5860 *J. Med. Chem.* **2004,** *47,* 5860−5871

Fluorinated Phenylcyclopropylamines. 2. Effects of Aromatic Ring Substitution and of Absolute Configuration on Inhibition of Microbial Tyramine Oxidase

Thomas C. Rosen,[†] Shinichi Yoshida,[‡,§] Roland Fröhlich,[†,||] Kenneth L. Kirk,[‡] and Günter Haufe*,[†]

Organisch-Chemisches Institut, Universität Münster, Corrensstr. 40, D-48149 Münster, Germany, and Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20892

Received January 13, 2004

A series of para-substituted diastereopure *cis*- and *trans*-2-fluoro-2-arylcyclopropylamines were synthesized and these were investigated as inhibitors of microbial tyramine oxidase from *Arthrobacter* sp. All compounds were shown to be competitive inhibitors of this enzyme. The nature of the para-substituents in the more potent trans-isomer (cis-relationship between fluorine and the amino group) of 2-fluoro-2-arylcyclopropylamine influenced the inhibitory potency in a consistent fashion. Thus, electron-withdrawing groups (F, Cl) slightly decreased the activity, while the methyl group (+ I substituent) increased the activity by a factor of ca. 7 compared to *trans*-2-fluoro-2-phenylcyclopropylamine and by a factor of 90 compared to tranylcypromine. Activity also was strongly dependent on the absolute configuration. The (1*S*,2*S*)-enantiomer of 2-fluoro-2-phenylcyclopropylamine was an excellent inhibitor of tyramine oxidase whereas the (1*R*,2*R*)-enantiomer was essentially devoid of activity.

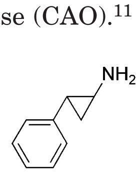
Introduction

Monoamine oxidases, prevalent in mammals, plants and both prokaryontic and eukaryontic microorganisms, catalyze the oxidation of amines to aldehydes. They have been classified into two groups, copper- (EC 1.4.3.6) and flavin-containing amine oxidases (EC 1.4.3.4).[1]

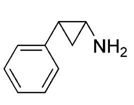
Copper-containing amine oxidases (CAO) are strongly inhibited by semicarbazide and hence are also referred to as semicarbazide-sensitive amine oxidases (SSAO). This property is used to distinguish them from enzymes of the other class, which are inhibited by acetylenic inhibitors, such as clorgyline and deprenyl.[2] They constitute a wide family of enzymes that include beef and sheep plasma amine oxidase, lysil oxidase, diamine oxidase and a tissue-bound oxidase. Different studies have shown that CAOs also contain covalently bound quinones as organic cofactors,[4] an important example of which has been identified as 2,4,5-trihydroxyphenylalanine quinone (TPQ), elaborated from a tyrosine precursor in the polypeptide chain.[3] The crystal structures of CAO of *Escherichia coli*, *Arthrobacter globiformis*, *Hansenula polymorpha* and pea seedling have also been reported, and the mechanism for the oxidation of amines by these enzymes has been discussed in detail.[4]

The copper-containing, semicarbazide-sensitive amine oxidases (CAO) are involved in diverse biological processes such as wound healing, detoxification of amines, cell growth, signaling and apoptosis.[5] Stimulation of these enzymes correlates with an increased glucose uptake.[6] Recently, CAO expression was suggested to be a source of oxidative stress in the blood vessel wall in Alzheimer's disease and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.[7] Yu et al. have proposed that metabolites of CAO-catalyzed deaminations could be implicated in certain diseases.[5] In fact, elevated CAO-activity was found for patients with diabetes mellitus and vascular diseases.[8] Amine oxidases are also implicated in the formation of vascular plaques linked to congestive heart failure.[9]

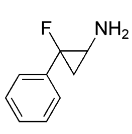
Because of the diverse physiological role of CAOs, selective inhibitors of these enzymes have potential as useful pharmacological and medicinal agents. Tranylcypromine (**1a**, *trans*-2-phenylcyclopropylamine), an analogue of amine substrates of CAOs, was demonstrated to be a potent inhibitor of the enzymes.[10] Since fluorine is well-known to alter the chemistry and biological behavior of organic molecules, we have undertaken an investigation of the effects of fluorocyclopropanes on the activities of amine substrates and inhibitors. As part of this study we recently reported that *trans*-2-fluoro-2-phenylcyclopropylamine (**2a**) is an excellent inhibitor of commercially available tyramine oxidase from *Arthrobacter* sp. Inhibition was reversible and competitive, and the IC_{50} was 10 times lower than that of the nonfluorinated parent, tranylcypromine (**1a**). In this study, we also confirmed earlier reports that the commercial enzyme is a copper-containing amine oxidase (CAO).[11]



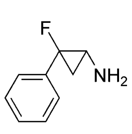
1a



1b



2a



3a

The effects of fluorine substitution were dependent on the geometry of the molecule, in that the cis-isomer **3a** was 50-fold less potent than the trans-isomer **2a**, and

---

* To whom correspondence should be addressed. Phone: +49-251-83-33281. Fax: +49-251-83-39772. E-mail: haufe@uni-muenster.de.

[†] Universität Münster.

[‡] National Institute of Diabetes, and Digestive and Kidney Diseases.

[§] Present address: Industrial Research Institute of Tottori Prefecture, Tottori 689-1112, Japan.

[||] X-ray analysis.

10.1021/jm049957t CCC: $27.50

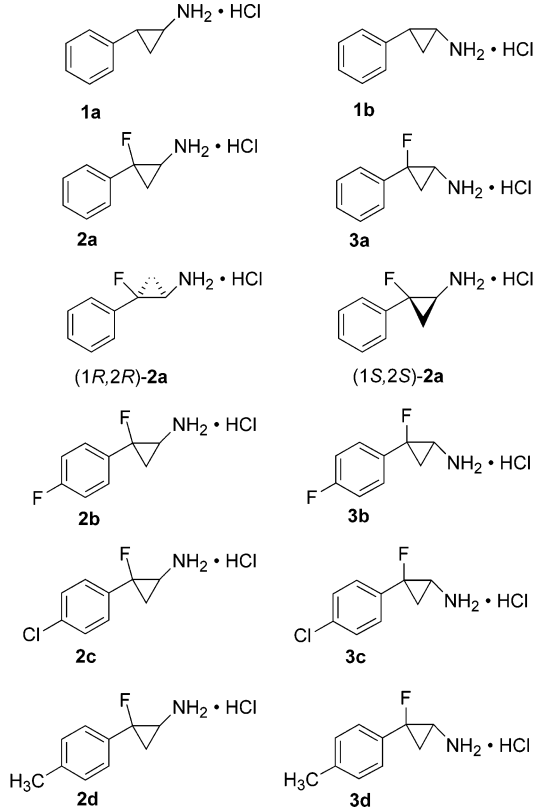


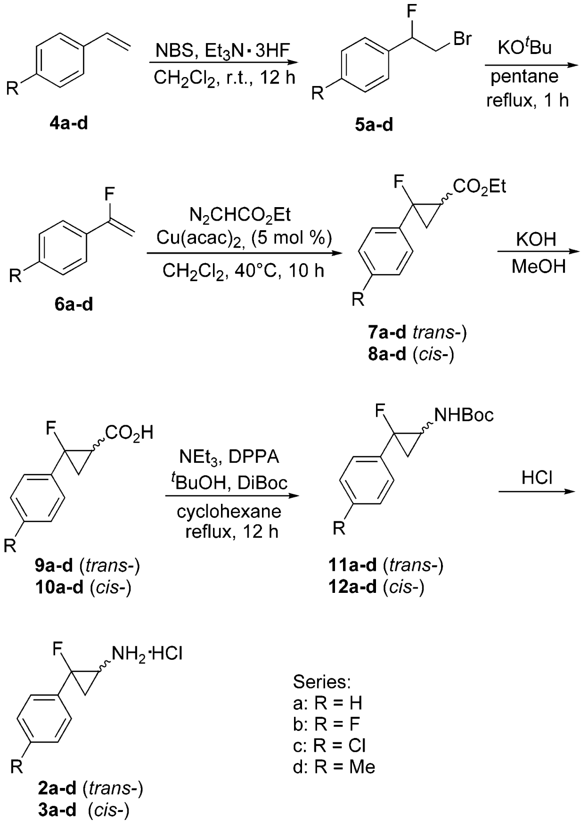
Figure 1. Compounds used in this study.

was 5-fold less potent than **1a** or **1b**. It is interesting to note that the cis-isomer **1b** is essentially equal to its trans-isomer **1a** in inhibitory action, but was shown to be an irreversible inhibitor of the enzyme. Thus, fluorine exerts a positive influence on inhibition of one diastereomer and a negative influence on the other. To explore further the mechanistic aspects of the influence of fluorine substitution, and also to attempt to find even more potent inhibitors, we prepared a series of 2-aryl-2-fluorocyclopropylamines having either electron-donating or electron-withdrawing groups in the para-position of the aromatic ring. In addition, to examine more closely the steric aspects of this inhibition, we prepared the enantiomers of **2a**. In this report we describe the preparation of these compounds and the results of inhibition studies with tyramine oxidase from *Arthrobacter* sp. The compounds investigated in this study are shown in Figure 1.

Results

Chemistry. The protocol that was used to prepare *trans*-2-fluoro-2-phenylcyclopropylamine **2a**[12] was applied also for the preparation of a series of para-substituted analogues. First, bromofluorination of para-substituted styrenes **4b**–**d** according to the published procedure[13] produced 2-bromo-1-fluoro-[1-(4-(para-substituted-phenyl)]ethanes **5b**–**d**. Base-catalyzed elimination of HBr analogous to a known procedure[14] gave the corresponding 1-fluorostyrenes **6b**–**d**. Subsequent Cu(acac)$_2$-catalyzed cyclopropanation of **6b**–**d** with ethyl diazoacetate gave ethyl 2-aryl-2-fluorocyclopropanecarboxylates as 1:1 mixtures of cis- and trans-diastereoisomers **7b**–**d** and **8b**–**d**. Separation by silica gel chromatography yielded diastereopure esters. After saponification, the resulting acids **9b**–**d** and **10b**–**d** were subjected to Curtius rearrangement[15] to give the carbamates **11b**–**d** and **12b**–**d**. Acid-catalyzed hydrolysis converted these carbamates to the target para-substituted 2-aryl-2-fluorocylcopropylamines **2b**–**d** and **3b**–**d** (Scheme 1). In addition to spectroscopic data, X-ray structural analysis of **9b**, **10b** and **10c** confirmed cis/trans configurations at the three-membered ring (Supporting Information).

Scheme 1



Analogous to the procedure used for the resolution of the nonfluorinated counterparts[16] the enantiomers of *trans*-2-fluoro-2-phenylcyclopropane carboxylic acid (**9a**) were separated via diasteromeric amides **13** and **14** formed by reaction of racemic **9a** with (*S*)-1-phenylethylamine. The amides were separated by silica gel chromatography and converted to optically pure (1*R*,2*R*)-(+)-2-fluoro-2-phenylcyclopropanecarboxylic acid (1*R*,2*R*)-**9a** and (1*S*,2*S*)-(−)-2-fluoro-2-phenylcyclopropanecarboxylic acid (1*S*,2*S*)-**9a** by hydrolysis of the corresponding *N*-nitrosamides prepared according to a method described by White.[17] Curtius rearrangement and removal of the Boc group with hydrogen chloride as previously reported for the racemic compound[12] gave (1*S*,2*S*)-(+)-2-fluoro-2-phenylcyclopropylamine hydrochloride (1*S*,2*S*)-**2a** and (1*R*,2*R*)-(−)-2-fluoro-2-phenylcyclopropylamine hydrochloride (1*R*,2*R*)-**2a** (Scheme 2). The absolute stereochemistry of compound **14** was determined by X-ray structural analysis (Figure 2 and Supporting Information).

Influence of Para-Substituents of 2-Fluoro-2-phenylcyclopropylamine on the Inhibition of Microbial Tyramine Oxidase. The activity of microbial tyramine oxidase from *Arthrobacter* sp. was measured in the presence of different concentrations of the inhibitor. IC$_{50}$ values (inhibitor concentration at 50% remain-

Scheme 2

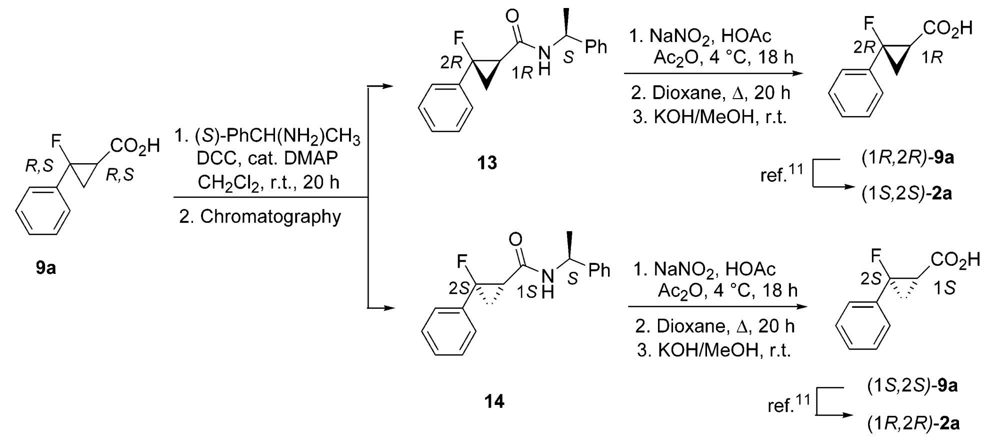


Table 1. IC_{50} Values, Inhibition Type and pK_a Values for Compounds

compd	isomer type	NH_2/F relation	R	pK_a[a]	IC_{50} (μM)	inhibition type
1a	trans		H	8.47	35 ± 6	competitive
1b	cis		H	8.50	33 ± 1	irreversible
2a	trans	cis	H	7.35	3.6 ± 1.5	competitive
2b	trans	cis	F	7.31	8.1 ± 1.6	competitive
2c	trans	cis	Cl	7.19	3.7 ± 0.3	competitive
2d	trans	cis	Me	7.41	0.39 ± 0.17	competitive
3a	cis	trans	H	6.98	190 ± 90	partially irreversible[b]
3b	cis	trans	F	6.88	75 ± 12	partially irreversible[b]
3c	cis	trans	Cl	6.81	89 ± 25	partially irreversible[b]
3d	cis	trans	Me	7.04	51 ± 5	nd

[a] Ionization constants (pK_a) were determined pH-metric in 0.1 M KNO_3 at 21 °C. [b] The term "partially irreversible" is used when time-dependent inhibition, but no clear concentration-dependent inhibition was observed; nd, not determined.

