 2,4,5-trihydroxyphenylalanine (topa), which is impor-

Scheme 5



tant for its catalytic activity. On the other hand, the CAO of *Arthrobacter* P1 was reported to contain pyrroloquinoline quinone as the organic cofactor.[18] The ultraviolet spectrum of the Sigma tyramine oxidase in question displays a maximum at 410 nm and a shoulder at around 470−480 nm. Moreover, addition of phenylhydrazine (4 μM) to the enzyme solution resulted in an increase of an absorption peak at 435 nm. All CAOs have a peak around 480 nm in the visible spectrum,[19] and amine oxidases containing topa quinone react with phenylhydrazine to produce an absorption band at 430−440 nm.[14,17,20] These results suggest that the Sigma tyramine oxidase is a copper/topa quinone type amine oxidase. However, direct evidence has not been obtained yet as to the nature of the cofactor contained in this enzyme.

Inhibition of Tyramine Oxidase by 2-Fluoro-1-phenylcyclopropylamine and (2-Fluoro-1-phenylcyclopropyl)methylamines. The inhibition of tyramine oxidase as a function of concentrations of 2-fluoro-1-phenylcyclopropylamine and 2-fluoro-1-phenylcyclopropylmethylamines was investigated, and IC_{50} values (inhibitor concentration at 50% remaining activity) were determined graphically from the inhibition curves obtained (Figure 3). The IC_{50} values are summarized in Table 1.

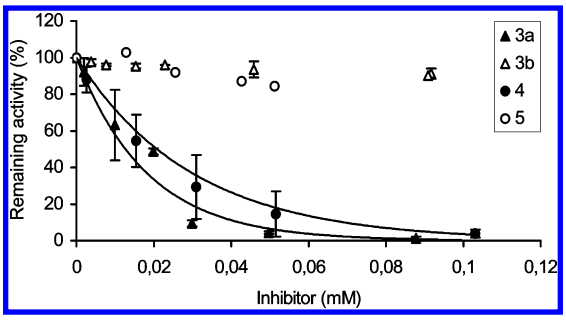


Figure 3. Effect of the concentration of fluorinated phenylcyclopropane carbonylhydrazide (**4**), 2-fluoro-1-phenylcyclopropylamine (**5**), and methlyamines (**3a** and **3b**) on the inhibition of tyramine oxidase.

Table 1. IC_{50} Values and Inhibition Type for 2-Fluoro-1-phenylcyclopropylamines and Methylamines[a]

compd	amine/fluorine relationship	IC_{50} (mM)	inhibition type
3a	trans	0.012 ± 0.001	noncompetitive
3b	cis	0.66 ± 0.21	nd
4	trans	0.020 ± 0.006	irreversible
5	trans	ni	nd
semicarbazide		0.0067 ± 0.0002	nd

[a] ni, no inhibition detected at 0.1 mM scale. nd, not determined.

Compounds **3a** and **4** were both strong inhibitors of tyramine oxidase and had comparable activity. Interestingly, inhibition by compound **3b**, the cis isomer of **3a**, was very low, showing that the configuration of fluorine is important for inhibitory activity. Although 1-phenylcyclopropylamine is known to be a potent inhibitor of flavin-containing MAO,[21,22] compound **5** was a weak inhibitor for the Sigma tyramine oxidase used in this study. To investigate the inhibition manner (reversible or irreversible), compounds **3a** and **4** were assessed by the previously described method of Kitz and Wilson.[23] As a result, the hydrazide **4** resulted in time- and concentration-dependent loss of activity (cf. Figure 10 in the Supporting Information). This result indicates that compound **4** functions as a typical irreversible inhibitor of the enzyme, with 3-fold lower activity than semicarbazide, the classic inhibitor (Table 1). No time- and concentration-dependent inactivation by compound **3a** was observed. However, further kinetic analysis on **3a** showed that inhibition of tyramine oxidase by this compound was noncompetitive, indicating that the enzyme has a separate binding site for this compound (cf. Figure 11 in the Supporting Information).

Inhibition of Tyramine Oxidase by 2-Fluoro-2-phenylcyclopropylamines and (2-Fluoro-2-phenylcyclopropyl)alkylamines. The inhibition of tyramine oxidase as a function of varying concentrations of 2-fluoro-2-phenylcyclopropylamines and (2-fluoro-2-phenylcyclopropyl)alkylamines was also examined (Figures 4 and 5 and Table 2).

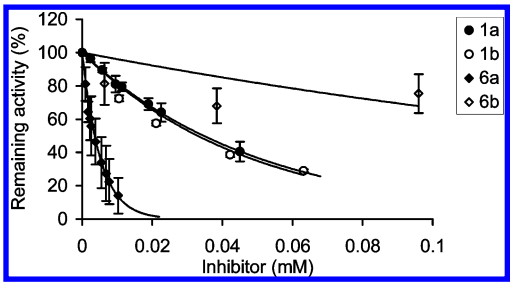


Figure 4. Effect of the concentration of phenylcyclopropylamines (**1a** and **1b**) and 2-fluoro-2-cyclopropylamines (**6a** and **6b**) on the inhibition of tyramine oxidase.

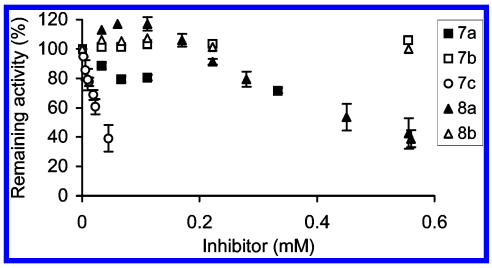


Figure 5. Effect of the concentration of 2-fluoro-2-phenylcyclopropylalkylamines (**7a**, **7b**, **8a**, and **8b**) on the inhibition of tyramine oxidase.

Table 2. IC_{50} Values and Inhibition Type for 2-Fluoro-2-phenylcyclopropylamines and Methylamines[a]

compd	isomer type	amine/fluorine relationship	IC_{50} (mM)	inhibition type
1a	trans		0.035 ± 0.006	competitive
1b	cis		0.033 ± 0.001	irreversible
6a	trans	cis	0.0036 ± 0.0015	competetive
6b	cis	trans	0.19 ± 0.09	irreversible (weak)
7a	trans	cis	1.24 ± 0.06	uncompetitive
7b	cis	trans	ni	nd
7c	cis	−	0.033 ± 0.007	nd
8a	trans	cis	0.49 ± 0.09	competitive
8b	cis	trans	ni	nd
9a	trans	cis	ni	nd
9b	cis	trans	ni	nd

[a] ni, no inhibition detected at millimolar concentrations. nd, not determined.

Compound **6a**, with a cis arrangement of fluorine and the amino group, was a very potent inhibitor, having an IC_{50} value 10 times lower than the values for the nonfluorinated compounds **1a** (tranylcypromine) and its cis isomer **1b**. In contrast, the other diastereomer **6b**

was less active by more than 1 order of magnitude compared to **6a** and about 6 times less active compared to **1a** or **1b**. This observation may have mechanistic implications as discussed below. Looking to the homologues of **6a** and **6b**, the *trans*-methylamine **7a** is about 3 orders of magnitude less active than **6a** and the *trans*-ethylamine **8a** is about 2 orders of magnitude less active than **6a**. The corresponding cis isomers **7b** and **8b** did not show any inhibition on the millimolar scale (Figure 5). These results suggest that the presence of the free amino group, directly bonded to the cyclopropane ring, and a fluorine atom in the cis configuration relative to the amino group are structural features that increase tyramine oxidase inhibition. Kinetic analysis (cf. Figure 12 in the Supporting Information) showed that both compounds **1a** and **6a** functioned as competitive inhibitors of tyramine oxidase (Table 2). This indicates that the mechanism for the inhibition of tyramine oxidase by these compounds is different from that of monoamine oxidase, which has been shown to be irreversibly inhibited by 2-phenylcyclopropylamine (**1a**).[24]

Discussion

In this study, we found that the compounds **3a**, **4**, and **6a** are noncompetitive, irreversible, and competitive inhibitors for tyramine oxidase, respectively. In addition, we confirmed that tranylcypromine **1a**, which is well-known as an irreversible inhibitor of the flavin-containing MAO,[7] is a reversible and competitive inhibitor of tyramine oxidase. A comparison of the activities of **1a** and **6a**, all competitive inhibitors, indicates that the presence of fluorine has a strong influence on activity, depending on its relative configuration to the amino group. Thus, a cis relationship of fluorine and the amino group (**6a**) greatly enhances activity whereas fluorine trans to the amine (**6b**) substantially decreases activity.

Details of the mechanism for the oxidation of amines by copper/topa quinone amine oxidase from *Arthrobacter globiformis* have been proposed in a recent report.[25] The catalytic reaction of amine oxidase proceeds by a ping-pong transamination mechanism consisting of an initial oxidative deamination of the substrate and a subsequent two-electron reduction of molecular oxygen to hydrogen peroxide. In the initial deamination, the organic cofactor, topa, forms a covalent adduct with the amine substrate as a Schiff base. The phenylhydrazone derivatives of topa quinone were identified in the active center of copper-containing amine oxidases incubated with phenylhydrazine.[17] Carbazide **4** presumably also forms a covalent adduct with topa quinone that results in the irreversible inhibition of tyramine oxidase.