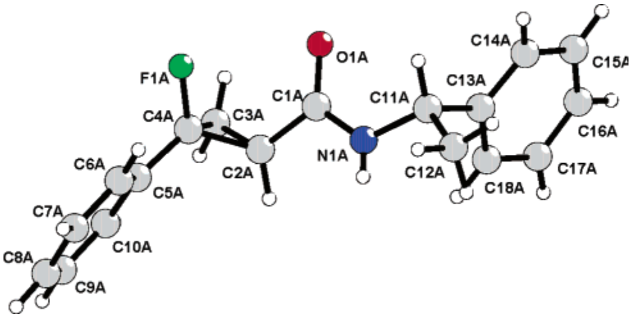


Figure 2. X-ray structure of compound **14**.

ing activity) were determined graphically from the inhibition curves obtained (Figure 3). The IC_{50} values together with pK_a values and inhibition type are summarized in Table 1.

The influence of fluorine substituents on the acidity of neighboring groups is well documented.[18] In one example, Fuller et al. have reported a lowering effect of β-fluorine substitution on the pK_a of several amine drugs.[19] In the case of the title phenylcyclopropylamines, introduction of a fluorine substituent in a cis-relationship to the amino group caused a decrease in basicity of more than 1 order of magnitude (cf. pK_a values of compounds **1a** and **2a** in Table 1). An even stronger influence was observed when fluorine is attached in a trans-orientation to the amino function (cf. compounds **1b** and **3a**). Para-substituents on the phenyl ring also influence the basicity of the amino group. As would be expected, electron-donating methyl group increased the pK_a value in both stereoisomeric series (cf. compounds **2a** and **2d** or **3a** and **3d**, respectively), while electron-withdrawing substituents lowered the basicity in both series.

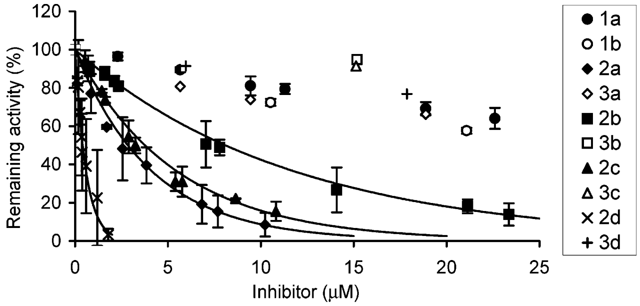


Figure 3. Effect of para-substitution of 2-fluoro-2-phenylcyclopropylamines (**2a**−**d** and **3a-d**) on the inhibition of microbial tyramine oxidase. For comparison the inhibition curves of nonfluorinated phenylcyclopropylamines **1a** and **1b** were added.

As shown in Figure 3 and Table 1, the diastereomeric nonfluorinated phenylcyclopropylamines, **1a** and **1b**, both inhibited tyramine oxidase and had comparable activity. However, the trans-isomer was a competitive inhibitor, while the cis-isomer was an irreversible inhibitor. The inhibitory potency was changed by introduction of a fluorine atom at 2-position of phenylcyclopropylamines. Compound **2a** had a 10-fold higher inhibitory than tranylcypromine **1a**, whereas the cis-isomer, **3a**, was 5-fold less potent than *cis*-tranylcypromine (**1b**).[11]

As mentioned before for compounds **2a** and **3a**, all other compounds in the series with cis-configuration of the fluorine with respect to the amino group (**2b**−**d**) exhibited significantly higher activity compared to their diastereomers **3b**−**d**. In this series (**2a**−**d**) the nature of the substituent in the para-position of the aromatic ring had a significant effect on their inhibitory activity against tyramine oxidase that correlated with the electron-donating ability of this group. Thus, compound **2b** (p-F) had a 2.9-fold lower inhibitory activity than the parent compound **2a**. The p-Cl substituent (**2c**) reduced the activity by 1.3-fold. In contrast, for compound **2d** (p-Me) a 7.2-fold higher inhibitory activity relative to the unsubstituted compound **2a** was observed.

In addition, the compounds **2a**−**d** did not show time- and concentration-dependent inactivation, indicating that the inhibition of tyramine oxidase is reversible.

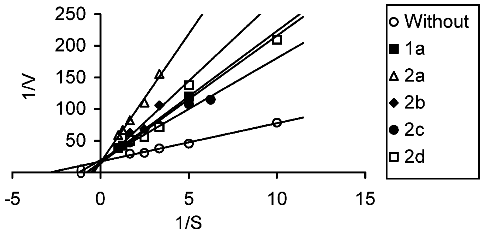


Figure 4. Lineweaver–Burk plot for the inhibition of tyramine oxidase by compounds **1a** (30 μM), **2a** (6 μM), **2b** (7 μM), **2c** (3 μM) and **2d** (1 μM). The benzylamine oxidation was monitored as described in Experimental Section in the presence and absence of the inhibitor. No time- and concentration-dependent inactivation was observed for these compounds.

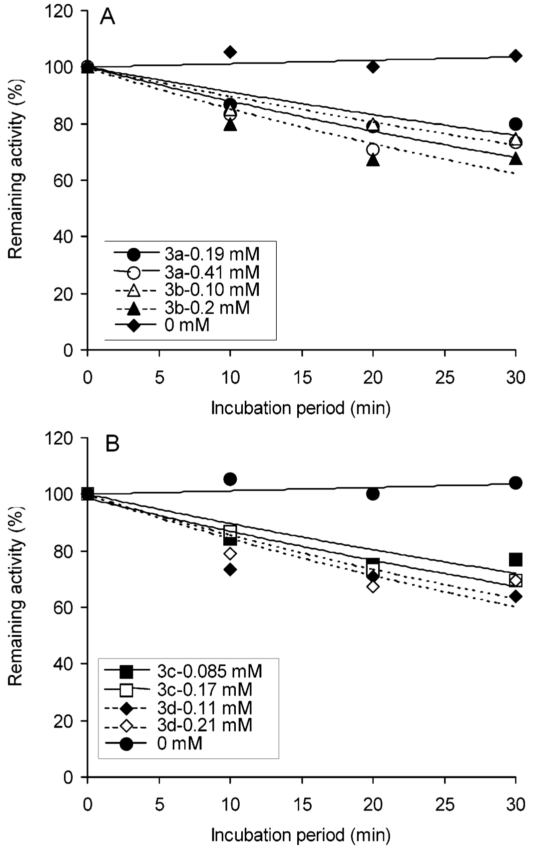


Figure 5. Time- and concentration-dependent inactivation of tyramine oxidase by para-substituted *cis*-2-fluoro-2phenylcyclopropylamines (graph **A** for **3a** and **3b**, graph **B** for **3c** and **3d**).

Kinetic analysis confirmed that these compounds are competitive inhibitors (Figure 4).

On the other hand, for compounds **3a–d** time dependence of the inhibition was observed, while the concentration dependence was not significant (Figure 5).

Enantioselectivity of the Tyramine Oxidase Inhibition. In experiments described below we have shown that tyramine oxidase from *Arthrobacter* sp. was not inhibited by (1*R*,2*R*)-enantiomer of 2-fluoro-2-phenylcyclopropylamine ((1*R*,2*R*)-**2a**) under the condition used in this study. The entire inhibition was due to the (1*S*,2*S*)-enantiomer ((1*S*,2*S*)-**2a**), which strongly inhibited this tyramine oxidase (Figure 6).

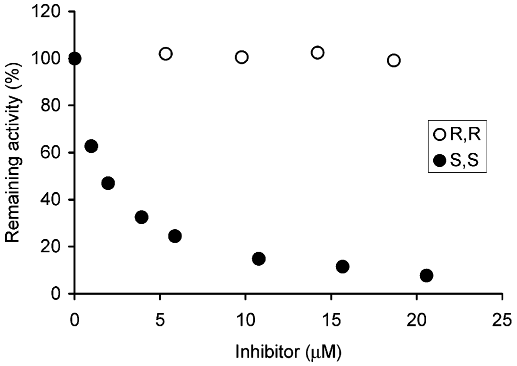


Figure 6. Effect of the concentration of 2-fluoro-2-phenylcyclopropylamine enantiomers ((1*R*,2*R*)-(−)-**2a** and (1*S*,2*S*)-(+)-**2a**) on the inhibition of microbial tyramine oxidase.

Clinical studies with the enantiomers of tranylcypromine, which in practice is administered in racemic from, have shown that only the (1*S*,2*R*)-(+)-enantiomer produces an improvement of the symptoms of depression, while the (1*R*,2*R*)-(−)-isomer is ineffective. Differences concerning the general state of being of patients were not detected.[20]

Discussion

In this study, we found that para-substitution of the aromatic ring of 2-fluoro-2-arylcyclopropylamines resulted in a substantial change in the inhibitory activity for microbial tyramine oxidase (*Arthrobacter* sp.). In the series with cis-orientation of fluorine and the amino group (compounds **2**), substituents with a −I-effect (F, Cl) lead to lower activity, while the presence of a *p*-methyl group (+I-substituent) increased the activity (compound **2d** compared to the unsubstituted **2a**). As described before,[11] and as is apparent from Table 1, compounds with cis-orientation of fluorine and the amino group are more active than the diastereomeric amines. In the less active compound having a trans-orientation of fluorine and the amino group, a similar influence of the para-substituent on inhibitory activity is also seen (Table 1, compounds **3**). However, in this series all para-substituted compounds **3b–d** are more active than compound **3a**.

As seen in Table 1, substituents have the expected effect on amine basicity. Thus, the increased activity of **2d** might be related to the increased basicity due to the methyl substituent. However, the increased activity of **2a** ($pK_a = 7.35$) compared to **1a** ($pK_a = 8.47$) reveals that activity is not only related to amine basicity. Indeed, from the data in Table 1 it can be seen that the presence of fluorine and the relative orientation of the fluorine atom and the amino group have strong influence on inhibition potency. Substituent effects, particularly in the more active amine-fluorine cis-series, further affect the activity of the compounds. The 10-fold increase in activity resulting from methyl substitution is the most significant substituent effect seen. The smaller effects of halogen substitution in this series, as well as the relatively modest substituent effects seen with compounds **3a–d** make interpretation difficult. Compounds possessing a broader variety of substituents are being prepared to explore this issue further.

In Figure 7 a part of the oxidation mechanism of amines by CAO is presented.[4e] CAO has a copper ion and an organic cofactor, TPQ, in its active site.[4e] For tranylcypromine the formation of Schiff's base adducts such as **15** with TPQ of *Escherichia coli* amine oxidase

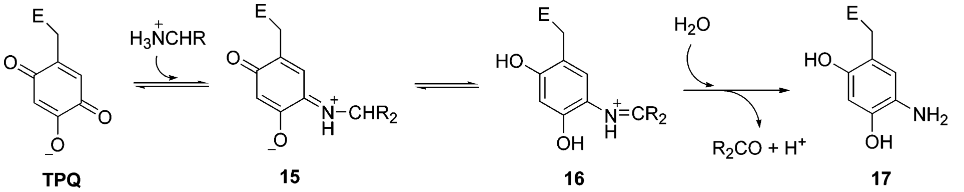


Figure 7. Mechanism for the oxidation of amines by CAO, adapted from the literature.[4e]

was described.[10a] The nucleophilic attack of the amino function on the carbonyl group of TPQ is the initial step of the formation of **15**. Since higher basicity of the amino group should favor this step, this mechanism is consistent with higher activity found for **2d**, which bears an electron-donating methyl substituent. This is also consistent with decreased activity of **2b** and **2c** bearing electron-withdrawing substituents, but does not explain the differernt influence of the α-fluoro substituent in the diastereomeric series **2** and **3**. Consequently, the relative inhibitory potency of the compounds cannot be dependent only on pK_a values. For the conversion of intermediate **15** to **16** base-catalyzed deprotonation of the α-carbon is necessary.[4e] This reaction would result in the formation of a rather unstable intermediate, which is expected to undergo ring cleavage reactions. Since reversible inhibition was observed, the metabolic pathway to **16** and formation of **17** are improbable.

We have already discussed the possibility of chelation of copper with fluorine and amine to explain the strong inhibitory activity of *trans*-2-fluoro-2-phenylcyclopropylamine (**2a**) and the higher activity of compounds with cis-configuration of the fluorine atom in relation to the amino group.[11] Again, increasing electron density on the nitrogen would increase its donor ability toward the metal center of TPQ. The copper center is considered to be involved in the activation of a water molecule responsible for the protonation of the C-2 oxygen of **15**.[4e] Coordination of the fluorine atom to copper could prevent water from binding to the metal center. Thus, compound **16** might not be formed. However, inhibition of other CAO with other types of copper chelators has been shown to be noncompetitive in nature,[21] to be expected if the inhibition is occurring at a site apart from the binding site. Since the tranylcypromine analogues in our study display competitive inhibition, if chelation is involved, this would presumably involve enhanced binding of the inhibitor associated with the active site. Till now there is no clear evidence whether chelation with copper is involved in inactivation of the enzyme.

A clearer understanding of the molecular mechanism of the potent inhibitory activity of compounds used in this study clearly will require more study. As one part of our efforts to gain more information, we are currently investigating in more detail coordination ability of copper ions with the amino group.

We also observed strong enantioselectivity in the inhibition of CAO by *trans*-2-fluoro-2-phenylcyclopropylamines (**2a**). Tranylcypromine (**1a**) is a competitive inhibitor of CAO. However, CAO is not inhibited by the (1*R*,2*S*)-(−)-enantiomer (trans-configuration) of tranylcypromine.[10] Crystallographic studies have shown that the (1*S*,2*R*)-(+)-enantiomer of tranylcypromine forms an adduct with *Escherichia coli* CAO.[10a] Similar enantioselectivity of tranylcypromine (**1a**) was reported in the inhibition of *Arthobacter globiformis* CAO.[10b] The authors suspected steric exclusion of (1*R*,2*S*)-(−)-tranylcypromine from the active site of CAO. This enantioselectivity is consistent with our results. However, it should be noted that, although stereochemical preferences have been described to be important for the inactivation of different CAOs, this is dependent on the particular amine oxidase being examined.[22]

We have recently reported the inhibitory activity of compounds **1**, **2**, and **3** against recombinant human liver monoamine oxidases A and B (MAO A and MAO B).[23] The diastereoisomeric tranylcypromines **1a** and **1b** were found to be moderately active nonselective irreversible inhibitors ($IC_{50} = 20\ \mu M$ and $19\ \mu M$, respectively). For both isoforms, fluorine substitution of the cyclopropane ring resulted in a higher activity in the trans-series, **2a** (12 or 6.4 μM), while lower or equal activity was observed in the cis-series, **3a** (65 or 19 μM). Similarly to the results presented in this study, only one enantiomer, (1*S*,2*S*)-**2a**, was active. In addition the aryl ring substitution had moderate effects on activities, depending on the amine-fluorine orientation, the nature of the para-substituent, and the MAO isoform, For example, in the cis-series, the *p*-chloro derivative **3c**, which was the most active in this series (IC_{50} 4.8 μM) was shown to have 1:19 MAO B selectivity. Among these results, the most relevant to the present study is the fact that the most active competitive tyramine oxidase inhibitor, **2d**, (IC_{50} 0.39 μM) was found to be a substantially weaker (irreversible) inhibitor of MAO A and MAO B ($IC_{50} = 13\ \mu M$ for both enzymes). (For the classic CAO irreversible inhibitor, semicarbazide, we observed an IC_{50} of 6.7 μM.[11]) The significant selectivity of this reversible inhibitor for CAO relative to MAO A and B could have important clinical implications. As discussed above, overexpression of CAO in blood vessels of patients with advanced diabetes,[24] in congestive heart failure,[25] and Alzheimers disease[7] may be responsible for vascular deterioration in these patients. In clinical approaches based on CAO inhibition, selectivity over MAO inhibition would be quite important.[24]

Experimental Section

General Methods. ^1H (300 MHz), ^{13}C (75 MHz) and ^{19}F (282 MHz) NMR spectra, if not stated otherwise, were recorded on a 300 MHz spectrometer, and chemical shifts are reported in ppm relative to TMS, $CDCl_3$ or $CFCl_3$. Mass spectra were obtained using different techniques by the staff of Organisch-Chemisches Institut, Universität Münster. Solvents and other reagents were purchased from commercial suppliers. Elemental analyses were performed by the Mikroanalytisches Laboratorium, Organisch-Chemisches Institut, Universität Münster. Analytical TLC was performed on Kieselgel 60 GF254 (Merck), and flash chromatography was performed with silica gel 60 (230−400 mesh, Merck). Melting points were determined using DSC.

Compounds **2a**, **3a**, **5a**−**c** and **6a**−**c** as well as **7a**, **7c**, **8a** and **8c** were prepared as previously described.[12−14] X-ray data sets were collected with Enraf Nonius CAD4 and Nonius KappaCCD diffractometers.

2-Bromo-1-fluoro-1-(4-methylphenyl)ethane (5d). Analogous to our published procedure,[13] to an ice cooled solution of 4-methylstyrene (**4d**) (9.45 g, 80.0 mmol) in CH_2Cl_2 (80 mL) were added $Et_3N{\cdot}3HF$ (40 mL, 244 mmol) and *N*-bromosuccinimide (NBS) (17.0 g, 95.5 mmol). After 30 min at 0 °C the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was poured into ice−water (500 mL) and neutralized with NH_4OH. After separation of the phases, the aqueous phase was extracted with CH_2Cl_2 (600 mL) and the combined organic layers were washed with 0.1 M HCl (600 mL), 5% $NaHCO_3$ and H_2O (200 mL). The phases were dried ($MgSO_4$), and all volatiles were removed under reduced pressure. After silica gel chromatography (pentane), 2-bromo-1-fluoro-1-(4-methylphenyl)ethane **5d** was obtained as a colorless oil (Yield: 14.95 g, 86%). This was contaminated with 4% of the 1-bromo-2-fluoro regioisomer. Data for **5d**: ^1H NMR ($CDCl_3$) δ 2.36 (3 H, s, CH_3), 3.60 (1 H, ddd, *J* = 4.3 Hz, *J* =11.2 Hz, *J* = 26.7 Hz, CH_2), 3.69 (1 H, ddd, *J* = 7.9 Hz, *J* = 11.2 Hz, *J* = 15.3 Hz, CH_2), 5.57 (1 H, ddd, *J* = 4.3 Hz, *J* = 7.9 Hz, *J* = 46.9 Hz, C*H*), 7.13−7.25 (4 H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 21.6 (q, CH_3), 34.2 (dt, *J* = 29.3 Hz, CH_2), 92.8 (dd, *J* = 178.0 Hz, *C*HF), 125.7 (dd, *J* = 5.1 Hz, aromatic), 129.4 (d, aromatic), 134.2 (d, *J* = 20.3 Hz, aromatic), 139.2 (s, aromatic); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −172.75 (ddd, *J* = 15.3 Hz, *J* = 26.7 Hz, *J* = 46.9 Hz); MS *m/z* (%) 218/216 (8/9), 198/196 (2/2), 137 (5), 123 (100), 118 (7), 117 (7), 115 (16), 103 (12), 91 (7), 77 (9), 65 (6), 63 (4), 58 (2), 51 (2), 39 (5). IR (NaCl) ν 3029 (m), 2966 (m), 2923 (m), 2863 (w), 1915 (w), 1615 (m), 1518 (s), 1453 (w), 1420 (s), 1381 (w), 1346 (m), 1290 (w), 1242 (w), 1219 (s), 1207 (s), 1184 (m), 1113 (w), 1065 (s), 1026 (w), 985 (s), 945 (w), 924 (w), 867 (m), 823 (s), 772 (m), 726 (m), 694 (w), 652 (s); Anal. ($C_9H_{10}BrF$) C, H. The ^1H NMR chemical shifts are in good agreement with those of a 100 MHz spectrum described in the literature.[26]

(1-Fluorovinyl)-4-methylbenzene (6d). Analogous to a published procedure,[14] under ice cooling, KO^tBu (14.7 g, 131 mmol) was added slowly to a solution of **5d** (14.22 g, 65.5 mmol) in 400 mL of pentane. After the reaction mixture was refluxed for 1 h, it was cooled to room temperature and was poured into 400 mL of ice−water. After separation of the layers, the aqueous phase was extracted with 300 mL of pentane. The combined organic layers were washed with 5% $NaHCO_3$ (300 mL), 0.05 M HCl (150 mL) and H_2O (300 mL) and then dried ($MgSO_4$). All volatiles were removed under reduced pressure. After fractional distillation pure regioisomer **6d** was isolated as a colorless liquid (Yield: 7.55 g, 85%). Data for **6d**: Bp 68 °C/11 mbar; ^1H NMR ($CDCl_3$) δ 2.34 (3 H, s, CH_3), 4.76 (1 H, dd, *J* = 3.3 Hz, *J* = 17.9 Hz, CH_AH_B), 4.94 (dd, *J* = 3.3 Hz, *J* = 49.8 Hz, 1 H, CH_AH_B), 7.14 (2 H, dd, *J* = 8.0 Hz, *J* = 0.7 Hz, aromatic), 7.42 (2 H, d, *J* = 8.0 Hz, aromatic); ^{13}C NMR ($CDCl_3$) δ 21.2 (q, CH_3), 88.5 (dt, *J* = 22.9 Hz, CH_AH_B), 124.6 (dd, *J* = 6.4 Hz, aromatic), 129.1 (dd, aromatic), 129.3 (ds, *J* = 29.3 Hz, aromatic), 139.4 (s, aromatic), 163.2 (ds, *J* = 250.5 Hz, *C*F); ^{19}F NMR ($CDCl_3$) δ −107.98 (dd, *J* = 17.2 Hz, *J* = 49.7 Hz); MS *m/z* (%) 137 (100), 136 (96), 122 (10), 116 (38), 110 (17), 102 (4), 92 (7), 89 (5), 84 (6), 65 (3), 63 (4), 57 (2), 51 (3); Anal. (C_9H_9F). The ^1H NMR chemical shifts and IR absorptions are in good agreement with those described in reference 26.

***cis*- and *trans*-(±)-2-Fluoro-2-(4-fluorophenyl)cyclopropanecarboxylic Acid Ethyl Ester (7b and 8b).** Under dry conditions, $Cu(acac)_2$ (24 mg, 0.09 mmol) was dissolved in anhydrous CH_2Cl_2 (4 mL). After the solution was stirred for several minutes, a few drops of phenylhydrazine were added and stirring was continued. To this solution was added (1-fluorovinyl)-4-fluorobenzene (**6b**) (420 mg, 3 mmol), synthesized as previously described.[27] The mixture was heated to reflux, and a solution of ethyl diazoacetate (513 mg, 4.5 mmol) in CH_2Cl_2 (8 mL) was added via a syringe pump over 5−6 h. The solution was refluxed for an additional 4 h, after which time it was cooled and diluted with CH_2Cl_2 (150 mL). After the solution was washed with saturated Na_2CO_3 and H_2O (300 mL), the organic portion was dried ($MgSO_4$) and all volatiles were removed under vacuum. GC analysis of the crude product revealed a conversion of 95% and formation of a 1:1 mixture of cis/trans diastereoisomers. The diastereomers were separated by silica gel chromatography (pentane/CH_2Cl_2, 2:1). The esters **7b** or **8b** were isolated as colorless oils.

Data for 7b: (Yield: 233 mg, 33%) ^1H NMR ($CDCl_3$) δ 1.28 (3 H, t, *J* = 7.2 Hz, CH_3), 1.57 (1 H, ddd, *J* = 7.0 Hz, *J* = 9.3 Hz, *J* = 10.5 Hz, CH_X), 2.14 (1 H, ddd, *J* = 3.2 Hz, *J* = 7.7 Hz, *J* = 9.3 Hz, CH_AH_B), 2.21−2.32 (1 H, m, CH_AH_B), 4.18−4.28 (2 H, m, OCH_2), 7.00−7.33 (4 H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 14.1 (q, CH_3), 18.4 (dt, *J* = 12.7 Hz, CH_AH_B), 28.6 (dd, *J* = 12.7 Hz, CH_X), 61.1 (t, OCH_2), 80.4 (ds, *J* = 227.6 Hz, *C*F), 115.5 (dd, *J* = 21.6 Hz, aromatic), 127.0 (ddd, *J* = 5.7 Hz, *J* = 8.3 Hz, aromatic), 133.2 (dds, *J* = 3.8 Hz, *J* = 21.6 Hz, aromatic), 162.9 (ds, *J* = 248.0 Hz, aromatic-*C*F), 167.5 (ds, *J* = 2.5 Hz, *C*=O); ^{19}F NMR ($CDCl_3$) δ −113.67 (1 F, m, aromatic), −185.25 (1 F, m, aliphatic). MS *m/z* (%) 226 (37), 208 (5), 197 (19), 181 (18), 178 (20), 170 (29), 153 (100), 151 (48), 143 (63), 140 (7), 133 (35), 128 (4), 123 (21), 107 (6), 101 (6), 95 (4), 83 (5), 75 (4), 57 (4), 55 (4), 39 (2); IR (NaCl) ν 3060 (w), 2984 (w), 2934 (w), 2911 (w), 1734 (s), 1611 (m), 1521 (s), 1438 (m), 1398 (w), 1383 (m), 1363 (m), 1341 (m), 1302 (w), 1271 (m), 1221 (s), 1163 (s), 1113 (w), 1096 (w), 1078 (w), 1056 (w), 1036 (w), 1001 (w), 963 (m), 889 (m), 864 (w), 841 (s), 816 (m), 766 (w), 725 (w). Anal. ($C_{12}H_{12}F_2O_2$) C, H, N.

Data for 8b: (Yield: 206 mg, 30%) ^1H NMR ($CDCl_3$) δ 1.03 (3 H, t, *J* = 7.0 Hz, CH_3), 1.78 (1 H, ddd, *J* = 7.5 Hz, *J* = 10.2 Hz, *J* = 18.4 Hz, CH_AH_B), 1.92 (1 H, ddd, *J* = 7.5 Hz, *J* = 7.5 Hz, *J* = 12.2 Hz, CH_AH_B), 2.54 (1 H, ddd, *J* = 7.5 Hz, *J* = 10.2 Hz, *J* = 17.8 Hz, CH_X), 3.92 (2 H, q, *J* = 7.0 Hz, OCH_2), 7.00−7.54 (4 H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 13.9 (q, CH_2CH_3), 16.5 (dt, *J* = 11.4 Hz, CH_AH_B), 27.7 (dd, *J* = 15.8 Hz, CH_X), 60.7 (t, CH_2CH_3), 82.3 (ds, *J* = 221.1 Hz, *C*F), 115.2 (dd, *J* = 21.6 Hz, aromatic), 129.2 (dds, *J* = 3.2, *J* = 21.0 Hz, aromatic), 130.4 (ddd, *J* = 3.1 Hz, *J* = 8.4 Hz, aromatic), 163.1 (dds, *J* = 3.2 Hz, *J* = 248.6 Hz, aromatic-*C*F), 168.7 (s, *C*=O); ^{19}F NMR ($CDCl_3$) δ −112.35 (1 F, m, aromatic), −152.10 (1 F, m, aliphatic); MS *m/z* (%) 226 (48), 198 (24), 181 (15), 178 (20), 170 (37), 153 (100), 151 (47), 143 (69), 140 (12), 133 (72), 128 (6), 123 (25), 101 (8), 95 (4), 83 (4), 76 (4), 57 (6), 55 (7), 39 (2); IR (NaCl) ν 3063 (w), 2985 (m), 2938 (m), 2909 (w), 2877 (w), 1731 (s), 1610 (s), 1520 (s), 1468 (m), 1437 (s), 1399 (s), 1382 (s), 1363 (m), 1342 (s), 1300 (m), 1270 (m), 1221 (s), 1163 (s), 1111 (m), 1077 (m), 1053 (m), 1037 (m), 1018 (w), 1003 (w), 965 (m), 890 (s), 866 (m), 841 (s), 818 (m), 797 (w), 767 (w), 725 (w); Anal. ($C_{12}H_{12}F_2O_2$) C, H, N.