As noted above, CAOs are efficiently inhibited by chelating compounds. With this in mind, it is intriguing to consider the facility with which C−F bonds can interact with metal ions.[26] Chelation of copper with fluorine and amine in a cis relationship leading to a favored five-menbered chelate would offer a possible explanation of the effectiveness of these compounds as inhibitors (Figure 6). Such chelation of course is absent in both of the nonfluorinated tranylcypromines **1a** and **1b**, a fact that could explain the almost equal inhibitory activities of these isomers. However, structural studies of the active site of another CAO suggest caution in

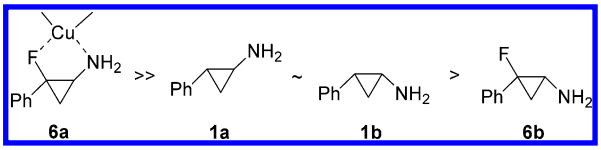


Figure 6. Effect of stereochemistry on proposed chelation of copper ion in the active center and relative order of activity.

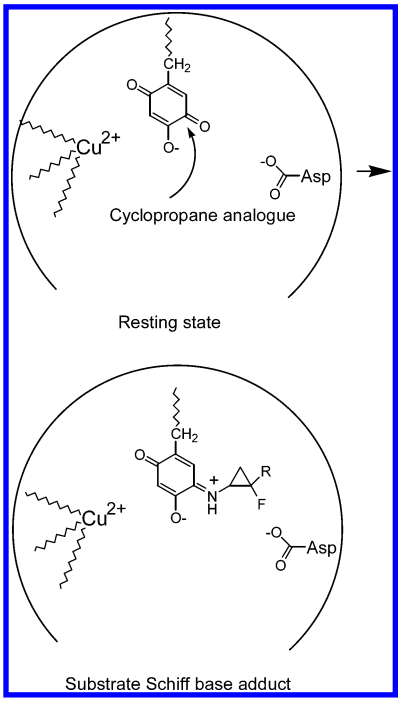


Figure 7. Possible orientation of the adduct in the active site of tyramine oxidase.

proposing chelation of the fluoroamine with copper. Thus, Saysell et al. describes that the 1*S*,2*R*-(+)-trans enantiomer of tranylcypromine is a reversible inhibitor of the topa-quinone copper-containing amine oxidase of *E. coli* (ECAO).[7] In this report, they note that crystallographic studies have shown that the 1*S*,2*R*-(+)-trans enantiomer of tranylcypromine forms an adduct with wild-type ECAO in which the inhibitor is covalently bound at the O-5 position of 2,4,5-trihydroxyphenylalanine (TQP), the site of substrate binding. Other literature reports on the crystal structures of copper enzymes indicate that the copper ion is situated at the opposite site at the O-5 position of topaquinone.[27,28] If our fluorinated compounds bind to O-5 in a manner similar to the binding of tranylcypromine described above, chelation to copper ion would seem to be sterically disfavored (Figure 7). However, the structures of these enzymes are not necessarily the same as that of the tyramine oxidase used in our study.

Multiple roles have been postulated for the conserved aspartate, present in the active site of CAOs during the catalytic cycle, including accepting a proton from the amine substrate during oxidation.[7,27,28] Interaction of fluorine in the proper configuration with this conserved aspartate residue could be considered as contributing to the behavior of the fluorinated analogues (Figure 7), but obviously, much more work will be necessary to clarify the mechanism by which fluorine exerts its influence.

All homologous 2-fluoro-2-phenylcyclopropylalkylamines **7a** and **8a** with the cis configuration of fluorine

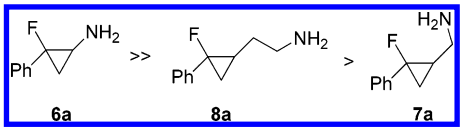


Figure 8. Effect of fluorine in the cis configuration related to the amino group and relative inhibitory activity.

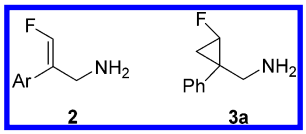


Figure 9. Analogy of compounds **2** and **3a**.

and the aminoalkyl groups are much less active compared to **6a** (Figure 8). This would be consistent with the involvement of chelation, though in this case **7a** would be predicted to be more active than **8a** because of the formation of a more stable six-membered chelate in the former case. We are currently investigating the coordination of these fluoroamines with metal ions. The corresponding cis compounds **7b** and **8b** were even less active, showing no activity at millimolar concentrations. Interestingly, the nonfluorinated cis-configured (2-phenylcyclopropyl)methylamine (**7c**) showed almost identical inhibitory activity compared to *cis*-tranylcypromine (**1b**) (Table 2).

The electronic properties of double bonds and cyclopropane rings are considered similar.[29] Thus, we felt there could be similarities in the activities of amine oxidases. However, compound **2** has been reported to be an irreversible inhibitor of CAO,[8] while we determined that **3a** is a reversible and noncompetitive inhibitor (Figure 9). The greatly decreased activity of **3b** suggests that chelation with copper is not relevant in this series.

Summary

We have prepared two series of fluorine-substituted cyclopropylamines and cyclopropylalkylamines. Our initial examination of these as inhibitors of amine oxidases has been carried out with tyramine oxidase, shown by us and by others to be a copper-containing amine oxidase. We have found that fluorine substitution has a marked affect on the behavior of these compounds as inhibitors of tyramine oxidase, particularly in the 2-fluoro-2-phenyl series. A possible mechanism for the enhanced activity of *trans*-2-fluoro-2-phenylcyclopropylamine relative to the unsubstituted parent tranylcypropmine, as well as to the cis isomer, could involve chelation of copper with the fluorine and amino group in a 1,4-cis relationship. Studies on the metal coordination properties of these analogues are in progress. We are also extending these studies to include analogues variously substituted on the aromatic ring. In addition, the compounds are now being studied as inhibitors of flavin-containing MAO A and MAO B.

Experimental Section

General Methods. ^{1}H (300 MHz), ^{13}C (75 MHz), and ^{19}F (282 MHz) NMR spectra, if not stated otherwise, were recorded on 300 MHz spectrometers, and chemical shifts are reported in ppm relative to TMS or $CFCl_3$. The multiplicities of the ^{13}C signals, other than ^{13}C−^{19}F couplings, were assigned using the DEPT procedure and are designated s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of a doublet), dt (doublet of a triplet), etc. Mass spectra were obtained either by the staff of the Laboratory of Bioorganic Chemistry, NIDDK, NIH, or by the staff of Organisch-Chemisches Institut, Universität Münster. Solvents and other reagents were purchased from Sigma-Aldrich Chemical Co. Elemental analyses were performed either by Atlantic Microlab, Inc. or by the Microanalytical Laboratory of the Organisch-Chemisches Institut, Universität of Münster. Analytical TLC was performed on Kieselgel 60 GF254 (Merck), and flash chromatography was performed with silica gel 60 (230−400 mesh, Merck).

***tert*-Butyl *cis*-(2-Fluoro-2-phenylcyclopropyl)carbamate (12b).** A mixture of *cis*-2-fluoro-2-phenylcyclopropanecarboxylic acid (**11b**), prepared as previously described,[11] (500 mg, 2.78 mmol), dry triethylamine (323 mg, 3.2 mmol), anhydrous *tert*-butyl alcohol (2.06 g, 27.8 mmol), and diphenylphosphorylazide (845 mg, 3.07 mmol) were dissolved in anhydrous cyclohexane (85 mL) under argon. The mixture was refluxed for 18 h, after which time di-*tert*-butyl carbonate (714 mg, 4.1 mmol) was added to the reaction mixture. After heating for an additional 2 h, the mixture was cooled to room temperature. The residue was concentrated under vacuum and diluted with ethyl acetate (70 mL). The organic phase was washed with 5% citric acid, water, saturated $NaHCO_3$, and brine. Nonconverted di-*tert*-butyl carbonate was removed by bulb-to-bulb distillation (60 °C at 1.2×10^{-1} mbar). The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate, 6:1) (yield: 278 mg, 87%). Data for **12b**: mp 123 °C; ^{1}H NMR (CD_3OD) δ 1.31 (9 H, s, CH_3), 1.56 (1 H, ddd, J = 6.0 Hz, J = 8.1 Hz, J = 11.7 Hz, CH_AH$_B$), 1.74 (1 H, ddd, J = 8.1 Hz, J = 9.8 Hz, J = 21.9 Hz, CH$_A$$H_B$), 3.20−3.30 (1 H, m, C$H_X$), 7.30−7.50 (5 H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 18.5 (br s, CH$_A$H$_B$), 28.1 (q, CH$_3$), 34.2 (br s, CH$_X$), 79.9 (s, O−C(CH$_3$)), 81.1 (ds, J = 217.4 Hz, CF), 126.9 (d, aromatic), 128.3 (d, aromatic), 137.7 (ds, J = 20.3, aromatic), 155.7 (s, N−C(O)−O); ^{19}F NMR (CD_3OD) δ −170.05 (m); GC/MS *m*/*z* (%) 249 (1), 230 (1), 195 (4), 177 (7), 175 (4), 151 (12), 150 (9), 148 (14), 130 (66), 103 (16), 77 (10), 59 (32), 57 (100), 51 (9), 41 (49). Anal. ($C_{14}H_{18}FNO_2$) C, H, N.