***cis*- and *trans*-(±)-2-Fluoro-2-(4-methylphenyl)cyclopropanecarboxylic Acid Ethyl Ester (7d and 8d).** Analogous to the procedure described above, **6d** (1.36 g, 10.0 mmol) was reacted with $Cu(acac)_2$ (84 mg, 0.52 mmol) and ethyl diazoacetate (1.71 g, 15 mmol). GC analysis of the crude product revealed a conversion of 75% and formation of a 1:1 mixture of cis/trans diastereoisomers. The diastereomers were separated by silica gel chromatography (pentane/Et_2O, 40:1). In addition to fractions containing pure **7d** or **8d**, a fraction containing both diastereomers (303 mg, 1.34 mmol, 14%) was obtained. The esters were isolated as colorless oils.

Data for 7d: (Yield: 607 mg, 27%) ^1H NMR ($CDCl_3$) δ 1.29 3 H, (q, *J* = 7.2 Hz, CH_2CH_3), 1.57 (1 H, ddd, *J* = 6.9 Hz, *J* = 8.8 Hz, *J* = 10.5 Hz, CH_AH_B), 2.15 (ddd, *J* = 7.6 Hz, *J* = 8.8 Hz, *J* = 10.5 Hz, 1 H, CH_X), 2.25 (1 H, ddd, *J* = 6.9 Hz, *J* = 7.6 Hz, *J* = 20.0 Hz, CH_AH_B), 2.35 (s, 3 H, C_{ar}-CH_3), 4.18−4.29 (2 H, m, CH_2CH_3), 7.16−7.25 (4 H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 14.2 (q, CH_2CH_3), 18.7 (dt, *J* = 12.7 Hz, CH_AH_B), 21.0 (q, C_{ar}-CH_3), 28.7 (dd, *J* = 12.7 Hz, CH_X), 61.1 (t, CH_2-CH_3), 80.9 (ds, *J* = 227.6 Hz, *C*F), 124.9 (dd, *J* = 6.4 Hz, aromatic), 129.2 (d, aromatic), 134.5 (ds, *J* = 21.6 Hz, aromatic), 138.3 (s, aromatic), 167.9 (s, *J* = 2.5 Hz, *C*=O); ^{19}F NMR ($CDCl_3$) δ −186.37 (dm, *J* = 20.0 Hz). MS *m/z* (%) 222 (58), 207 (5), 193 (20), 177 (17), 174 (14), 172 (15), 166 (24), 164 (22), 149 (100), 147 (26), 139 (60), 133 (32), 129 (38), 119 (14), 115 (7), 109 (11), 101 (5), 91 (6), 77 (5), 65 (2), 55 (3), 39

(1); IR (NaCl) ν 3099 (w), 3034 (w), 2983 (m), 2927 (m), 2874 (w), 1737 (s), 1616 (w), 1520 (w), 1438 (s), 1399 (s), 1384 (s), 1306 (s), 1268 (m), 1239 (m), 1181 (s), 1107 (m), 1071 (w), 1045 (w), 1002 (m), 974 (w), 903 (w), 883 (w), 860 (w), 846 (w), 815 (s), 789 (w), 721 (w); Anal. ($C_{13}H_{15}FO_2$) C, H.

Data for 8d: (Yield: 420 mg, 19%) ^{1}H NMR (CDCl$_3$) δ 1.03 (3 H, q, J = 7.2 Hz, CH$_2$C*H*$_3$), 1.77 (1 H, ddd, J = 7.2 Hz, J = 10.3 Hz, J = 19.1 Hz, CH$_A$*H*$_B$), 1.93 (1 H, ddd, J = 7.2 Hz, J = 7.4 Hz, J = 12.2 Hz, C*H*$_A$H$_B$), 2.34 (3 H, d, J = 1.9 Hz, C$_{ar}$-C*H*$_3$), 2.53 (1 H, ddd, J = 7.4 Hz, J = 10.3 Hz, J = 17.9 Hz, C*H*$_X$), 3.93 (t, J = 7.2 Hz, 2 H, C*H*$_2$CH$_3$), 7.14–7.17 (2 H, m, aromatic), 7.33–7.37 (2 H, m, aromatic); ^{13}C NMR (CDCl$_3$) δ 13.9 (q, CH$_2$*C*H$_3$), 16.5 (dt, J = 10.2 Hz, *C*H$_A$H$_B$), 21.2 (q, C$_{ar}$-*C*H$_3$), 27.7 (dd, J = 16.5 Hz, *C*H$_X$), 60.6 (t, *C*H$_2$CH$_3$), 83.0 (ds, J = 220.0 Hz, *C*F), 128.5 (dd, J = 2.5 Hz, aromatic), 128.9 (d, aromatic), 130.2 (ds, J = 20.3 Hz, aromatic), 139.2 (ds, J = 2.5 Hz, aromatic), 169.0 (s, *C*=O); ^{19}F NMR (CDCl$_3$) δ −152.52 (dm, J = 19.1 Hz); MS *m/z* (%) 222 (63), 207 (6), 193 (20), 177 (13), 174 (15), 172 (15), 166 (36), 164 (30), 149 (100), 147 (28), 139 (60), 133 (31), 129 (33), 119 (14), 115 (8), 109 (10), 101 (4), 91 (7), 77 (5), 65 (2), 55 (3), 39 (2); IR (NaCl) ν 3104 (w), 3061 (w), 2984 (s), 2930 (m), 2877 (w), 1731 (s), 1617 (w), 1522 (m), 1466 (m), 1439 (s), 1397 (s), 1380 (s), 1362 (m), 1342 (s), 1267 (m), 1220 (s), 1163 (s), 1101 (m), 1076 (w), 1039 (m), 1001 (w), 961 (m), 887 (s), 866 (m), 823 (s), 800 (w), 760 (m), 721 (w); Anal. ($C_{13}H_{15}FO_2$) C, H.

General Procedure for Hydrolysis with KOH. A solution of the cyclopropanecarboxylic ethyl ester (**7** or **8**) (1 mmol) in methanol (2 mL) was added to KOH (0.56 g, 10 mmol) in methanol (5 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature and then poured into water and extracted with CH$_2$Cl$_2$ (25 mL). The organic layer was discarded and the aqueous phase was acidified with concentrated HCl to pH 1 and extracted with CH$_2$Cl$_2$ (2 × 25 mL). The organic phases were dried (Na$_2$SO$_4$) and all volatiles removed under vacuum. The acids were isolated as white powders and further purified by recrystallization.

***trans*-(±)-2-Fluoro-2-(4-fluorophenyl)cyclopropanecarboxylic Acid (9b).** Using the same procedure as above, hydrolysis of **7b** (226 mg, 1.00 mmol) gave, after recrystallization from CH$_2$Cl$_2$/pentane at −20 °C, **9b** as a colorless, crystalline solid (Yield: 290 mg, 95%). Data for **9b**: Mp 114 °C; ^{1}H NMR (CDCl$_3$) δ 1.67 (1 H, ddd, J = 7.2 Hz, J = 9.3 Hz, J = 10.6 Hz, C*H*$_X$), 2.16 (1 H, ddd, J = 7.6 Hz, J = 9.3 Hz, J = 11.8 Hz, C*H*$_A$H$_B$), 2.30 (1 H, ddd, J = 7.2 Hz, J = 7.6 Hz, J = 19.9 Hz, CH$_A$*H*$_B$), 7.04–7.36 (4 H, m, aromatic), 11.30 (1 H, br, COO*H*); ^{13}C NMR (CDCl$_3$) δ 19.1 (dt, J = 12.7 Hz, *C*H$_A$H$_B$), 28.3 (dd, J = 11.4 Hz, *C*H$_X$), 81.2 (ds, J = 228.9 Hz, *C*F), 115.7 (dd, J = 21.7 Hz, aromatic), 127.3 (ddd, J = 5.7 Hz, J = 8.3 Hz, aromatic), 132.7 (dds, J = 3.8 Hz, J = 21.6 Hz, aromatic), 162.9 (dds, J = 249.2 Hz, aromatic), 174.2 (s, *C*=O); ^{19}F NMR (CDCl$_3$) δ −113.26 (1 F, m, aromatic), −183.47 (1 F, m, aliphatic); MS as trimethylsilyl ester *m/z* (%) 270 (6), 255 (23), 225 (6), 215 (35), 180 (51), 151 (17), 133 (57), 123 (36), 115 (7), 107 (2), 77 (26), 73 (100), 47 (2), 45 (7); Anal. ($C_{12}H_{13}FO_2$) C, H. The structure of **9b** was confirmed by X-ray structural analysis (cf. Supporting Information).

***cis*-(±)-2-Fluoro-2-(4-fluorophenyl)cyclopropanecarboxylic Acid (10b).** Using the general procedure, hydrolysis of **8b** (204 mg, 0.90 mmol) with KOH gave, after recrystallization from CH$_2$Cl$_2$/pentane at −20 °C, **10b** as a colorless, crystalline solid (Yield: 167 mg, 93%) Data for **10b**: Mp 98 °C (CH$_2$Cl$_2$/pentane); ^{1}H NMR (CDCl$_3$) δ 1.77–1.93 (2 H, m, C*H*$_A$*H*$_B$), 2.48 (1 H, ddd, J = 7.5 Hz, J = 10.0 Hz, J = 17.4 Hz, C*H*$_X$), 6.90–7.50 (4 H, m, aromatic), 11.06 (s1 H, COO*H*); ^{13}C NMR (CDCl$_3$) δ 17.4 (dt, J = 10.2 Hz, *C*H$_A$H$_B$), 27.5 (dd, J = 17.8 Hz, *C*H$_X$), 82.9 (ds, J = 222.6 Hz, *C*F), 115.4 (dd, J = 21.7 Hz, aromatic), 128.5 (dds, J = 3.2 Hz, J = 20.8 Hz, aromatic), 130.5 (ddd, J = 3.2 Hz, J = 8.2 Hz, aromatic), 163.3 (dds, J = 3.2 Hz, J = 248.6 Hz, aromatic), 175.2 (s, *C*=O); ^{19}F NMR (CDCl$_3$) δ −111.93 (1 F, m, aromatic), −151.26 (1 F, m, aliphatic); MS as trimethylsilyl ester *m/z* (%) 270 (7), 255 (14), 225 (5), 215 (21), 180 (51), 152 (16), 133 (42), 123 (41), 115 (6), 107 (2), 77 (21), 73 (100), 47 (3), 45 (8); Anal. ($C_{12}H_{13}FO_2$) C, H. The structure of **10b** was confirmed by X-ray structural analysis (cf. Supporting Information).

***trans*-(±)-2-(4-Chlorophenyl)-2-fluorocyclopropanecarboxylic Acid (9c).** Using the same procedure, hydrolysis of **7c** (145 mg, 0.6 mmol) gave, after recrystallization from CH$_2$Cl$_2$/pentane, **9c** as a colorless, crystalline solid (Yield: 80 mg, 62%). Data for **9c**: Mp 138 °C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.69 (1 H, ddd, J = 7.4 Hz, J = 9.3 Hz, J = 10.6 Hz, C*H*$_A$H$_B$), 2.18 (1 H, ddd, J = 2.5 Hz, J = 7.6 Hz, J = 9.3 Hz, C*H*$_X$), 2.33 (1 H, ddd, J = 7.4 Hz, J = 7.6 Hz, J = 20.3 Hz, CH$_A$*H*$_B$), 7.25–7.39 (4 H, m, aromatic); ^{13}C NMR (CDCl$_3$) δ 19.1 (dt, J = 12.6 Hz, *C*H$_A$H$_B$), 28.6 (dd, J = 11.4 Hz, *C*H$_X$), 80.6 (ds, J = 228.9 Hz, *C*F), 126.2 (dd, J = 6.4 Hz, aromatic), 128.8 (d, aromatic), 134.4 (s, aromatic), 135.9 (ds, J = 22.8 Hz, aromatic), 170.7 (ds, J = 2.5 Hz, *C*=O); ^{19}F NMR (CDCl$_3$, 188.30 MHz) δ −186.84 (m); MS as trimethylsilyl ester *m/z* (%) 288/286 (2/6), 273/271 (3/11), 251 (1), 235 (4), 233/231 (6/16), 207 (5), 198/196 (7/21), 160 (22), 151/149 (4/13), 141/139 (7/24), 133 (21), 115 (12), 107 (2), 77 (23), 73 (100), 45 (7); IR (KBr) ν 3558 (m), 3478 (br), 3418 (br), 3236 (w), 3093 (w), 2928 (w), 2860 (w), 2637 (w), 1702 (s), 1641 (m), 1620 (m), 1497 (w), 1451 (m), 1431 (m), 1404 (w), 1369 (w), 1314 (m), 1243 (m), 1223 (m), 1107 (m), 1096 (w), 1060 (w), 1021 (m), 972 (w), 935 (m), 895 (w), 869 (w), 817 (m), 782 (w), 737 (w), 660 (m). Anal. ($C_{10}H_8ClFO_2$) C, H.

***cis*-2-(4-Chlorophenyl)-2-fluorocyclopropanecarboxylic Acid (10c).** Using the same procedure, hydrolysis of **8c** (231 mg, 0.95 mmol) gave, after recrystallization from CH$_2$Cl$_2$/pentane, **10c** as a colorless, crystalline solid (Yield: 188 mg, 92%). Data for **10c**: Mp 103 °C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.83–2.04 (2 H, m, C*H*$_A$*H*$_B$), 2.52 (ddd, J = 7.6 Hz, J = 10.1 Hz, J = 17.6 Hz, 1 H, C*H*$_X$), 7.32–7.39 (4 H, m, aromatic); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 17.3 (dt, J = 10.4 Hz, *C*H$_A$H$_B$), 27.6 (dd, J = 17.3 Hz, *C*H$_X$), 82.8 (ds, J = 222.0 Hz, *C*F), 128.6 (d, aromatic), 129.7 (dd, J = 4.4 Hz, aromatic), 131.1 (ds, J = 20.5 Hz, aromatic), 135.4 (ds, J = 3.2 Hz, aromatic), 174.1 (s, *C*=O); ^{19}F NMR (CDCl$_3$, 188.30 MHz) δ −153.56 (m); MS as trimethylsilyl ester *m/z* (%) 288/286 (7/15), 273/271 (20/53), 251 (2), 235 (27), 233/231 (22/60), 207 (14), 198/196 (22/69), 171/169 (1/3), 161 (52), 151/149 (12/37), 141/139 (14/57), 133 (56), 115 (24), 107 (6), 101 (3), 77 (26), 73 (100), 63 (2), 45 (8); IR (KBr) ν 3112 (w), 3064 (w), 2922 (w), 2762 (w), 2663 (w), 2572 (w), 1700 (s), 1603 (w), 1500 (m), 1456 (m), 1427 (m), 1385 (w), 1359 (w), 1336 (m), 1254 (s), 1185 (s), 1097 (s), 1017 (m), 966 (w), 888 (s), 834 (s), 765 (w), 734 (w), 660 (m), 572 (w), 528 (m); Anal. ($C_{10}H_8ClFO_2$) C, H. The structure of **10c** was confirmed by X-ray structural analysis (cf. Supporting Information).

***trans*-(±)-2-Fluoro-2-(4-methylphenyl)cyclopropanecarboxylic Acid (9d).** Hydrolysis as described above of **7d** (524 mg, 2.32 mmol) gave, after recrystallization from CH$_2$Cl$_2$/pentane (1:4), **9d** as a white, amorphous solid (Yield: 335 mg, 75%). Data for **9d**: Mp 112 °C (CH$_2$Cl$_2$/pentane); ^{1}H NMR (CDCl$_3$) δ 1.66 (1 H, ddd, J = 6.9 Hz, J = 9.1 Hz, J = 10.5 Hz, C*H*$_X$), 2.16 (1 H, ddd, J = 7.6 Hz, J = 9.1 Hz, J = 10.3 Hz, C*H*$_A$H$_B$), 2.29 (1 H, ddd, J = 6.9 Hz, J = 7.6 Hz, J = 20.0 Hz, CH$_A$*H*$_B$), 2.36 (s, C*H*$_3$), 7.17–7.25 (4 H, m, aromatic), 11.29 (1 H, br, CO$_2$*H*); ^{13}C NMR (CDCl$_3$) δ 19.2 (dt, J = 12.7 Hz, *C*H$_A$H$_B$), 21.1 (q, *C*H$_3$), 28.4 (dd, J = 11.4 Hz, *C*H$_X$), 81.6 (ds, J = 230.2 Hz, *C*F), 125.2 (dd, J = 5.1 Hz, aromatic), 129.3 (d, aromatic), 134.0 (ds, J = 21.6 Hz, aromatic), 138.7 (s, aromatic), 174.4 (s, *C*=O); ^{19}F NMR (CDCl$_3$) δ −184.66 (ddd, J = 10.3 Hz, J = 10.5 Hz, J = 20.0 Hz); MS as trimethylsilyl ester *m/z* (%) 266 (12), 251 (31), 235 (6), 223 (6), 211 (25), 207 (10), 176 (71), 149 (13), 147 (13), 133 (21), 129 (48), 119 (41), 115 (23), 109 (3), 91 (2), 77 (28), 73 (100), 51 (1), 45 (6); IR (KBr) ν 3113 (br), 3055 (br), 2999 (br), 2926 (br), 2866 (br), 1691 (s), 1523 (w), 1451 (s), 1427 (s), 1388 (w), 1297 (s), 1245 (m), 1207 (s), 1131 (w), 1106 (m), 1053 (w), 1022 (w), 1010 (m), 965 (w), 897 (m), 866 (w), 834 (w), 811 (s), 789 (m), 769 (w), 714 (w), 658 (w), 642 (w), 569 (m), 491 (w); Anal. ($C_{11}H_{11}FO_2$) C, H.

***cis*-(±)-2-Fluoro-2-(4-methylphenyl)cyclopropanecarboxylic Acid (10d).** Using the general procedure for hydrolysis with KOH, **10d** was prepared from 333 mg (1.47 mmol) of

8d. After recrystallization from CH_2Cl_2/pentane (1:10), 212 mg (74%) of **10d** was isolated as white, amorphous solid. Data for **10d**: Mp 86 °C (CH_2Cl_2/pentane); ^{1}H NMR ($CDCl_3$) δ 1.79 (1 H, ddd, J = 7.2 Hz, J = 10.0 Hz, J = 18.8 Hz, CH_AH_B), 1.87 (ddd, J = 7.2 Hz, J = 7.4 Hz, J = 12.9 Hz, 1 H, CH_AH_B), 2.34 (3 H, s, CH_3), 2.46 (1 H, ddd, J = 7.4 Hz, J = 10.0 Hz, J = 17.6 Hz, CH_X), 7.11–7.32 (4 H, m, aromatic), 11.04 (1 H, br, CO_2H); ^{13}C NMR ($CDCl_3$) δ 17.3 (dt, J = 10.2 Hz, CH_AH_B), 21.2 (q, CH_3), 27.4 (dd, J = 17.8 Hz, CH_X), 83.5 (ds, J = 221.3 Hz, CF), 128.4 (dd, J = 3.8 Hz, aromatic), 129.0 (d, aromatic), 129.6 (ds, J = 19.1 Hz, aromatic), 139.4 (ds, J = 2.5 Hz, aromatic), 175.3 (s, C=O); ^{19}F NMR ($CDCl_3$) δ −150.34 (m); MS as trimethylsilyl ester *m/z* (%) 266 (13), 251 (16), 235 (1), 221 (6), 211 (19), 207 (5), 176 (47), 160 (2), 149 (4), 147 (7), 133 (16), 129 (31), 119 (33), 115 (7), 109 (2), 91 (3), 77 (12), 73 (100), 51 (1), 45 (10); IR (KBr) ν 3108 (w), 3069 (w), 3044 (w), 3023 (w), 2957 (br), 2928 (br), 2857 (w), 1691 (s), 1617 (w), 1524 (w), 1452 (s), 1426 (m), 1364 (w), 1338 (m), 1247 (s), 1182 (s), 1119 (w), 1100 (w), 1082 (w), 1043 (w), 1023 (w), 1008 (w), 964 (w), 932 (m), 918 (m), 883 (s), 823 (s), 756 (w), 666 (m), 625 (w), 571 (w), 521 (w), 488 (w); Anal. ($C_{11}H_{11}FO_2$) C, H.

(1*R*,2*R*)-(+)- and (1*S*,2*S*)-(−)-(2-Fluoro-2-phenyl)cyclopropanecarboxylic (*S*)-(1-Phenylethyl)amide (13 and 14). To a solution of *trans*-(±)-(2-fluoro-2-phenyl)cyclopropanecarboxylic acid (**9a**) prepared as described before[12] (360 mg, 2.0 mmol) in CH_2Cl_2 (20 mL) were added dicyclohexylcarbodiimide (DCC) (454 mg, 2.2 mmol), (*S*)-1-phenylethylamine (255 mg, 2.1 mmol) and a catalytic amount of *N*,*N*-(dimethylamino)-pyridine (DMAP). The reaction mixture was stirred for 20 h at room temperature. The precipitate that formed was removed by filtration. The diastereomeric amides were separated by silica gel chromatography (pentane/Et_2O, 1:1) and purified further by recrystallization from Et_2O/pentane [(+)-**13**] and ethyl acetate/pentane [(−)-**14**]. The amides were isolated as white, crystalline solids.

Data for (+)-13: (Yield: 175 mg, 35%) Mp 133 °C (ethyl acetate); $[\alpha]^{20}_D$ +146.5 (c = 1.0, $CHCl_3$, 99% d.s.); ^{1}H NMR ($CDCl_3$) δ 1.50 (3 H, d, J = 6.9 Hz, CH_3), 1.53 (ddm, J = 7.2 Hz, J = 10.5 Hz, 1 H, CH_X), 1.98–2.06 (1 H, dm, J = 7.9 Hz, CH_AH_B), 2.21 (1 H, ddd, J = 7.4 Hz, J = 7.9 Hz, J = 20.5 Hz, CH_AH_B), 5.14–5.27 (1 H, m, CH), 6.05 (1 H, d, J = 6.2 Hz, NH), 7.20–7.38 (10 H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 18.4 (dt, J = 11.4 Hz, CH_AH_B), 21.7 (q, CH_3), 31.0 (dd, J = 12.7 Hz, CH_X), 49.1 (d, CH), 80.6 (ds, J = 223.8 Hz, CF), 124.1 (dd, J = 7.6 Hz, aromatic), 126.1 (d, aromatic), 127.3 (d, aromatic), 128.0 (d, aromatic), 128.5 (d, aromatic), 128.6 (d, aromatic), 138.0 (ds, J = 21.6 Hz, aromatic), 143.0 (s, aromatic), 165.6 (s, C=O); ^{19}F NMR ($CDCl_3$) δ −189.69 (m); MS *m/z* (%) 283 (3), 263 (3), 248 (5), 220 (2), 207 (3), 179 (34), 161 (14), 159 (13), 145 (7), 143 (9), 135 (14), 120 (5), 115 (39), 105 (100), 91 (8), 77 (28), 62 (4), 51 (7); IR (KBr) ν 3292 (s), 3069 (w), 3041 (w), 2971 (w), 2925 (w), 1648 (s), 1550 (s), 1495 (w), 1450 (m), 1430 (w), 1385 (s), 1320 (w), 1251 (w), 1232 (m), 1134 (w), 1115 (w), 1075 (w), 1037 (w), 1024 (w), 1001 (w), 982 (w), 893 (m), 845 (w), 802 (w), 759 (m), 743 (w), 698 (m), 670 (w); Anal. ($C_{18}H_{18}FNO$) C, H. N.

Data for (−)-14: (Yield: 172 mg, 35%) Mp 149 °C (ethyl acetate); $[\alpha]^{20}_D$ −182.3 (c = 1.0, $CHCl_3$, >99% d.s.). ^{1}H NMR ($CDCl_3$) δ 1.41–1.51 (1 H, m, CH_X), 1.44 (3 H, d, J = 6.9 Hz, CH_3), 1.91–1.99 (1 H, m, CH_AH_B), 2.21 (ddd, J = 7.4 Hz, J = 7.4 Hz, J = 20.7 Hz, 1 H, CH_AH_B), 5.09–5.19 (1 H, m, CH), 6.21 (1 H, d, J = 6.7 Hz, NH), 7.21–7.38 (10 H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 18.4 (dt, J = 11.4 Hz, CH_AH_B), 21.8 (q, CH_3), 31.0 (dd, J = 11.4 Hz, CH_X), 49.3 (d, CH), 80.5 (ds, J = 225.1 Hz, CF), 124.0 (dd, J = 6.4 Hz, aromatic), 126.2 (d, aromatic), 127.3 (d, aromatic), 127.9 (d, aromatic), 128.5 (d, aromatic), 128.6 (d, aromatic), 138.2 (ds, J = 21.6 Hz, aromatic), 143.3 (s, aromatic), 165.4 (s, C=O); ^{19}F NMR ($CDCl_3$) δ −190.87 (m); MS *m/z* (%) 283 (3), 263 (4), 248 (6), 220 (2), 207 (4), 179 (31), 161 (11), 159 (13), 145 (12), 135 (7), 115 (42), 105 (100), 91 (11), 77 (28), 62 (4), 51 (7); IR (KBr) ν 3304 (s), 3063 (w), 3028 (w), 3004 (w), 2974 (w), 2929 (w), 2870 (w), 1668 (m), 1642 (s), 1543 (s), 1496 (w), 1452 (m), 1430 (w), 1386 (m), 1321 (m), 1281 (w), 1225 (s), 1111 (w), 1078 (w), 1032 (w), 1006 (w), 997 (w), 979 (m), 919 (w), 890 (m), 847 (w), 796 (w), 756 (s), 696 (s); Anal. ($C_{18}H_{18}FNO$) C, H, N. The structure of (−)-**14** was confirmed by X-ray structural analysis (Figure 2 and Supporting Information).

(1*R*,2*R*)-(+)-2-Fluoro-2-phenylcyclopropanecarboxylic Acid (1*R*,2*R*)-(+)-9a. The procedure developed by White[17] was followed. To a solution of (+)-**13** (306 mg, 1.08 mmol) in a mixture of Ac_2O (3.7 mL) and AcOH (0.6 mL) was added $NaNO_2$ (0.68 g, 9.8 mmol) at 4 °C. The reaction mixture stirred for 18 h at 4 °C, then allowed to warm to room temperature and poured into H_2O (10 mL). The aqueous phase was extracted with CH_2Cl_2 (75 mL), and the combined organic layers were washed with 5% Na_2CO_3 and H_2O (25 mL) and dried (Na_2SO_4). Complete conversion of the amide was detected by GC. All volatiles were removed under vacuum, and the residue was dissolved in 1,4-dioxane (10 mL) and refluxed for 20 h. After all volatiles were removed under vacuum, the residue was dissolved in methanol (10 mL) and KOH (250 mg, 4.45 mmol) was added. The reaction mixture was stored at room temperature for 8 h and then was concentrated, and H_2O (15 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (20 mL) and then acidified with concentrated HCl to pH 1. The aqueous phase was extracted with CH_2Cl_2 (100 mL), the combined organic phases were dried (Na_2SO_4), and all volatiles were removed under vacuum. After recrystallization from CH_2Cl_2/pentane (1*R*,2*R*)-(+)-**9a** was isolated as white powder (Yield: 100 mg, 51%). Data for (1*R*,2*R*)-(+)-**9a**: $[\alpha]^{20}_D$ +293.5 (c = 1.0, $CHCl_3$).