***cis*-2-Fluoro-2-phenylcyclopropylamine Hydrochloride (6b).** A suspension of *tert*-butyl *cis*-(2-fluoro-2-phenylcyclopropyl)carbamate (**12b**) (145 mg, 0.58 mmol) in 1.2 N aqueous HCl/glacial acetic acid (1:1, 5 mL) was stirred at room temperature for 1 h. After removal of all volatiles, the residue was washed with Et_2O and placed under vacuum. The product was isolated as a white solid (yield: 70 mg, 64%). Data for **6b**: mp >150 °C (dec); ^{1}H NMR (methanol-d_4) δ 1.80−2.05 (2 H, m, C$H_A$$H_B$), 3.44 (1 H, ddd, J = 10.3 Hz, J = 6.0 Hz, J = 14.1 Hz, CH_X), 7.50−7.70 (5 H, m, aromatic); ^{13}C NMR (methanol-d_4) δ 16.3 (dt, J = 12.7 Hz, CH$_A$H$_B$), 33.0 (dd, J = 21.6 Hz, CH$_X$), 80.6 (ds, J = 220.0 Hz, CF), 130.8 (d, aromatic), 131.0 (dd, J = 3.8 Hz, aromatic), 132.1 (d, aromatic), 132.2 (ds, J = 21.6 Hz, aromatic); ^{19}F NMR (methanol-d_4) δ −159.69 (m); MS *m*/*z* (%) 151 (8), 150 (19), 131 (11), 130 (100), 103 (32), 102 (5), 101 (5), 77 (16), 74 (15), 51 (11). Anal. ($C_9H_{11}ClFN$) C, H, N.

***cis*-2-Fluoro-2-phenylcyclopropanecarboxylic Amide (9b).** To a solution of *cis*-2-fluoro-2-phenylcyclopropancarboxylic acid (**11b**) (0.50 g, 2.78 mmol) in benzene (15 mL) thionyl chloride (2.4 g, 20 mmol) was added dropwise. The reaction mixture was heated under reflux for 7−8 h, after which all volatiles were removed by distillation. The resulting residue was dissolved in 1,4-dioxane (10 mL), and the solution was chilled in ice. To this mixture concentrated aqueous NH_4OH (15 mL) was added. The mixture was stirred at 0 °C for 30 min and at room temperature for an additional 30 min. The aqueous phase was then extracted with ethyl acetate (×3), and the combined organic layers were washed two times with saturated NH_4Cl and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was recrystallized from cyclohexane/ethyl acetate (1:2) (yield: 0.41 g, 82%). Data for **9b**: mp 114 °C; ^{1}H NMR (DMSO-d_6) δ 1.66 (1 H, ddd, J = 6.7 Hz, J = 10.3 Hz, J = 20.0 Hz, CH_AH$_B$), 1.76−1.82 (1 H, m, CH$_A$$H_B$), 2.53 (1 H, ddd, J = 7.9 Hz, J = 10.3 Hz, J = 20.3 Hz, CH_X), 7.28−7.44 (5 H, m, aromatic); ^{13}C NMR (DMSO-d_6) δ 14.7 (dt, J = 16.2 Hz, CH$_A$H$_B$), 28.5 (dd, J = 14.0

Hz; *C*H$_X$), 82.9 (ds, J = 216.2 Hz, *C*F), 128.2 (d, aromatic), 128.3 (dd, J = 3.8 Hz, aromatic), 128.9 (d, aromatic), 134.0 (ds, J = 20.4 Hz, aromatic), 168.5 (s, *C*ONH$_2$); ^{19}F NMR (DMSO-d_6) δ −151.88 (m); GC/MS m/z (%) 179 (37), 162 (19), 159 (23), 135 (61), 134 (26), 133 (63), 130 (40), 124 (20), 115 (100), 109 (25), 107 (15), 89 (14), 83 (14), 77 (13), 63 (17), 57 (15), 51 (19), 44 (35), 39 (17); IR (KBr) $\tilde{\nu}$ 3458 (br), 3299 (br), 3168 (m), 1671 (s), 1619 (m), 1507 (w), 1461 (w), 1415 (w), 1349 (w), 1304 (w), 1280 (w), 1187 (m), 954 (w), 885 (m), 874 (m), 777 (m), 750 (w), 703 (s), 624 (m), 573 (m), 550 (m) cm^{-1}. Anal. ($C_{10}H_{10}FNO$) C, H, N. The structure of **9b** was confirmed by X-ray structural analysis.[11b]

***trans*-(±)-2-Fluoro-2-phenylcyclopropanecarboxylic Amide (9a).** The trans amide **9a** was synthesized from *trans*-2-fluoro-2-phenylcyclopropanecarboxylic acid (**11a**) prepared as previously described[11a] (0.50 g, 2.78 mmol) by the same method as described for the cis isomer **9b**. The trans amide was recrystallized from ethyl acetate (yield: 0.41 g, 82%). Data for **9a**: mp 199 °C; ^{1}H NMR (DMSO-d_6) δ 1.53−1.62 (1 H, m, CH$_A$*H*$_B$), 2.00−2.11 (1 H, m, C*H*$_A$H$_B$), 2.16−2.23 (1 H, m, C*H*$_X$), 7.28−7.44 (5 H, m, aromatic); ^{13}C NMR (DMSO-d_6) δ 17.2 (dt, J = 11.5 Hz, *C*H$_A$H$_B$), 30.3 (dd, J = 12.7 Hz, *C*H$_X$), 80.7 (ds, J = 223.8 Hz, *C*F), 124.3 (dd, J = 7.6 Hz, aromatic), 127.9 (d, aromatic), 128.6 (d, aromatic), 138.7 (ds, J = 21.6 Hz, aromatic), 167.1 (ds, J = 2.5 Hz, *C*ONH$_2$); ^{19}F NMR (DMSO-d_6) δ −188.97 (m); GC/MS m/z (%) 179 (50), 162 (26), 159 (23), 135 (83), 134 (28), 133 (64), 130 (39), 124 (21), 115 (100), 109 (25), 107 (14), 89 (10), 83 (13), 77 (12), 63 (10), 57 (10), 51 (14), 44 (27), 39 (11); IR (KBr) $\tilde{\nu}$ 3350 (br), 3174 (br), 3035 (w), 1651 (s), 1462 (m), 1448 (m), 1416 (m), 1344 (m), 1274 (w), 1243 (w), 1141 (m), 1101 (m), 1042 (w), 1031 (w), 1011 (m), 971 (m), 922 (w), 894 (m), 857 (m), 823 (w), 812 (w), 762 (m), 746 (m), 695 (s), 571 (m) cm^{-1}. Anal. ($C_{10}H_{10}FNO$) C, H, N. The structure of **9a** was confirmed by X-ray structural analysis.[11b]

***cis*-(2-Fluoro-2-phenylcyclopropyl)methylamine Hydrochloride (7b).** A 1 M borane/THF solution (4.8 mL) was added to anhydrous THF (10 mL) under argon. The mixture was chilled in an ice bath, and a solution of cis amide **9b** (358 mg, 2 mmol) in dry THF (20 mL) was added dropwise. After the mixture was heated under reflux for 6−7 h, the reaction was quenched by careful addition of 6 M aqueous HCl (10 mL). The THF was removed by distillation at reduced pressure, and the residual aqueous solution was washed with Et$_2$O (×2), neutralized with 40% NaOH, and then extracted with Et$_2$O (×3). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under vacuum until the volume was reduced to about 20 mL. The solution was cooled in an ice bath and gaseous HCl was passed through, leading to immediate precipitation of a white solid. The mixture was stirred for an additional 15 min at 0 °C and then concentrated under vacuum. The product was purified by recrystallization from ethanol/Et$_2$O (1:4) to give **7b** as a white solid (yield: 204 mg, 51%). Data for **7b**: mp >230 °C; ^{1}H NMR (CD$_3$OD, 600 MHz) δ 1.49 (1 H, ddm, J = 7.5 Hz, J = 9.7 Hz, CH$_A$*H*$_B$), 1.64 (1 H, ddd, J = 7.5 Hz, J = 10.9 Hz, J = 19.1 Hz, C*H*$_A$H$_B$), 1.96−2.05 (1 H, m, C*H*$_X$), 2.06−2.10 (1 H, m, C*H*$_2$NH$_3^+$), 3.09−3.12 (1 H, m, C*H*$_2$NH$_3$), 4.86 (3 H, s, N*H*$_3^+$), 7.42−7.50 (5 H, m, aromatic); ^{13}C NMR (CD$_3$OD) δ 15.7 (dt, J = 12.7 Hz, *C*H$_A$H$_B$), 22.9 (dd, J = 22.9 Hz, *C*H$_X$), 40.8 (t, *C*H$_2$NH$_3^+$), 83.1 (ds, J = 214.9 Hz, *C*F), 129.5 (dd, J = 3.8 Hz, aromatic), 130.2 (d, aromatic), 130.7 (dd, ^4J = 2.5 Hz, aromatic), 135.4 (ds, J = 20.3 Hz, aromatic); ^{19}F NMR (CD$_3$OD, 564.3 MHz) δ −160.57 (ddm, J = 9.7 Hz, J = 19.1 Hz); MS/ESI m/z (%) 166 (15), 149 (100), 129 (28); IR (NaCl) $\tilde{\nu}$ 3116 (br), 3000 (s), 2975 (s), 2898 (s), 2688 (w), 1953 (br), 1599 (m), 1579 (m), 1490 (s), 1454 (s), 1401 (w), 1336 (m), 1210 (s), 1186 (w), 1105 (w), 1069 (w), 1042 (w), 1029 (w), 980 (w), 944 (w), 884 (m), 872 (m), 810 (w), 770 (s), 702 (s), 600 (w) cm^{-1}. Anal. ($C_{10}H_{13}ClFN$) C, H, N. ^{1}H−^{1}H COSY supported the analysis results of ^{1}H NMR.