(1*S*,2*S*)-(−)-2-Fluoro-2-phenylcyclopropanecarboxylic Acid (1*S*,2*S*)-(−)-9a. Using the same procedure as above, hydrolysis of (−)-**14** (126 mg, 0.445 mmol) gave, after recrystallization from CH_2Cl_2/pentane as a white powder (Yield: 63 mg, 79%). Data for (1*S*,2*S*)-(−)-**9a**: $[\alpha]^{20}_D$ −292.9 (c = 1.0, $CHCl_3$).

General Procedure for Curtius Degradation of 2-Fluoro-2-phenylcyclopropanecarboxylic Acids. The corresponding 2-fluoro-2-arylcyclopropanecarboxylic acid (1.25 mmol), anhydrous NEt_3 (152 mg, 1.5 mmol), anhydrous ^{t}BuOH (927 mg, 12.5 mmol) and diphenylphosphoryl azide (DPPA) (378 mg, 1.38 mmol) were dissolved in anhydrous cyclohexane (15 mL) under argon. After the reaction mixture was refluxed for 15–18 h, di-*tert*-butyl carbonate (Boc_2O) (410 mg, 1.9 mmol) was added and the resulting solution refluxed for an additional 2 h. The mixture was cooled to room temperature, and ethyl acetate (40 mL) was added. The organic phase was washed with 5% citric acid, H_2O, sat. $NaHCO_3$ and brine (20 mL). Unreacted Boc_2O was removed by bulb-to-bulb distillation. The carbamates were isolated by silica gel chromatography.

***tert*-Butyl *trans*-(±)-[2-Fluoro-2-(4-fluorophenyl)-cyclopropyl]carbamate (11b).** Using the same procedure, **9b** (191 mg, 0.96 mmol) gave, after silica gel chromatography (cyclohexane/ethyl acetate, 10:1), **11b** (Yield: 172 mg, 66%). For elemental analysis the product was recrystallized from ethyl acetate/pentane at −20 °C. Data for **11b**: Mp 126 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (1 H, ddd, J = 6.0 Hz, J = 8.1 Hz, J = 21.7 Hz, CH_AH_B), 1.47 (9 H, s, CH_3), 1.46–1.56 (1 H, m, CH_AH_B), 2.93 (br s, 1 H, CH_X), 4.98 (1 H, br s, NH), 7.02–7.08 (2 H, m, aromatic), 7.32–7.39 (2 H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 19.4 (dt, J = 11.4 Hz, CH_AH_B), 28.3 (q, CH_3), 33.5 (dm, J = 10.2 Hz, CH_X), 78.7 (ds, J = 218.7 Hz, CF), 79.9 (s, C-O), 115.4 (dd, J = 21.6 Hz, aromatic), 127.7–128.4 (md, aromatic), 133.1 (dds, J = 4.4 Hz, J = 22.3 Hz, aromatic), 156.3 (s, C=O), 162.6 (ds, J = 246.7 Hz, C-7 aromatic); ^{19}F NMR ($CDCl_3$) δ −119.91 (1 F, s, aromatic), −187.20 (1 F, s, aliphatic); MS *m/z* (%) 213 (4), 195 (5), 193 (3), 168 (23), 166 (38), 153 (11), 148 (100), 140 (40), 133 (17), 121 (70), 101 (66), 96 (21), 95 (17), 75 (19), 59 (7), 57 (38), 51 (5), 41 (21); IR (KBr) ν 3370 (s), 3093 (w), 3051 (w), 3014 (w), 2988 (m), 2941 (w), 1685 (s), 1610 (w), 1518 (s), 1445 (w), 1395 (w), 1386 (s), 1375 (m), 1301 (w), 1278 (m), 1251 (m), 1231 (m), 1210 (m), 1162 (s), 1119 (w), 1104 (w), 1076 (w), 1062 (w), 1030 (w), 1001 (w), 894 (w), 883 (w), 870 (w), 823 (s), 809 (m), 783 (w), 756 (w), 675 (w), 600 (w); Anal. ($C_{14}H_{17}F_2NO_2$) C, H, N.

***tert*-Butyl *cis*-(±)-[2-Fluoro-2-(4-fluorophenyl)cyclopropyl]carbamate (12b).** Using the general procedure for the Curtius degradation, from **10b** (284 mg, 1.43 mmol) after silica gel chromatography (cyclohexane/ethyl acetate 4:1) **12b** was isolated as a white solid (Yield: 307 mg, 80%). For elemental analysis the product was recrystallized from ethyl acetate/pentane at −20 °C. Data for **12b**: Mp 131 °C (ethyl acetate/pentane); ^{1}H NMR (CDCl$_3$) δ 1.25−1.39 (1 H, m, CH_AH$_B$), 1.32 (9 H, s, CH_3), 1.75 (1 H, ddd, *J* = 8.2 Hz, *J* = 9.7 Hz, *J* = 21.5 Hz, CH$_A$$H_B$), 3.25−3.30 (1 H, m, C$H_X$), 4.38 (1 H, br s, N$H$), 7.03−7.09 (2 H, m, aromatic), 7.35−7.45 (2 H, m, aromatic); ^{13}C NMR (CDCl$_3$) δ 17.8−18.2 (mt, CH$_A$H$_B$), 28.1 (q, CH$_3$), 33.8−34.1 (md, CH$_X$), 79.9 (s, O-C), 80.8 (ds, *J* = 217.4 Hz, CF), 115.2 (dd, *J* = 21.6 Hz, aromatic), 129.0−129.8 (m, aromatic), 155.7 (s, C═O), 162.8 (ds, *J* = 246.7 Hz, aromatic); ^{19}F NMR (CDCl$_3$) δ −113.59 (1 F, br s, aromatic), −167.58 (1 F, br s, aliphatic); MS *m/z* (%) 213 (2), 195 (3), 168 (8), 166 (14), 153 (8), 148 (100), 140 (21), 133 (7), 121 (28), 101 (22), 96 (7), 95 (4), 75 (7), 59 (4), 57 (20), 51 (1), 41 (9); IR (KBr) ν 3383 (s), 3010 (w), 2993 (w), 2972 (w), 2939 (w), 1682 (s), 1611 (w), 1602 (w), 1520 (s), 1445 (w), 1395 (w), 1387 (w), 1370 (m), 1350 (w), 1280 (m), 1259 (w), 1228 (m), 1203 (w), 1165 (m), 1093 (w), 1062 (m), 1022 (w), 1013 (w), 988 (w), 946 (w), 917 (w), 883 (w), 869 (w), 825 (m), 814 (w), 784 (w), 760 (w), 752 (w), 633 (w); Anal. ($C_{14}H_{17}F_2NO_2$) C, H, N.

***tert*-Butyl *trans*-(±)-[2-Fluoro-2-(4-chlorophenyl)cyclopropyl]carbamate (11c).** Using the general procedure, Curtius rearrangement of **9c** (190 mg, 0.89 mmol) produced, after silica gel chromatography (cyclohexane/ethyl acetate, 10:1), **11c**, isolated as a white, voluminous solid (Yield: 146 mg, 58%). For elemental analysis the product was recrystallized from ethyl acetate/pentane at −20 °C. Data for **11c**: Mp 141 °C; ^{1}H NMR (CDCl$_3$) δ 1.35−1.53 (2 H, m, C$H_A$$H_B$), 1.47 (9 H, s, C$H_3$), 2.94 (1 H, br s, C$H_X$), 4.92 (1 H, br s, N$H$), 7.25−7.36 (4 H, m, aromatic); ^{13}C NMR (CDCl$_3$) δ 19.9 (dt, *J* = 14.4 Hz, CH$_A$H$_B$), 28.3 (q, CH$_3$), 34.0 (dd, *J* = 9.2 Hz, CH$_X$), 78.5 (ds, *J* = 218.3 Hz, CF), 80.0 (s, C-O), 126.6 (d, aromatic), 128.7 (d, aromatic), 134.0 (s, aromatic), 136.1 (ds, *J* = 19.2, aromatic), 156.2 (s, C═O); ^{19}F NMR (CDCl$_3$) δ −190.68 (br s); MS *m/z* (%) 231/229 (3/1), 213/211 (2/1), 185 (16), 176 (6), 165 (11), 163 (32), 156 (5), 137 (5), 133 (7), 130 (8), 121 (4), 101 (6), 94 (2), 77 (3), 59 (17), 57 (100), 51 (2), 41 (17); IR (KBr) ν 3342 (s), 3009 (w), 2986 (w), 2933 (w), 1683 (s), 1525 (s), 1498 (m), 1441 (w), 1386 (m), 1371 (m), 1310 (w), 1290 (m), 1252 (m), 1211 (w), 1171 (m), 1115 (w), 1095 (w), 1074 (w), 1032 (w), 1013 (w), 998 (w), 897 (w), 872 (w), 836 (w), 813 (m), 783 (w), 756 (w), 736 (w), 654 (w), 619 (w); Anal. ($C_{14}H_{17}ClFNO_2$) C, H, N.

***tert*-Butyl *cis*-(±)-[2-Fluoro-2-(4-chlorophenyl)cyclopropyl]carbamate (12c).** Using the same procedure, **10c** (346 mg, 1.61 mmol) gave, after silica gel chromatography (cyclohexane/ethyl acetate, 10:1), **12c** (250 mg, 55%) as a white, voluminous solid. For elemental analysis the product was recrystallized from ethyl acetate/pentane at −20 °C. Data for **12c**: Mp 147 °C; ^{1}H NMR (CDCl$_3$) δ 1.25−1.46 (1 H, m, CH_AH$_B$), 1.31 (9 H, s, CH_3), 1.77 (1 H, ddd, *J* = 8.2 Hz, *J* = 9.6 Hz, *J* = 21.5 Hz, CH$_A$$H_B$), 3.22−3.30 (1 H, m, C$H_X$), 4.39 (1 H, br s, N$H$), 7.30−7.45 (4 H, m, aromatic); ^{13}C NMR (CDCl$_3$) δ 18.3 (br m, CH$_A$H$_B$), 28.0 (q, CH$_3$), 34.4 (br s, CH$_X$), 80.1 (s, C−O), 80.7 (ds, *J* = 216.4 Hz, CF), 128.4 (d, aromatic), 132.5 (ds, *J* = 20.3, aromatic), 134.3 (ds, *J* = 6.4 Hz, aromatic), 155.6 (s, C═O); ^{19}F NMR (CDCl$_3$) δ −170.45 (m); MS *m/z* (%)231/229 (3/1), 213/211 (2/1), 185 (14), 176 (14), 165 (8), 163 (29), 154 (7), 137 (5), 133 (12), 130 (7), 121 (6), 101 (6), 77 (1), 59 (17), 57 (100), 51 (2), 41 (18); IR (KBr) ν 3378 (s), 3013 (w), 2988 (w), 2974 (w), 2940 (w), 1675 (s), 1516 (s), 1498 (s), 1444 (w), 1386 (m), 1371 (m), 1345 (w), 1277 (m), 1256 (w), 1231 (w), 1202 (w), 1164 (w), 1097 (m), 1060 (m), 1012 (m), 987 (w), 918 (w), 883 (w), 866 (w), 819 (m), 785 (w), 758 (w), 735 (w), 717 (w), 602 (w); Anal. ($C_{14}H_{17}ClFNO_2$) C, H, N.

***tert*-Butyl *trans*-(±)-[2-Fluoro-2-(4-methylphenyl)cyclopropyl]carbamate (11d).** Using the above procedure, **9d** (243 mg, 1.25 mmol) gave, after silica gel chromatography (cyclohexane/ethyl acetate 10:1), **11d** as a white, voluminous solid (Yield: 252 mg, 76%). For elemental analysis the product was recrystallized from ethyl acetate/pentane at −20 °C. Data for **11d**: Mp 98 °C; ^{1}H NMR (CDCl$_3$) δ 1.37 (1 H, ddd, *J* = 6.1 Hz, *J* = 8.1 Hz, *J* = 22.2 Hz, CH$_A$$H_B$), 1.47 (9 H, s, C−(C$H_3$)$_3$), 1.54 (1 H, ddd, *J* = 8.1 Hz, *J* = 8.3 Hz, *J* = 12.7 Hz, CH_AH$_B$), 2.35 (3 H, s, CH_3), 2.95 (br s, 1 H, CH_X), 4.95 (1 H, br s, NH), 7.15−7.25 (4 H, m, aromatic); ^{13}C NMR (CDCl$_3$) δ 19.9 (dt, *J* = 11.4 Hz, CH$_A$H$_B$), 21.1 (q, C−(CH$_3$)$_3$), 28.3 (q, CH$_3$), 33.6 (dm, CH$_X$), 79.1 (ds, *J* = 218.7 Hz, CF), 79.9 (s, C-O), 125.4 (dd, *J* = 5.1 Hz, aromatic), 129.1 (d, aromatic), 134.4 (ds, *J* = 19.1 Hz, aromatic), 138.0 (s, aromatic), 156.3 (s, C═O); ^{19}F NMR (CDCl$_3$) δ −188.76 (br s); MS *m/z* (%) 209 (6), 191 (2), 189 (9), 176 (6), 171 (5), 164 (13), 148 (21), 144 (51), 137 (13), 133 (4), 130 (16), 117 (11), 115 (10), 103 (2), 91 (5), 77 (2), 65 (3), 59 (17), 57 (100), 41 (31); IR (KBr) ν 3379 (s), 3096 (w), 3036 (w), 3017 (w), 2986 (m), 2929 (w), 1686 (s), 1516 (s), 1459 (w), 1445 (w), 1395 (w), 1386 (w), 1371 (m), 1308 (w), 1279 (m), 1252 (w), 1211 (w), 1168 (s), 1110 (w), 1079 (w), 1066 (w), 1033 (w), 1002 (w), 893 (w), 875 (m), 808 (m), 787 (w), 757 (w), 672 (w); Anal. ($C_{15}H_{20}FNO_2$) C, H, N.