***trans*-(2-Fluoro-2-phenylcyclopropyl)methylamine Hydrochloride (7a).** The trans methylamine **7a** was synthesized from *trans*-2-fluoro-2-phenylcyclopropanecarboxylic amide (**9a**) (358 mg, 2 mmol) by the same method as described for the cis isomer **7b** (yield: 206 mg, 51%). Data for **7a**: mp 160 °C; ^{1}H NMR (methanol-d_4, 600 MHz) δ 1.42−1.57 (2 H, m, C*H*$_A$*H*$_B$), 1.68−1.79 (1 H, m, C*H*$_X$), 3.21−3.35 (2 H, m, C*H*$_2$NH$_3^+$), 4.75 (3 H, s, N*H*$_3^+$), 7.32−7.42 (5 H, m, aromatic); ^{13}C NMR (methanol-d_4, MHz) δ 19.5 (dt, J = 12.4 Hz, *C*H$_A$H$_B$), 23.9 (dd, J = 11.0 Hz, *C*H$_X$), 40.0 (dd, J = 8.5 Hz, *C*H$_2$NH$_3^+$), 82.6 (ds, J = 218.2 Hz, *C*F), 126.0 (dd, J = 5.5 Hz, aromatic), 129.4 (d, aromatic), 129.9 (d, aromatic), 139.6 (ds, J = 21.0 Hz, aromatic); ^{19}F NMR (methanol-d_4, 564.3 MHz) δ −190.65 (m); MS/ESI m/z (%) 166 (12), 149 (100), 129 (34); IR (NaCl) $\tilde{\nu}$ 3043 (br), 3006 (s), 2960 (s), 2920 (s), 2578 (w), 2485 (w), 2014 (br), 1603 (m), 1525 (m), 1453 (m), 1411 (s), 1336 (w), 1228 (m), 1144 (w), 1121 (w), 1079 (w), 1037 (m), 984 (m), 873 (m), 857 (w), 764 (w), 752 (m), 695 (s) cm^{-1}. Anal. ($C_{10}H_{13}ClFN$) C, H, N. ^{1}H−^{1}H COSY supported the analysis results of ^{1}H NMR. The structure of **7a** was confirmed by X-ray structural analysis (cf. Supporting Information).

***cis*-(2-Phenylcyclopropyl)methylamine Hydrochloride (7c).** Under an argon atmosphere, LiAlH$_4$ (80 mg, 2.1 mmol) was suspended in absolute THF (3 mL). A solution of the cis amide **9b** (179 mg, 1 mmol) in absolute THF (10 mL) was added dropwise, and the mixture was refluxed for 45 min. After the reaction was carefully quenched with water (2 mL), the resulting white precipitate was filtered and washed with THF. The combined organic layers were dried over Na$_2$SO$_4$. Gaseous HCl was passed through the resulting yellow solution with stirring for 15 min at 0 °C. A white solid precipitated, which was recrystallized from Et$_2$O/ethanol (3:1) to give **1b** (yield: 50 mg, 27%). Data for **7c**: mp 217−217.5 °C; ^{1}H NMR (DMSO-d_6) δ 0.96−1.11 (2 H, m, C*H*$_A$*H*$_B$), 1.34−1.38 (1 H, m, Ph−C*H*), 2.01−2.09 (1 H, m, C*H*−CH$_2$NH$_3^+$), 2.75−2.92 (2 H, m, CH$_2$NH$_3^+$), 7.11−7.28 (5 H, m, aromatic); ^{13}C NMR (DMSO-d_6) δ 14.3 (t, *C*H$_A$H$_B$), 20.2 (d, Ph−*C*H), 21.8 (d, *C*H−CH$_2$-NH$_3^+$), 42.8 (t, *C*H$_2$NH$_3^+$), 125.7 (d, aromatic), 126.1 (d, aromatic), 128.3 (d, aromatic), 142.0 (s, aromatic); MS m/z (%) 185/183 (0.3/1), 147 (5), 130 (8), 129 (16), 115 (34), 106 (100), 104 (21), 99 (7), 91 (25), 78 (21), 77 (19), 65 (9), 63 (10), 56 (24), 51 (16).

***cis*-(2-Fluoro-2-phenylcyclopropyl)methyl Tosylate (14b).** To an ice-cooled solution of *cis*-(2-fluoro-2-phenylcyclopropyl)methanol (**13b**) (0.60 g, 3.6 mmol), prepared as previously described,[30] and triethylamine (0.73 mg, 7.2 mmol) in anhydrous CH$_2$Cl$_2$ (20 mL) was added slowly a solution of 4-toluenesulfonyl chloride (0.82 g, 4.3 mmol) in anhydrous CH$_2$Cl$_2$ (10 mL). The solution was allowed to warm to room temperature and stirred for 24 h. The organic phase was poured into a mixture consisting of ice (15 g) and concentrated HCl (5 mL). The organic layer was washed with water (×2) and dried over MgSO$_4$. After removal of all volatiles under vacuum, the resulting residue was recrystallized from pentane/Et$_2$O (6:1) to give the tosylate **14b** as a white solid (yield: 0.95 g, 82%). This product was stable at −20 °C but decomposed at room temperature. Data for **14b**: mp 72 °C; ^{1}H NMR (CDCl$_3$) δ 1.14−1.22 (1 H, m, CH$_A$*H*$_B$), 1.49−1.61 (1 H, m, C*H*$_A$H$_B$), 1.94−2.12 (1 H, m, C*H*$_X$), 2.42 (3 H, s, C*H*$_3$), 3.60−3.75 (2 H, m, C*H*$_2$O), 7.25−7.93 (9 H, m, aromatic); ^{13}C NMR (CDCl$_3$) δ 14.0 (dt, J = 11.5 Hz, *C*H$_A$H$_B$), 21.5 (q, *C*H$_3$), 22.8 (dd, J = 16.5 Hz, *C*H$_X$), 69.3 (dt, *C*H$_2$O), 81.9 (ds, J = 216.2 Hz, *C*F), 127.7 (d, aromatic), 128.2 (dd, J = 3.8 Hz, aromatic), 128.6 (d, aromatic), 129.2 (dd, J = 2.5 Hz, aromatic), 129.7 (d, aromatic), 133.1 (s, aromatic), 133.5 (ds, J = 20.4 Hz, aromatic), 144.7 (s, aromatic); ^{19}F NMR (CDCl$_3$) δ −160.01 (m); MS m/z (%) 322 (1), 301 (1), 283 (1), 263 (1), 190 (1), 165 (2), 155 (29), 148 (100), 135 (29), 133 (38), 128 (30), 115 (56), 105 (49), 91 (72), 77 (22), 75 (48), 57 (32), 51 (23); IR (NaCl) $\tilde{\nu}$ 3066 (w), 3045 (w), 2993 (w), 1604 (m), 1506 (w), 1462 (m), 1413 (w), 1360 (s), 1336 (m), 1310 (w), 1293 (w), 1262 (w), 1194 (s), 1180 (s, ν(SO$_3$)), 1119 (w), 1098 (m), 1074 (m), 938 (s), 827 (s), 808 (m), 793 (m), 758 (m), 694 (s), 668 (s), 574 (s), 556 (s), 522 (m), 489 (s). Anal. ($C_{17}H_{17}FO_3S$) C, H. The structure of **14b** was confirmed by X-ray structural analysis (cf. Supporting Information).

***trans*-(2-Fluoro-2-phenylcyclopropyl)methyl Tosylate (14a).** The trans tosylate **14a** was synthesized from *trans*-(2-fluoro-2-phenylcyclopropyl)methanol (**13a**)[30] (0.60 g, 3.6 mmol)

by the same method as described for the cis isomer **14b** (yield: 0.91 g, 79%). Data for **14a**: mp 63 °C; ^{1}H NMR ($CDCl_3$) δ 1.24−1.40 (2 H, m, CH_AH_B), 1.59−1.71 (1 H, m, CH_X), 2.42 (3 H, s, CH_3), 4.20−4.45 (2 H, m, CH_2O), 7.19−7.81 (9 H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 17.9 (dt, J = 12.7 Hz, *C*H$_A$H$_B$), 21.6 (q, *C*H$_3$), 23.4 (dd, J = 11.4 Hz, *C*H$_X$), 69.0 (dt, J = 10.2 Hz, *C*H$_2$O), 80.8 (ds, J = 220.0 Hz, *C*F), 124.7 (dd, J = 6.4 Hz, aromatic), 127.8 (d, aromatic), 128.5 (d, aromatic), 129.8 (d, aromatic), 133.4 (s, aromatic), 137.8 (ds, J = 20.3 Hz, aromatic), 144.7 (s, aromatic); ^{19}F NMR ($CDCl_3$) δ −190.30 (m). MS *m*/*z* (%) 321 (1), 205 (7), 171 (3), 165 (2), 155 (19), 148 (100), 135 (9), 133 (43), 127 (36), 115 (28), 105 (48), 99 (43), 91 (30), 77 (22), 75 (48), 57 (58), 51 (24); IR (NaCl) $\tilde{\nu}$ 3072 (w), 3040 (w), 2964 (w), 2926 (w), 1639 (w), 1618 (w), 1597 (w), 1500 (w), 1457 (m), 1412 (w), 1364 (s), 1336 (m), 1192 (m), 1174 (s), 1099 (w), 1038 (w), 998 (w), 944 (s), 839 (s), 874 (m), 839 (s), 822 (m), 793 (m), 748 (m), 696 (s), 670 (s), 588 (m), 556 (s), 538 (m) cm^{-1}. Anal. ($C_{17}H_{17}FO_3S$) C, H.