***tert*-Butyl *cis*-(±)-[2-Fluoro-2-(4-methylphenyl)cyclopropyl]carbamate (12d).** Using the same procedure, **10d** (310 mg, 1.60 mmol) gave, after silica gel chromatography (cyclohexane/ethyl acetate 10:1), **12d** isolated as a white, voluminous solid. (Yield: 327 mg, 77%). For elemental analysis the product was recrystallized from ethyl acetate/pentane at −20 °C. Data for **12d**: Mp 125 °C; ^{1}H NMR (CDCl$_3$) δ 1.34 (10 H, s, CH_AH$_B$ and C−(CH_3)$_3$), 1.74 (1 H, ddd, *J* = 8.6 Hz, *J* = 9.1 Hz, *J* = 21.5 Hz, CH$_A$$H_B$), 2.37 (3 H, s, C$H_3$), 3.20−3.36 (1 H, m, C$H_X$), 4.18 (1 H, br s, N$H$), 7.18−7.32 (4 H, m, aromatic); ^{13}C NMR (CDCl$_3$) δ 18.4 (dt, *J* = 11.9 Hz, CH$_A$H$_B$), 21.1 (q, C−(CH$_3$)$_3$), 28.1 (q, CH$_3$), 33.9 (dm, CH$_X$), 79.8 (s, C−O), 81.1 (ds, *J* = 216.1 Hz, CF), 127.3 (dm, aromatic), 129.1 (d, aromatic), 130.6 (ds, *J* = 22.0 Hz, aromatic), 138.5 (ds, *J* = 8.2 Hz, aromatic), 155.8 (s, C═O); ^{19}F NMR (CDCl$_3$) δ −167.63 (br s); MS *m/z* (%) 209 (1), 191 (2), 189 (4), 176 (6), 172 (2), 164 (4), 162 (9), 148 (7), 144 (100), 135 (7), 133 (5), 130 (47), 117 (19), 115 (39), 109 (4), 103 (7), 91 (20), 89 (5), 77 (4), 65 (7), 59 (3), 57 (22), 44 (10), 41 (22); IR (KBr) ν 3383 (s), 3091 (w), 3038 (w), 3013 (w), 2986 (m), 2933 (w), 2875 (w), 1687 (s), 1525 (s), 1513 (s), 1442 (w), 1395 (w), 1371 (m), 1348 (w), 1277 (m), 1255 (m), 1227 (w), 1178 (s), 1121 (w), 1097 (w), 1062 (m), 1020 (w), 983 (m), 918 (m), 883 (w), 866 (w), 813 (m), 784 (w), 760 (w), 751 (w); Anal. ($C_{15}H_{20}FNO_2$) C, H, N.

***tert*-Butyl (1*R*,2*R*)-(−)-(2-Fluoro-2-phenylcyclopropyl)carbamate (1*R*,2*R*)-(−)-11a).** Using the same procedure, Curtius degradation of (1*S*,2*S*)-(−)-**9a** (71 mg, 0.394 mmol) gave, after silica gel chromatography (cyclohexane/ethyl acetate, 6:1), (1*R*,2*R*)-(−)-**11a**) isolated as a white solid. (Yield: 14 mg, 14%). Analysis by chiral GC revealed an enantiomeric excess of > 98%. Data for (1*R*,2*R*)-(−)-**11a**. α_D^{20} −89.3 (*c* = 1.0, CHCl$_3$), >98% ee.

***tert*-Butyl (1*S*,2*S*)-(+)-(2-Fluoro-2-phenylcyclopropyl)carbamate (1*S*,2*S*)-(+)-11a.** Using the same procedure, (1*R*,2*R*)-(+)-**9a**) (96 mg, 0.531 mmol) gave, after silica gel chromatography (cyclohexane/ethyl acetate, 6:1), (1*S*,2*S*)-(+)-**11a** isolated as a white solid (Yield: 46 mg, 35%). Analysis by chiral GC revealed an enantiomeric excess of > 98%. Data for (1*S*,2*S*)-(+)-**11a**: α_D^{20} +89.9 (*c* = 1.0, CHCl$_3$), >98% ee.

General Procedure for Deprotection with HCl in Methanol. The corresponding Boc protected amine (1 mmol) was dissolved in methanolic HCl (20 mL) and stirred for 2−3 h at room temperature. All volatiles were removed under vacuum. The resulting white residue was washed with Et$_2$O (40 mL), and the product was purified by recrystallization from MeOH/Et$_2$O.

General Procedure for Deprotection with THF/HCl. The corresponding Boc protected amine (1 mmol) was dissolved in a mixture of THF (10 mL) and 6 M HCl (10 mL). The reaction mixture was stirred for 12 h at room temperature. All volatiles were removed under vacuum and the resulting white residue was dried for 24 h over P$_2$O$_5$ under vacuum. The product was purified by recrystallization from MeOH/Et$_2$O.

***trans*-(±)-2-Fluoro-2-(4-fluorophenyl)cyclopropylamine Hydrochloride (2b).** Using the same procedure, **2b**

was synthesized from **11c** (107 mg, 0.40 mmol). After recrystallization from methanol/Et_2O, **2b** was isolated as a white solid (Yield: 68 mg, 83%). Data for **2b**: Mp. > 160 °C (decomp). ^{1}H NMR (methanol-d_4, 400 MHz) δ 1.79–1.86 (2 H, m, CH_AH_B), 3.05–3.09 (1 H, m, CH_X), 4.84 (3 H, s, NH_3^+), 7.16–7.20 (2 H, m, aromatic), 7.50–7.53 (2 H, m, aromatic); ^{13}C NMR (methanol-d_4, 100.63 MHz) δ 17.8 (dt, $J = 12.4$ Hz, CH_AH_B), 32.5 (dd, $J = 10.4$ Hz, CH_X), 79.1 (ds, $J = 219.2$ Hz, CF), 117.0 (dd, $J = 22.1$ Hz, aromatic), 130.0 (ddd, $J = 5.0$ Hz, $J = 8.6$ Hz, aromatic), 132.7 (dds, $^{4}J = 3.2$ Hz, $J = 21.3$ Hz, aromatic), 164.9 (dds, $^{5}J = 2.2$ Hz, $J = 247.5$ Hz, aromatic); ^{19}F NMR (Methanol-d_4) δ −112.57 (1 F, m, aromatic), −184.81 (1 F, m, aliphatic); MS (ESI) *m/z* (%) 170 (100), 153 (4), 150 (42); IR (KBr) ν 3550 (m), 3476 (m), 3375 (s), 3100 (w), 3016 (w), 2997 (w), 2972 (w), 2938 (w), 2924 (w), 1691 (s), 1515 (s), 1457 (w), 1445 (w), 1393 (w), 1369 (m), 1348 (w), 1281 (m), 1259 (w), 1227 (w), 1195 (w), 1166 (m), 1096 (w), 1064 (m), 1022 (w), 989 (w), 920 (w), 886 (w), 813 (m), 785 (w), 759 (w), 751 (w), 620 (m), 585 (m); Anal. ($C_9H_{10}ClF_2N$) C, H, N.

***cis*-(±)-2-Fluoro-2-(4-fluorophenyl)cyclopropylamine Hydrochloride (3b).** Using the general procedure for deprotection with THF/HCl, **3b** was synthesized using **12b** (148 mg, 0.55 mmol). After recrystallization from methanol/Et_2O, **2c** was isolated as a white solid (Yield: 104 mg, 93%). Data for 3b: Mp 155 °C (decomp); ^{1}H NMR (methanol-d_4) δ 1.78 (1 H, ddd, $J = 6.0$ Hz, $J = 9.5$ Hz, $J = 10.0$ Hz, CH_AH_B), 1.95 (1 H, ddd, $J = 9.5$ Hz, $J = 10.0$ Hz, $J = 20.0$ Hz, CH_AH_B), 3.40 (1 H, ddd, $J = 6.0$ Hz, $J = 10.0$ Hz, $J = 13.9$ Hz, CH_X), 4.78 (3 H, s, NH_3^+), 7.23–7.29 (2 H, m, aromatic), 7.67–7.72 (2 H, m, aromatic); ^{13}C NMR (methanol-d_4) δ 16.4 (dt, $J = 14.0$ Hz, CH_AH_B), 32.9 (dd, $J = 21.6$ Hz, CH_X), 80.0 (ds, $J = 220.0$ Hz, CF), 117.5 (dd, $J = 22.9$ Hz, aromatic), 128.3 (dds, $J = 3.8$ Hz, $J = 20.3$ Hz, aromatic), 133.6 (ddd, $J = 2.5$ Hz, $J = 8.9$ Hz, aromatic), 162.8 (dds, $J = 3.8$ Hz, $J = 249.2$ Hz, aromatic); ^{19}F NMR (methanol-d_4) δ −110.47 (1 F, dm, $J = 3.8$ Hz, aromatic), −158.47 (1 F, dm, $J = 3.8$ Hz, aliphatic); MS (ESI) *m/z* (%)170 (20), 153 (100), 150 (10), 133 (38), 127 (5), 123 (22), 30 (38); IR (KBr) ν 3553 (m), 3484 (s), 3414 (s), 2934 (br), 1636 (m), 1608 (s), 1564 (m), 1520 (s), 1489 (m), 1459 (m), 1412 (w), 1397 (w), 1314 (m), 1242 (s), 1191 (w), 1158 (w), 1096 (w), 1071 (m), 1048 (w), 1014 (m), 960 (w), 915 (m), 880 (m), 846 (s), 823 (m), 792 (w), 726 (w), 655 (w). Anal. ($C_9H_{10}ClF_2N$) C, H, N.

***trans*-(±)-2-Fluoro-2-(4-chlorophenyl)cyclopropylamine Hydrochloride (2c).** Using the general procedure for deprotection with THF/HCl, **11c** (113 mg, 0.395 mmol) was hydrolyzed to give **2c** as a white solid (Yield: 61 mg, 80%). Data for **2c**: Mp > 166 °C (decomp); ^{1}H NMR (methanol-d_4) δ 0.64–0.73 (2 H, m, CH_AH_B), 1.90–1.95 (1 H, m, CH_X), 3.17 (3 H, s, NH_3^+), 6.25–6.32 (4 H, m, aromatic); ^{13}C NMR (methanol-d_4) δ 17.9 (dt, $J = 12.7$ Hz, CH_AH_B), 32.5 (dd, $J = 10.2$ Hz, CH_X), 78.7 (ds, $J = 218.7$ Hz, CF), 126.6 (dd, $J = 5.1$ Hz, aromatic), 130.0 (d, aromatic), 135.3 (ds, $J = 21.6$ Hz, aromatic), 136.1 (ds, $J = 2.5$ Hz, aromatic); ^{19}F NMR (methanol-d_4) δ −188.35 (m); MS (ESI) *m/z* (%) 186 (30), 168 (13), 166 (100), 131 (39); IR (KBr) ν 3553 (s), 3479 (s), 3418 (s), 2916 (br), 2923 (w), 2678 (w), 1639 (m), 1619 (m), 1522 (w), 1499 (w), 1450 (w), 1315 (w), 1287 (w), 1244 (w), 1104 (w), 1073 (w), 1016 (w), 1008 (w), 966 (w), 900 (w), 876 (w), 830 (m), 795 (w), 741 (w), 624 (m); Anal. ($C_9H_{10}Cl_2FN$) C, H, N.

***cis*-(±)-2-Fluoro-2-(4-chlorophenyl)cyclopropylamine Hydrochloride (3c).** Using the general procedure for deprotection with HCl in methanol, **3c** was synthesized from **12c** (98 mg, 0.343 mmol). After recrystallization from methanol/Et_2O (1:3) **3c** was isolated as a white solid (Yield: 61 mg, 80%). Data for **3c**: Mp > 145 °C (decomp); ^{1}H NMR (methanol-d_4) δ 1.80 (1 H, ddd, $J = 6.2$ Hz, $J = 6.2$ Hz, $J = 9.3$ Hz, CH_AH_B), 1.96 (1 H, ddm, $J = 6.2$ Hz, $J = 19.8$ Hz, CH_AH_B), 3.41 (1 H, ddd, $J = 6.2$ Hz, $J = 10.1$ Hz, $J = 14.0$ Hz, CH_X), 4.77 (3 H, s, NH_3^+), 7.52–7.65 (4 H, m, aromatic); ^{13}C NMR (methanol-d_4) δ 16.0 (dt, $J = 12.7$ Hz, CH_AH_B), 32.7 (dd, $J = 22.9$ Hz, CH_X), 79.6 (ds, $J = 221.3$ Hz, CF), 130.5 (d, aromatic), 132.2 (ds, $J = 5.1$, aromatic), 137.7 (s, aromatic); ^{19}F NMR (methanol-d_4) δ −160.33 (m); MS (ESI) *m/z* (%) 188/186 (100/32), 102 (57); IR (KBr) ν 3418 (br), 2925 (s), 2858 (s), 1748 (w), 1645 (m), 1466 (w), 1458 (w), 1386 (m), 1263 (w), 1127 (m), 837 (w); Anal. ($C_9H_{10}Cl_2FN$) C, H, N.