***cis*-(2-Fluoro-2-phenylcyclopropyl)acetonitrile (15b).** To a solution of cis tosylate **14b** (0.64 g, 2.0 mmol) dissolved in anhydrous DMF (20 mL) was added NaCN (0.21 g, 4.0 mmol). The solution was stirred at room temperature for 22 h and then poured into 5% aqueous $NaHCO_3$ (50 mL). The solution was extracted with cyclohexane (×4), and the combined organic layer was washed with brine and dried over $MgSO_4$. All volatiles were removed under vacuum, and the residue was purified by silica gel chromatography (cyclohexane/ethyl acetate, 15:1) to give the cis nitrile **15b** as an oil (0.31 g, 89%). (When the reaction was performed at 100 °C cis/trans isomerization was detected by ^{19}F NMR.) Data for **17b**: bp 131−133 °C, 6.5 × 10^{-2} mbar; ^{1}H NMR ($CDCl_3$) δ 1.17−1.25 (1 H, m, CH$_A$*H*$_B$), 1.55−1.70 (1 H, m, C*H*$_A$H$_B$), 1.89−2.13 (3 H, m, C*H*$_X$ and C*H*$_2$CN), 7.37−7.50 (5 H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 15.1 (dt, J = 12.8 Hz, *C*H$_A$H$_B$), 17.4 (t, C*H*$_2$CN), 19.7 (dd, J = 17.8 Hz, C*H*$_X$), 81.6 (ds, J = 217.4 Hz, *C*F), 117.8 (s, *C*N), 128.3 (dd, J = 3.8 Hz, aromatic), 128.8 (d, aromatic), 129.5 (dd, J = 2.5 Hz, aromatic), 133.0 (ds, J = 20.3 Hz, aromatic); ^{19}F NMR ($CDCl_3$) δ −160.99 (m). GC/MS *m*/*z* (%) 175 (9), 154 (5), 135 (100), 115 (64), 109 (12), 83 (7), 77 (7), 75 (7), 63 (7), 51 (9), 39 (6); IR (NaCl) $\tilde{\nu}$ 3094 (m), 3067 (m), 2252 (s), 1608 (w), 1504 (m), 1453 (s), 1419 (s), 1383 (m), 1345 (s), 1298 (m), 1231 (m), 1198 (s), 1133 (m), 1103 (m), 1067 (m), 976 (m), 884 (m), 809 (w), 768 (s), 703 (s), 605 (m) cm^{-1}. Anal. ($C_{11}H_{10}FN$) C, H, N.

***trans*-(2-Fluoro-2-phenylcyclopropyl)acetonitrile (15a).** The trans nitrile **15a** was synthesized from the corresponding trans tosylate **14a** (0.64 g, 2.0 mmol) by the same method as described for the cis isomer **15b** (yield: 0.32 g, 92%). Data for **17a**: bp 113 °C, 7.2 × 10^{-2} mbar; ^{1}H NMR ($CDCl_3$) δ 1.26−1.63 (3 H, m, CH_AH_B and CH_X), 2.69 (2 H, d, J = 6.9 Hz, CH_2-CN), 7.24−7.40 (5 H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 16.1 (dt, J = 10.2 Hz, *C*H$_A$H$_B$), 18.9 (dt, J = 11.4 Hz, *C*H$_2$CN), 20.9 (dd, J = 11.5 Hz, *C*H$_X$), 80.2 (ds, J = 222.0 Hz, *C*F), 118.4 (s, *C*N), 124.6 (dd, J = 6.4 Hz, aromatic), 128.2 (d, aromatic), 128.6 (d, aromatic), 137.6 (ds, J = 21.6 Hz, aromatic); ^{19}F NMR ($CDCl_3$) δ −190.69 (m); GC/MS *m*/*z* (%) 175 (12), 155 (7), 147 (8), 135 (100), 115 (57), 109 (13), 83 (6), 77 (7), 63 (7), 51 (9), 39 (6); IR (NaCl) $\tilde{\nu}$ 3093 (m), 3066 (m), 3036 (m), 2970 (w), 2935 (w), 2254 (s), 1607 (m), 1502 (s), 1456 (s), 1421 (s), 1399 (m), 1318 (m), 1291 (m), 1242 (s), 1116 (s), 1080 (m), 1057 (w), 1034 (s), 1006 (s), 880 (m), 802 (w), 758 (s), 699 (s), 623 (m). Anal. ($C_{11}H_{10}FN$) C, H, N.

***cis*-(2-Fluoro-2-phenylcyclopropyl)ethylamine Hydrochloride (8b).** To a solution of *cis*-(2-fluoro-2-phenylcyclopropyl)acetonitrile (**15b**) (175 mg, 1 mmol) in anhydrous Et_2O (10 mL) stirred under argon was added slowly a 1 M borane/THF solution (2 mL). The reaction mixture was refluxed for 2 h and cooled to room temperature, and 2 mL of concentrated HCl was added. The mixture was concentrated under vacuum, and the remaining aqueous phase was neutralized with 40% NaOH and extracted with Et_2O (×3). The combined organic layers were dried over Na_2SO_4. The obtained solution was concentrated under vacuum to a volume of 20 mL. Gaseous HCl was passed through this solution at 0 °C. A white solid formed with stirring for 15 min at 0 °C. All volatiles were removed under vacuum. The product was recrystallized from Et_2O/ethanol (4:1) and isolated as a white powder (yield: 56 mg, 26%). Data for **8b**: mp 170 °C; ^{1}H NMR (CD_3OD) δ 1.08−1.28 (2 H, m, CH_AH_B), 1.42−1.80 (3 H, m, CH_XCH_2), 2.80−2.96 (2 H, m, CH_2-NH_3^+), 4.88 (3 H, s, NH_3^+), 7.36−7.47 (5 H, m, aromatic); ^{13}C NMR (CD_3OD) δ 15.9 (dt, J = 13.0 Hz, CH$_A$H$_B$), 22.9 (dd, J = 15.1 Hz, *C*H$_X$), 28.0 (t, CH$_X$*C*H$_2$), 40.1 (t, *C*H$_2$NH$_3^+$), 83.3 (ds, J = 221.4 Hz, *C*F), 129.0 (d, aromatic), 129.8 (d, aromatic), 129.9 (d, aromatic), 136.5 (ds, J = 23.0 Hz, aromatic); ^{19}F NMR (CD_3OD) δ −161.31 (m); MS/ESI *m*/*z* (%) 180 (100), 163 (7), 160 (66), 143 (12), 132 (11), 117 (53); IR (KBr) $\tilde{\nu}$ 3057−2901 (br), 2583 (w), 2494 (w), 2032 (br), 1620 (m), 1607 (m), 1527 (m), 1475 (w), 1457 (m), 1385 (w), 1344 (w), 1322 (w), 1265 (m), 1202 (m), 1176 (m), 1068 (w), 1018 (m), 982 (w), 905 (m), 867 (m), 767 (s), 702 (s), 604 (w) cm^{-1}.

***trans*-(2-Fluoro-2-phenylcyclopropyl)ethylamine Hydrochloride (8a).** *trans*-(2-Fluoro-2-phenylcyclopropyl)ethylamine hydrochloride (**8a**) was synthesized from the corresponding trans nitrile **15a** (175 mg, 1 mmol) by the same method as described for the cis isomer **8b** (yield: 75 mg, 35%). Data for **8a**: mp 175 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.19−1.28 (1 H, m, CH$_A$*H*$_B$), 1.33−1.39 (1 H, m, C*H*$_A$H$_B$), 1.42−1.50 (1 H, m, C*H*$_X$), 1.85−2.01 (2 H, m, CH$_X$C*H*$_2$), 2.81−2.98 (2 H, m, C*H*$_2$NH$_3^+$), 3.40 (3 H, s, N*H*$_3^+$), 7.27−7.41 (5 H, m, aromatic); ^{13}C NMR (DMSO-d_6), δ 19.3 (dt, J = 10.2 Hz, *C*H$_A$H$_B$), 23.0 (dd, J = 11.4 Hz, *C*H$_X$), 25.5 (dt, J = 7.6 Hz, CH$_X$*C*H$_2$), 38.7 (t, *C*H$_2$NH$_3^+$), 81.3 (ds, J = 216.2 Hz, *C*F), 124.0 (dd, J = 6.8 Hz, aromatic), 127.5 (d, aromatic), 128.6 (d, aromatic), 139.6 (ds, J = 21.6 Hz, aromatic); ^{19}F NMR (DMSO-d_6) δ −192.31 (m); GC/MS *m*/*z* (%) 179 (5), 162 (2), 155 (12), 149 (10), 147 (9), 135 (9), 125 (11), 115 (12), 109 (18), 99 (60), 97 (33), 95 (22), 91 (7), 83 (58), 78 (21), 77 (15), 71 (68), 69 (72), 60 (44), 57 (100), 55 (100), 51 (16); IR (KBr) $\tilde{\nu}$ 3031−2976 (br), 2035 (br), 1600 (w), 1499 (s), 1454 (m), 1305 (w), 1242 (w), 1148 (w), 1119 (w), 1072 (m), 1031 (w), 1015 (w), 988 (w), 913 (w), 753 (s), 697 (s), 616 (m), 536 (w) cm^{-1}. ^{1}H−^{1}H COSY and ^{1}H−^{13}C correlation spectra supported the analysis results of ^{1}H NMR and ^{13}C NMR.

***trans*- and *cis*-(2-Fluoro-1-phenylcyclopropyl)methanol (18a, 18b).** A mixture of ethyl *trans*- and *cis*-(2-fluoro-1-phenyl-cyclopropane)carboxylate (**17a**, **17b**) (2 g, 9.6 mmol), prepared as previously described,[12] was dissolved in anhydrous toluene (20 mL) and stirred at −74 °C. DIBAL was added slowly, and the reaction solution was stirred for 4 h at the same temperature. The cooling bath was removed, and the solution was stirred overnight at room temperature. The solution was then cooled to 0 °C, and a toluene/methanol mixture (1:1) was added slowly. This was followed by the addition of 2 N aqueous HCl, and the mixture was then extracted with ether (×3). The ether layer was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. After evaporation, the obtained residue was purified and cis and trans isomers were separated by silica gel chromatography (ethyl acetate/*n*-hexane, 1:5). The products were obtained as oils (yield: trans isomer **18a**, 1.0 g, 63%; cis isomer **18b**, 0.3 g, 19%). Data for **18a**: ^{1}H NMR ($CDCl_3$) δ 1.17 (1H, ddd, J = 11.1 Hz, J = 6.3 Hz, J = 7.2 Hz, C*H*$_A$H$_B$), 1.31 (1H, ddd, J = 21.9 Hz, J = 7.2 Hz, J = 2.7 Hz, CH$_A$*H*$_B$), 1.62 (1H, broad, −O*H*), 3.49 (1H, dd, J = 11.4 Hz, 2.4 Hz, −C*H*H−OH), 3.56 (1H, d, J = 11.4 Hz, −CH*H*−OH,), 4.69 (1H, ddd, J = 64.8 Hz, J = 6.3 Hz, J = 2.7 Hz, CF*H*), 7.26−7.41 (5H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 15.82 (d, J = 10.3 Hz, *C*H$_A$H$_B$), 33.00 (d, J = 9.2 Hz, Ph(CH$_2$OH)*C*<), 68.12 (d, 2.3 Hz, −*C*H$_2$OH), 74.43 (d, J = 225.0 Hz, FH*C*), 127.71 (s, aromatic), 128.76 (s, aromatic), 130.87 (s, aromatic), 136.79 (d, J = 3.5 Hz, aromatic). ^{19}F NMR ($CDCl_3$, 282 MHz, relative to CF_3COOH), δ −137.03 (ddd, J = 67.1, 24.5, 12.4 Hz); IR (CH_2Cl_2) 3420 (br), 2919 (s), 2849 (s), 2360 (w), 1463 (m), 1036 (m), 701 (m); GC/MS (EI) *m*/*z* 166 (M$^+$), 147, 118, 91. Data for **18b**: ^{1}H NMR ($CDCl_3$) δ 1.29 (1H, ddd, J = 10.8 Hz, J = 7.2 Hz, J = 6.3 Hz, C*H*$_A$H$_B$), 1.35 (1H, ddd, J = 22.8 Hz, J = 7.2 Hz, J = 2.7 Hz, CH$_A$*H*$_B$), 1.64 (1H, broad, −O*H*), 3.91 (1H, dd, J = 11.7 Hz, 1.5 Hz, −C*H*H−OH), 4.04 (1H, d, J = 11.7 Hz, −CH*H*-OH),

4.83 (1H, ddd, J = 64.8 Hz, J = 6.3 Hz, J = 2.7 Hz, CF*H*), 7.24−7.37 (5H, m, aromatic); ^{13}C NMR δ 17.55 (d, J = 10.3 Hz, CH_AH_B), 33.04 (d, J = 10.3 Hz, Ph(CH_2OH)*C*<), 65.64 (d, J = 9.1 Hz, −*C*H_2OH), 77.73 (d, J = 226.8 Hz, FH*C*), 127.38 (s, aromatic), 128.85 (s, aromatic), 129.02 (d, J = 1.2 Hz, aromatic), 140.19 (s, aromatic); ^{19}F NMR ($CDCl_3$, 282 MHz, relative to CF_3COOH) δ −141.89 (ddd, J = 64.0, 21.4, 9.0 Hz); GC/MS (EI) m/z 166 (M^+), 147, 118, 91.

***trans*-(2-Fluoro-1-phenylcyclopropyl)methyl Mesylate (19a).** Triethylamine (0.38 mL, 2.7 mmol) and methanesulfonyl chloride (0.15 mL, 1.9 mmol) were added to a CH_2Cl_2 solution (6.6 mL) of compound **18a** (0.3 g, 1.8 mmol). The mixture was stirred at 0 °C for 2 h. The reaction mixture was washed with water, 10% aqueous HCl, saturated $NaHCO_3$, and brine in succession and was dried over $MgSO_4$. Solvent was removed by evaporation, and the residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 2:1). The product was obtained as an oil (yield: 0.37 g, 84%). Data for **19a**: ^{1}H NMR ($CDCl_3$) δ 1.33 (1H, ddd, J = 12.0 Hz, J = 6.3 Hz, J = 7.5 Hz, CH_AH_B), 1.48 (1H, ddd, J = 21.6 Hz, J = 7.5 Hz, J = 3.0 Hz, CH_AH_B), 3.14 (3H, s, −SO_3CH_3), 4.11 (1H, dd, J = 10.8 Hz, J = 2.4 Hz, −C*H*H−OMs), 4.20 (1H, d, J = 11.1 Hz, −CH*H*−OMs), 4.78 (1H, ddd, J = 63.9 Hz, J = 6.3 Hz, J = 3.0 Hz, CF*H*), 7.28−7.43 (5H, m, aromatic); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −214.63 (ddd, J = 64.1, 21.4, 12.1 Hz); IR (CH_2Cl_2) 2919 (s), 2050 (s), 2360 (w), 1472 (m), 1353 (m), 1175 (m), 947 (m).

***trans*-(2-Fluoro-1-phenylcyclopropyl)methylamine (3a).** Mesylate (**19a**) was dissolved in THF, and NH_3 gas was introduced dropwise by using a coldfinger condenser at −74 °C. After the cooling bath was removed, the mixture was stirred overnight at room temperature. The excess NH_3 then was flushed out with N_2, the solvent was removed by evaporation, and 1 N aqueous NaOH and ethyl acetate were added. The product was extracted with ethyl acetate (×3), and the organic layer was washed successively with 1 N NaOH (×3) and brine (×1) and then dried over $MgSO_4$. After removal of the solvent, the product was purified by silica gel chromatography. Elution with ethyl acetate removed impurities, and the target compound was eluted with a mixture ethyl acetate/acetic acid/methanol (10:1:10). Solvent was removed by evaporation, ethyl acetate was added, and the organic layer was washed with 6 N NaOH and brine (×1) and dried over $MgSO_4$. The product was obtained as a clear oil (yield: 82 mg, 57%). Data for **3a**: ^{1}H NMR ($CDCl_3$) δ 1.08 (1H, ddd, J = 10.8 Hz, J = 6.9 Hz, J = 6.3 Hz, CH_AH_B), 1.24 (2H, broad, −NH_2), 1.28 (1H, ddd, J = 21.9 Hz, J = 6.9 Hz, J = 2.7 Hz, CH_AH_B), 2.52 (1H, broad doublet, J = 12.9 Hz, −C*H*H−NH_2), 2.86 (1H, broad doublet, J = 13.5 Hz, −CH*H*−NH_2), 4.62 (1H, ddd, J = 65.1 Hz, J = 6.3 Hz, J = 2.7 Hz, CF*H*), 7.26−7.39 (5H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 16.46 (d, J = 10.3 Hz, *C*H_AH_B), 34.06 (d, J = 8.6 Hz, Ph(CH_2NH_2)*C*<), 49.69 (d, J = 1.7 Hz, −*C*H_2−NH_2), 75.05 (d, J = 225.0 Hz, FH*C*), 127.41 (s, aromatic), 128.61 (s, aromatic), 130.78 (s, aromatic), 137.36 (d, J = 4.0 Hz, aromatic); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −213.458 (ddd, J = 67.1, 24.2, 10.8 Hz); IR (KBr) $\tilde{\nu}$ 3358−3289 (br), 3057−3028(m), 2924 (w), 2861 (w), 1601 (m), 1579 (m), 1497 (m), 1445 (m), 1385 (w), 1366 (w), 1301 (w), 1222 (w), 1131 (w), 1074 (m), 1028 (s), 9555 (w), 918 (w), 875 (w), 847 (w), 807 (s), 765 (s), 702 (s), 639 (w), 611 (s) cm^{-1}; HRMS (FAB^+) calcd for $C_{10}H_{13}NF$ (M^+H^+) m/z = 166.1032, found 166.1035.

***cis*-(2-Fluoro-1-phenylcyclopropyl)methyl Mesylate (19b).** The cis isomer **19b** was synthesized from *cis*-(2-fluoro-1-phenylcyclopropyl)methanol (**18b**) (0.2 g, 1.2 mmol) by the same method as described for the trans isomer **19a**. To complete the reaction, the addition of trimethylamine (100 μL, 1.3 mmol) and methane sulfonyl chloride (250 μL, 1.8 mmol) was repeated three times at hourly intervals. Purification was carried out by silica gel chromatography (ethyl acetate/*n*-hexane, 1:5 (v/v) (yield: 0.27 g, 92%). Data for **19b**: ^{1}H NMR ($CDCl_3$) δ 1.36 (1H, dddd, J = 11.4 Hz, J = 7.8 Hz, J = 6.0 Hz, J = 0.9 Hz, CH_AH_B), 1.49 (1H, ddd, J = 23.1 Hz, J = 7.8 Hz, J = 3.0 Hz, CH_AH_B), 2.78 (3H, s, −SO_3CH_3), 4.48 (1H, ddd, J = 11.1 Hz, J = 1.8 Hz, J = 0.9 Hz, −CH*H*−OMs), 4.63 (1H, dd, J = 11.1 Hz, J = 1.8 Hz, −C*H*H−OMs), 4.88 (1H, ddd, J = 63.9 Hz, J = 6.0 Hz, J = 3.0 Hz, CF*H*), 7.28−7.35 (5H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 18.51 (d, J = 10.8 Hz, *C*H_AH_B), 29.94 (d, J = 9.7 Hz, Ph(CH_2OMs)*C*<), 37.44 (s, −SO_3CH_3), 72.91 (d, J = 9.7 Hz, −*C*H_2−OMs), 77.11 (d, J = 229.6 Hz, FH*C*), 128.06 (s, aromatic), 129.07 (s, aromatic), 129.14 (d, J = 28.6 Hz, aromatic), 138.54 (s, aromatic).

***cis*-(2-Fluoro-1-phenylcyclopropyl)methylamine (3b).** The cis isomer **3b** of (2-fluoro-1-phenylcyclopropyl)methylamine was synthesized from mesylate **19b** of the corresponding alcohol by the same method as described for the trans isomer. The reaction was carried out for 5 days (yield: 47.1 mg, 31%). Data for **3b**: ^{1}H NMR ($CDCl_3$) δ 1.13 (1H, ddd, J = 10.5 Hz, J = 6.9 Hz, J = 6.3 Hz, CH_AH_B), 1.22 (1H, ddd, J = 22.5 Hz, J = 6.9 Hz, J = 2.7 Hz, CH_AH_B), 1.48 (2H, broad s, −NH_2), 3.06 (1H, broad, d, 13.8 Hz, −C*H*H−NH_2), 3.13 (1H, broad d, 14.01 Hz, −CH*H*-NH_2), 4.80 (1H, ddd, J = 65.1 Hz, J = 6.3 Hz, J = 2.7 Hz, F*H*C), 7.22−7.37 (5H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 17.98 (d, J = 10.3 Hz, *C*H_AH_B), 34.12 (d, J = 6.3 Hz, Ph(CH_2NH_2)*C*<), 46.40 (d, J = 8.1 Hz, −*C*H_2−NH_2), 77.80 (d, J = 225.6 Hz, FH*C*), 127.32 (s, aromatic), 128.92 (s, aromatic), 129.28 (d, J = 1.74 Hz, aromatic), 140.75 (s, aromatic); IR (KBr) $\tilde{\nu}$ 3301 (br), 3060−2852 (m), 1655 (m), 1561 (m), 1497 (s), 1446 (m), 1382(w), 1259−923 (m), 801 (w), 764 (m), 663 (s), 614 (s) cm^{-1}; HRMS (FAB^+) calcd for $C_{10}H_{13}NF$ (M^+H^+) m/z = 166.1032, found 166.1023. Anal. ($C_{10}H_{12}FN$) C, H, N: C calcd 72.70, found 69.77; N calcd 8.48, found 7.70.

***trans*-2-Fluoro-1-phenylcyclopropane Carboxyhydrazide (4).** A mixture of trans and cis isomers **17a** and **17b** (0.3 g, 1.44 mmol) was added to an ethanol solution (3.9 mL) containing 3.6 mL (74.2 mmol) of hydrazine monohydrate. After the reaction mixture was stirred overnight, the solvent was removed in vacuo. The trans isomer **4** was obtained by crystallization from ethanol (yield: 0.13 g, 45%). Data for **4**: mp 164−166 ° C; ^{1}H NMR (CD_3OD) δ 1.61 (1H, ddd, J = 22.2 Hz, J = 6.6 Hz, J = 3.6 Hz, CH_AH_B), 1.78 (1H, ddd, J = 13.5 Hz, J = 6.6 Hz, J = 6.3 Hz, CH_AH_B), 5.06 (1H, ddd, J = 65.7 Hz, J = 6.3 Hz, J = 3.6 Hz, F*H*C), 7.34−7.43 (5H, m, aromatic); ^{13}C NMR (DMSO-d_6) δ 18.54 (d, J = 8.6 Hz, *C*H_AH_B), 33.72 (d, J = 10.9 Hz, Ph($CONHNH_2$)*C*<), 74.47 (d, J = 227.4 Hz, FH*C*), 127.79 (s, aromatic), 128.48 (s, aromatic), 131.23 (s, aromatic), 133.46 (d, J = 3.5 Hz, aromatic), 169.25 (s, >C=O); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −209.14 (ddd, J = 64.1, 21.4, 12.1 Hz); IR (CH_2Cl_2) 3372 (w), 2919 (s), 2050 (s), 2360 (w), 1685 (s), 1471 (m), 1463 (m), 1357 (w), 1241 (w), 1136 (w), 704 (m) cm^{-1}; HRMS (FAB^+) calcd for $C_{10}H_{12}ON_2F$ (M^+H^+) m/z = 195.0934, found 195.0925. Anal. ($C_{10}H_{11}FN_2O$) C, H, N.

***trans*-2-Fluoro-1-phenylcyclopropylamine Hydrochloride (5).** Hydrazide (**4**) (0.1 g, 0.52 mmol) and water in a 50 mL round-bottom flask were cooled in an ice bath and stirred while 6 N HCl (1.18 mL) was added. A layer of ether (1.0 mL) was added. After a few minutes, a solution of 0.8 mM $NaNO_2$ (0.93 L) was slowly added dropwise. The reaction mixture was stirred an additional 40 min at the same temperature. The mixture was then extracted five times with ether, and the ether solution was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. *tert*-Butyl alcohol (10 mL) was added to the residue, and the solution was refluxed overnight. The reaction mixture was evaporated to give crude carbamates, which was purified by silica gel column chromatography with ethyl acetate/*n*-hexane, 1:5. Purified carbamate was dissolved in 0.5 mL of ethyl acetate, and 3 N HCl (0.5 mL) was added. The mixture was vigorously stirred overnight at room temperature. Solvents were removed in vacuo to give **5** as a white powder (yield: 67.3 mg, 52%). Data for **5**: mp 147−150 °C. ^{1}H NMR (D_2O) δ 1.81 (1H, ddd, J = 12.6 Hz, J = 9.6 Hz, J = 7.2 Hz, CH_AH_B), 1.97 (1H, ddd, J = 23.1 Hz, J = 9.6 Hz, J = 3.6 Hz, CH_AH_B), 5.26 (1H, ddd, J = 62.1 Hz, J = 7.2 Hz, J = 3.6 Hz, F*H*C), 7.53−7.67 (5H, m, aromatic); ^{13}C NMR (D_2O) δ 16.84 (d, J = 10.9 Hz, *C*H_AH_B), 39.26 (d, J = 12.6 Hz, Ph-(NH_2)*C*<), 72.21 (d, J = 228.5 Hz, HF*C*), 129.60 (s, aromatic), 130.45 (s, aromatic), 130.55 (s, aromatic), 130.97 (d, J = 1.9 Hz, aromatic); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −214.48 (ddd, J = 62.6, 24.4, 13.7 Hz); IR (CH_2Cl_2) 2919 (s), 2050 (s), 2360

(w), 1472 (m), 720 (m); HRMS (FAB^+) calcd for $C_9H_{11}NF$ (M^+H^+) m/z = 152.0876, found 152.0869. Anal. ($C_9H_{11}ClFN$) C, H, N, Cl: C calcd 57.61, found 54.62; Cl calcd 18.89, found 18.18.

Enzyme Assay. The enzyme activity was measured spectrophotometrically at 31 °C by the modified method of Houslay[31] using 0.5 mL of standard reaction mixture containing 0.6 mM benzylamine, 0.1 M potassium phosphate buffer (pH 7.2), 6% dimethyl sulfoxide, and tyramine oxidase (commercially available from Sigma). The reaction was monitored at 250 nm, the maximun absorption wavelength of benzaldehyde. The enzyme activity was calculated by using 13 800 M^{-1} cm^{-1} as the extinction coefficient of benzaldehyde at 250 nm. One unit of the enzyme oxidizes 1 μmol of benzylamine to benzaldehyde per 1 min. Protein concentration was determined by the method of Bradford using bovine serum albumin as a standard.[32]

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Supporting Information Available: Figure 10 showing time- and concentration-dependent inactivation of tyramine oxidase by fluorinated phenylcyclopropane carboxyhydrazide **4**, Figure 11 showing the Lineweaver−Burk plot for the inhibition of tyramine oxidase by **3a**, Figure 12 showing the Lineweaver−Burk plot for the inhibition of tyramine oxidase by **1a** and **6a**, Figure 13 showing time- and concentration-dependent inactivation of tyramine oxidase by cis-fluorinated phenylcyclopropane **1b** and **6b**, and X-ray structural data for **7a** and **14b**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Singer, T. P.; Von Korff, R. W.; Murphy, D. L. *Monoamine Oxidase: Structure, Function and Altered Functions*; Academic Press: New York 1979.

(2) Mai, A.; Artico, M.; Esposito, M.; Sbardella, G.; Massa, S.; Befani, O.; Turini, P.; Giovannini, V.; Mondovi, B. 3-(1*H*-Pyrrol-1-yl)-2-oxazolidinones as Reversible, Highly Potent, and Selective Inhibitors of Monoamine Oxidase Type A. *J. Med. Chem.* **2002**, *45*, 1180−1183 and references therein. Fowler, C. J.; Ross, S. B. Selective Inhibitors of Monoamine Oxidase A and B: Biochemical, Pharmacological, and Clinical Properties. *Med. Res. Rev.* **1984**, *4*, 323−358 and references therein.

(3) Hacisalihoglu, A.; Jongejan, J. A.; Duine, J. A. Distribution of Amine Oxidases and Amine Dehydrogenases in Bacteria Grown on Primary Amines and Characterization of the Amine Oxidase from *Klebsiella oxytoca*. *Microbiology* **1997**, *143*, 505−512 and references therein. Klinman, J. P. Mechanisms Whereby Mononuclear Copper Proteins Functionalize Organic Substrates. *Chem. Rev.* **1996**, *96*, 2541−2561 and references therein.

(4) Enrique-Tarancón, G.; Marti, L.; Morin, N.; Lizcano, J. M.; Unzeta, M.; Sevilla, L.; Camps, M.; Palancín, M.; Testar, X.; Carpéné, C.; Zorzano, A. Role of Semicarbazide-Sensitive Amine Oxidase on Glucose Transport and GLUT4 Recruitment to the Cell Surface in Adipose Cells. *J. Biol. Chem.* **1998**, *273*, 8025−8032.

(5) Ferrer, I.; Lizcano, J. M.; Hernández, M.; Unzeta, M. Overexpression of Semicarbazide Sensitive Amine Oxidase in the Cerebral Blood Vessels in Patients with Alzheimer's Disease and Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy. *Neurosci. Lett.* **2002**, *321*, 21−24.

(6) Palfreyman, M. G.; Bey, P.; Sjoerdsman, A. Enzyme-Activated/Mechanism-Based Inhibitors. *Essays Biochem.* **1987**, *23*, 28−81.

(7) Saysell, C. G.; Tambyrajah, W. S.; Murray, J. M.; Wilmot, C. M.; Phillips, S. E. V.; McPherson, M. J.; Knowels, P. F. Probing the Catalytic Mechanism of *Escherichia coli* Amine Oxidase Using Mutational Variants and a Reversible Inhibitor as a Substrate Analogue. *Biochem. J.* **2002**, *365*, 809−816.

(8) Lyles, G. A.; Marshall, C. M. S.; McDonald, I. A.; Bey, P.; Palfreyman, M. G. Inhibition of Rat Aorta Semicarbazide-Sensitive Amine Oxidase by 2-Phenyl-3-haloallylamines and Related Compounds. *Biochem. Pharmacol.* **1987**, *36*, 2847−2853.

(9) Reviews. (a) Kirk, K. L. Fluorine Substituted Neuroactive Amines. In *Selective Fluorination in Organic and Bioorganic Chemistry;* Welch, J. T., Ed.; ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991; pp 136−155. (b) Schlosser, M. The Chemical and Physiological Size of Fluorine. In *Enantiocontrolled Synthesis of Fluoro-Organic Compounds. Stereochemical Challenges and Biomedicinal Targets*; Soloshonok, V. A., Ed.; John Wiley & Sons: Chichester, U.K., 1999; pp 613−659.

(10) Smart, B. E. Characteristics of C−F Systems. In *Organofluorine Chemistry, Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994; pp 57−88.

(11) (a) Meyer, O. G. J.; Fröhlich, R.; Haufe, G. Asymmetric Cyclopropanation of Vinyl Fluorides: Access to Enantiopure Monofluorinated Cyclopropane Carboxylates. *Synthesis* **2000**, 1479−1490. (b) Haufe, G.; Rosen, T. C.; Meyer, O. G. J.; Fröhlich, R.; Rissanen, K. Synthesis, Reactions and Structural Features of Monofluorinated Cyclopropanecarboxylates. *J. Fluorine Chem.* **2002**, *114*, 189−198.

(12) Sloan, M. J.; Kirk, K. L. Synthesis of a Fluorinated Analog of 1-Aminocyclopropane Carboxylic Acid. *Tetrahedron Lett.* **1997**, *38*, 1677−1680. Sloan, M. J.; Kirk, K. L.; Skolnick, P.; Kim, I.-H.; Layer, R. Synthesis of Fluoro-1-amino-carboxylic acids (FACC) and Examination of Its Affinity for the NMDA Receptor. *Proc.−NOBCChE* **2000**, *27*, 89−100.

(13) Wouters, J.; Perpete, P.; Hayen, P.; Anceau, N.; Durant, F. Kinetic Characterization of Tyramine Oxidase of *Arthrobacter* Species. *Biochem. Mol. Biol. Int.* **1994**, *32*, 737−743.

(14) Janes, S. M.; Klinman, J. P. An Investigation of Bovine Serum Amine Oxidase Active Site Stoichiometry: Evidence for an Aminotransferase Mechanism Involving Two Carbonyl Cofactors per Enzyme Dimer. *Biochemistry* **1991**, *30*, 4599−4605.

(15) Cooper, R. A.; Knowles, P. F.; Brown, D. E.; McGuirl, M. A.; Dooley, D. M. Evidence for Copper and 3,4,6-Trihydroxyphenylalanine Quinone Cofactors in an Amine Oxidase from the Gram-Negative Bacterium *Escherichia coli* K-12. *Biochem. J.* **1992**, *288*, 337−340.

(16) Matsuzaki, R.; Fukui, T.; Sato, H.; Ozaki, Y.; Tanizawa, K. Generation of the Topa Quinone Cofactor in Bacterial Monoamine Oxidase by Cupric Ion-Dependent Autooxidation of a Specific Tyrosyl Residue. *FEBS Lett.* **1994**, *351*, 360−364.

(17) Janes, S. M.; Palcic, M. M.; Scaman, C. H.; Smith, A. J.; Brown, D. E.; Dooley, D. M.; Mure, M.; Klinman, J. P. Identification of Topaquinone and Its Consensus Sequence in Copper Amine Oxidases. *Biochemistry* **1992**, *31*, 12147−12154.

(18) Dooley, D. M.; McIntire, W. S.; McGuirl, M. A.; Cote, C. E.; Bates, J. L. Characterization of the Active Site of *Arthrobacter* P1 Methylamine Oxidase: Evidence for Copper−Quinone Interactions. *J. Am. Chem. Soc.* **1990**, *112*, 2782−2789.

(19) Collison, D.; Knowles, P. F.; Mabbs, F. E.; Ruis, F. X.; Singh, I.; Dooley, D. M.; Cote, C. E.; McGuirl, M. A. Studies on the Active Site of Pig Plasma Amine Oxidase. *Biochem. J.* **1989**, *246*, 663−669.

(20) Brown, D. E.; McGuirl, M. A.; Dooley, D. M.; Janes, S. M.; Mu, D.; Klinman, J. P. The Organic Functional Group in Copper-Containing Amine Oxidases. Resonance Raman Spectra Are Consistent with the Presence of Topa Quinone 6-Hydroxydopa Quinone in the Active Site. *J. Biol. Chem.* **1991**, *266*, 4049−4051.

(21) Silverman, R. B.; Zieske, P. A. Mechanism of Inactivation of Monoamine Oxidase by 1-Phenylcyclopropylamine. *Biochemistry* **1985**, *24*, 2128−2138.

(22) Silverman, R. B.; Cesarone, J. M.; Lu, X. Stereoselective Ring Opening of 1-Phenylcyclopropylamine Catalyzed by Monoamine Oxidase-B. *J. Am. Chem. Soc.* **1993**, *115*, 4955−4961.

(23) Kitz, R.; Wilson, I. B. Esters of Methanesulfonic Acid as Irreversible Inhibitors of Acetylcholinesterase. *J. Biol. Chem.* **1962**, *237*, 3245−3249.

(24) Silverman, R. B. Mechanism of Inactivation of Monoamine Oxidase by *trans*-2-Phenylcyclopropylamine and the Structure of the Enzyme−Inactivator Adduct. *J. Biol. Chem.* **1983**, *258*, 14766−14769.

(25) Hirota, S.; Iwamoto, T.; Kishishita, S.; Okajima, T.; Yamauchi, O.; Tanizawa, K. Spectroscopic Observation of Intermediates Formed during the Oxidative Half-Reaction of Cooper/Topa Quinone-Containing Phenylethylamine Oxidase. *Biochemistry* **2001**, *40*, 15789−15796.

(26) (a) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. Activation of Carbon−Fluorine Bonds by Metal Complexes. *Chem. Rev.* **1994**, *94*, 373−431. (b) Plenio, H. The Coordination Chemistry of the C−F Unit in Fluoro Carbons. *Chem. Rev.* **1997**, *97*, 3363−3384.

(27) Li, R.; Klinman, J. P.; Mathews, F. S. Copper Amine Oxidase from *Hansenula polymorpha*: The Crystal Structure Determined at 2.4 Å Resolution Reveals the Active Conformation. *Structure* **1998**, *6*, 293−307.

(28) Mure, M.; Mills, S. A.; Klinman, J. P. Catalytic mechanism of the topa quinone containing copper amine oxidases. *Biochemistry* **2002**, *41*, 9269−9278.
(29) (a) Wiberg, K. B. Structures, energies and spectra of cyclopropanes. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, U.K., 1987; Vol. 1, pp 1−26. (b) Cremer, D.; Kralla, E.; Szabo, K. J. General and theoretical aspects of the cyclopropyl group. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, U.K., 1995; Vol. 2, pp 43−137. (c) Wiberg, K. B. Theoretical Models of Bonding. In *Methods of Organic Chemistry, Houben-Weyl*; de Meijere, A., Ed.; Thieme: Stuttgart, Germany, 1997; Vol. E17a, pp 1−27.
(30) Rosen, T. C.; Haufe, G. Synthesis of Enantiopure Monofluorinated Phenylcyclopropanes by Lipase-Catalyzed Kinetic Resolution. *Tetrahedron: Asymmetry* **2002**, *13*, 1397−1405.
(31) Houslay, M. D.; Tipton, K. F. The Reaction Pathway of Membrane-Bound Rat Liver Mitochondrial Monoamine Oxidase. *Biochem. J.* **1973**, *135*, 735−750.
(32) Bradford, M. M. A Rapid and Sensitive Method for the Quantitation of Microgram Quantities of Protein Utilizing the Principle of Protein−Dye Binding. *Anal. Biochem.* **1976**, *72*, 248−254.

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