***trans*-(±)-2-Fluoro-2-(4-methylphenyl)cyclopropylamine Hydrochloride (2d).** Using the general procedure for deprotection with THF/HCl, **2d** was synthesized from **11b** (53 mg, 0.263 mmol). After recrystallization from methanol/Et_2O **2d** was isolated as a white solid (Yield: 36 mg, 89%). Data for **2d**: Mp > 166 °C (decomp). ^{1}H NMR (methanol-d_4) δ 1.72–1.82 (2 H, m, CH_AH_B), 2.36 (3 H, s, CH_3), 2.98–3.04 (1 H, m, CH_X), 4.78 (3 H, br s, NH_3^+), 7.23–7.34 (4 H, m, aromatic); ^{13}C NMR (methanol-d_4) δ 17.9 (dt, $J = 12.7$ Hz, CH_AH_B), 21.5 (q, CH_3), 32.5 (dd, $J = 10.2$ Hz, CH_X), 79.5 (ds, $J = 218.7$ Hz, CF), 127.3 (dd, $J = 5.1$ Hz, aromatic), 130.8 (d, aromatic), 133.7 (ds, $J = 20.3$ Hz, aromatic), 140.8 (s, aromatic); ^{19}F NMR (methanol-d_4) δ −186.07 (m); MS (ESI) *m/z* (%) 166 (15), 149 (4), 146 (100), 131 (7); IR (KBr) ν 3050 (m), 2941 (br s), 2896 (br s), 2774 (w), 2714 (m), 2682 (m), 2659 (w), 2005 (m), 1605 (w), 1590 (w), 1521 (s), 1449 (w), 1385 (m), 1321 (w), 1296 (w), 1244 (w), 1212 (w), 1194 (w), 1176 (w), 1120 (w), 1109 (w), 1076 (m), 1055 (w), 1023 (w), 1007 (w), 963 (m), 898 (m), 876 (w), 822 (m), 799 (s), 786 (s), 650 (w); Anal. ($C_{10}H_{13}ClFN$) C, H, N.

***cis*-(±)-2-Fluoro-2-(4-methylphenyl)cyclopropylamine Hydrochloride (3d).** Using the general procedure for deprotection with HCl in methanol, **12b** (286 mg, 1.08 mmol) was converted to **3d**, isolated as a white solid (Yield: 193 mg, 89%). Data for **3d**; Mp >145 °C (decomp); ^{1}H NMR (methanol-d_4) δ 1.74 (1 H, ddd, $J = 6.0$ Hz, $J = 9.8$ Hz, $J = 10.0$ Hz, CH_AH_B), 1.90 (1 H, ddd, $J = 9.8$ Hz, $J = 9.8$ Hz, $J = 19.6$ Hz, CH_AH_B), 2.39 (3 H, s, CH_3), 3.36 (1 H, ddd, $J = 6.0$ Hz, $J = 9.8$ Hz, $J = 13.8$ Hz, CH_X), 4.78 (3 H, s, NH_3^+), 7.34 (2 H, d, $J = 7.9$ Hz, aromatic), 7.52 (2 H, d, $J = 7.9$ Hz, aromatic); ^{13}C NMR (methanol-d_4) δ 15.9 (dt, $J = 14.0$ Hz, CH_AH_B), 21.4 (q, CH_3), 32.5 (dd, $J = 21.6$ Hz, CH_X), 80.0 (ds, $J = 220.0$ Hz, CF), 130.6 (ds, $J = 20.3$ Hz, aromatic), 130.6 (dd, $J = 3.8$ Hz, aromatic), 130.9 (d, aromatic), 142.1 (ds, $^{5}J = 2.5$ Hz, aromatic); ^{19}F NMR (methanol-d_4) δ −158.48 (m); MS (ESI) *m/z* (%) 167 (11), 166 (100), 102 (5); IR (KBr) ν 3061 (m), 2875 (br s), 2775 (s), 2683 (m), 2647 (m), 2598 (m), 2007 (w), 1615 (w), 1592 (w), 1522 (w), 1499 (m), 1449 (w), 1386 (m), 1344 (m), 1204 (m), 1181 (w), 1123 (m), 1112 (m), 1066 (w), 1037 (w), 1012 (w), 956 (w), 915 (m), 865 (w), 826 (s), 806 (w), 733 (w); Anal. ($C_{10}H_{13}ClFN\cdot 1/3H_2O$) C, H, N.

(1*R*,2*R*)-(−)-2-Fluoro-2-phenylcyclopropylamine Hydrochloride [(1*R*,2*R*)-(−)-2a]. Using the general procedure for deprotection with THF/HCl, (1*R*,2*R*)-(−)-**2a** was synthesized from (1*R*,2*R*)-(−)-**11a** (29 mg, 0.155 mmol). After recrystallization from methanol/Et_2O, (1*R*,2*R*)-(−)-**2a** (17 mg, 58%) was isolated as a white solid. Data for (1*R*,2*R*)-(−)-**2a**: $[\alpha]_D^{20}$ −70.9 ($c = 1.0$, MeOH).

(1*S*,2*S*)-(+)-2-Fluoro-2-phenylcyclopropylamine Hydrochloride [(1*S*,2*S*)-(+)-2a]. Using the general procedure for deprotection with THF/HCl, (1*S*,2*S*)-(+)-**2a** was synthesized from (1*S*,2*S*)-(+)-**11a** (40 mg, 0.159 mmol). After recrystallization from methanol/Et_2O, (1*S*,2*S*)-(+)-**2a** was isolated as white solid (Yield: 26 mg, 87%). Data for (1*S*,2*S*)-(+)-**2a**: $[\alpha]_D^{20}$ +70.2 ($c = 1.0$, MeOH).

X-ray Data. *trans*-(±)-2-Fluoro-2-(4-fluorophenyl)cyclopropanecarboxylic Acid (9b). Formula $C_{10}H_8F_2O_2$, $M = 198.16$, colorless crystal 0.25 × 0.20 × 0.10 mm, $a = 5.853(1)$, $b = 7.167(1)$, $c = 21.175(3)$ Å, $\beta = 94.04(1)°$, $V = 886.1(2)$ Å^3, $\rho_{calcd} = 1.486$ g cm^{-3}, $\mu = 11.32$ cm^{-1}, empirical absorption correction via ψ scan data ($0.765 \le T \le 0.895$), $Z = 4$, monoclinic, space group $P2_1/n$ (No. 14), $\lambda = 1.54178$ Å, $T = 223$ K, $\omega/2\theta$ scans, 1849 reflections collected ($\pm h, +k, +l$), $[(\sin\theta)/\lambda] = 0.62$ Å^{-1}, 1803 independent ($R_{int} = 0.028$) and 1593 observed reflections [$I \ge 2\,\sigma(I)$], 129 refined parameters, $R = 0.037$, $wR^2 = 0.111$, max. residual electron density 0.21 (−0.20) e Å^{-3}, hydrogens calculated and refined as riding atoms.

***cis*-(±)-2-Fluoro-2-(4-fluorophenyl)cyclopropanecarboxylic Acid (10b).** Formula $C_{10}H_8F_2O_2$, $M = 198.16$, colorless crystal 0.50 × 0.10 × 0.05 mm, $a = 13.617(4)$, $b = 5.591(2)$, $c = 12.418(2)$ Å, $\beta = 109.78(2)°$, $V = 889.6(4)$ Å^3, $\rho_{calcd} = 1.480$ g cm^{-3}, $\mu = 11.28$ cm^{-1}, empirical absorption correction via ψ

scan data ($0.603 \leq T \leq 0.946$), $Z = 4$, monoclinic, space group $P2_1/c$ (No. 14), $\lambda = 1.54178$ Å, $T = 223$ K, $\omega/2\theta$ scans, 3585 reflections collected ($\pm h$, $-k$, $\pm l$), [(sin θ)/λ] = 0.62 Å^{-1}, 1795 independent ($R_{int} = 0.051$) and 942 observed reflections [$I \geq 2\sigma(I)$], 128 refined parameters, $R = 0.043$, $wR^2 = 0.091$, max. residual electron density 0.15 (−0.25) e Å^{-3}, hydrogens calculated and refined as riding atoms.

***trans*-(±)-2-(4-Chlorophenyl)-2-fluorocyclopropanecarboxylic Acid (9c).** Formula $C_{10}H_8ClFO_2$, $M = 214.61$, colorless crystal 0.25 × 0.20 × 0.03 mm, $a = 9.294(2)$, $b = 22.969(5)$, $c = 9.916(2)$ Å, $\beta = 111.28(2)°$, $V = 1972.5(7)$ Å^3, $\rho_{calcd} = 1.445$ g cm^{-3}, $\mu = 33.46$ cm^{-1}, empirical absorption correction via ψ scan data ($0.488 \leq T \leq 0.906$), $Z = 8$, monoclinic, space group $P2_1/n$ (No. 14), $\lambda = 1.54178$ Å, $T = 223$ K, $\omega/2\theta$ scans, 3114 reflections collected ($\pm h$, $-k$, $-l$), [(sin θ)/λ] = 0.62 Å^{-1}, 2931 independent ($R_{int} = 0.027$) and 1262 observed reflections [$I \geq 2\sigma(I)$], 255 refined parameters, $R = 0.065$, $wR^2 = 0.142$, max. residual electron density 0.38 (−0.37) e Å^{-3}, hydrogens calculated and refined as riding atoms.

(1*S*,2*S*)-(−)-(2-Fluoro-2-phenyl)cyclopropanecarboxylic (*S*)-(1-Phenylethyl)amide (14). Formula $C_{18}H_{18}FNO_2$, $M = 283.33$, colorless crystal 0.70 × 0.10 × 0.10 mm, $a = 9.762(1)$, $b = 12.912(1)$, $c = 24.489(1)$ Å, $V = 3086.8(4)$ Å^3, $\rho_{calcd} = 1.219$ g cm^{-3}, $\mu = 6.75$ cm^{-1}, empirical absorption correction via SORTAV ($0.649 \leq T \leq 0.936$), $Z = 8$, orthorhombic, space group $P2_12_12_1$ (No. 19), $\lambda = 1.54178$ Å, $T = 223$ K, ω and φ scans, 14575 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sin θ)/λ] = 0.59 Å^{-1}, 4056 independent ($R_{int} = 0.119$) and 2536 observed reflections [$I \geq 2\sigma(I)$], 390 refined parameters, $R = 0.069$, $wR^2 = 0.190$, max. residual electron density 0.54 (−0.22) e Å^{-3}, Flack parameter −0.2(4), hydrogens calculated and refined as riding atoms.

Enzyme Assay. Microbial tyramine oxidase was purchased from Sigma and was dissolved in 25 mM potassium phosphate (pH 7.2). Protein concentration was measured by the method of Bradford.[28] The activity of tyramine oxidase was measured spectrophotometrically using benzylamine as a substrate as already reported.[11]

Observation of Time-Dependent Inhibition. The experimentals were carried out by the previously described method of Kitz and Wilson[29] as follows. The incubation of tyramine oxidase with compound was carried out at 25 °C in 0.125 mL of 0.1 M potassium phosphate (pH 7.2) containing 0.021 μg of tyramine oxidase, 6% of dimethyl sulfoxide, and different concentrations of inhibitor. Aliquots (20 μL) were taken out periodically from the mixture, and diluted with 0.48 mL of assay solution followed by the observation of the increase of absorbance at 250 nm as described above.

Acknowledgment. This research project was supported in part by the Deutsche Forschungsgemeinschaft (Graduiertenkolleg “Hochreaktive Mehrfachbindungssysteme”) and the Fonds der Chemischen Industrie. We are grateful to Professor Klaus Müller and co-workers, F. Hoffmann La Roche Ltd, Basel, Switzerland, for pK_a measurements.

Supporting Information Available: Crystal data and structure refinement for *trans*-(±)-2-fluoro-2-(4-fluorophenyl)cyclopropanecarboxylic acid (**9b**), for *trans*-(±)-2-(4-chlorophenyl)-2-fluorocyclopropanecarboxylic acid (**9c**), for *cis*-(±)-2-fluoro-2-(4-fluorophenyl)cyclopropanecarboxylic acid (**10b**) and for (1*S*,2*S*)-(−)-(2-fluoro-2-phenyl)cyclopropanecarboxylic (*S*)-(1-phenylethyl)amide (**14**). 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) Callingham, B. A.; Barrand, M. A. Some Properties of Semicarbazide-Sensitive Amine Oxidases. *J. Neural. Transm. Suppl.* **1987**, *23*, 37−54.

(3) (a) Janes, S. M.; Mu, D.; Wemmer, D.; Smith, A. J.; Kaur, S.; Maltby, D.; Burlingame, A. L.; Klinman, J. P. A new redox cofactor in eukaryotic enzymes: 6-hydroxydopa at the active site of bovine serum amine oxidase. *Science* **1990**, *248*, 981−987. (b) Janes, S. M.; Klinman, J. P. An Investigation of Bovine Serum Amine Oxidase Active Site Stoichiometry: Evidence for an Aminotransferase Mechamism Involving Two Carbonyl Cofactors. *Biochemistry* **1991**, *30*, 4599−4605. (c) 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. (d) Klinman, J. P. The multi-functional topa-quinone copper amine oxidases. *Biochim. Biophys. Acta* **2003**, *1647*, 131−137.

(4) (a) Parsons, M. R.; Convery, M. A.; Wilmot, C. M.; Yadav, K. D. S.; Blakeley, V.; Corner, A. S.; Phillips, S. E. V.; McPherson, M. J.; Knowles, P. F. Crystal Structure of a Quinoenzyme: Copper Amine Oxidase of *Escherichia coli* at 2Å Resolution. *Structure* **1995**, *3*, 1171−1184. (b) Wilce, M. C. J.; Dooley, D. M.; Freeman, H. C.; Guss, J. M.; Matsunami, H.; McIntire, W. S.; Ruggiero, C. E.; Tanizawa, K.; Yamaguchi, H. Crystal Structure of the Copper-Containing Amine Oxidase from *Arthrobacter globiformis* in the Holo and Apo Forms: Implications for the Biogenesis of Topaquinone. *Biochemistry* **1997**, *36*, 16116−16133. (c) 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. (d) Kumar, V.; Dooley, D. M.; Freeman, H. C.; Guss, J. M.; Harvey, I.; McGuirl, M. A.; Wilce, M. C. J.; Zubak, V. M. Crystal Structure of a Eukaryotic (Pea Seeding) Copper-containing Amine Oxidase at 2.2 Å Resolution. *Structure* **1996**, *4*, 943−955. (e) Mure, M.; Mills, S. A.; Klinman, J. P. Catalytic Mechanism of the Topa Quinone Containing Copper Amine Oxidases. *Biochemistry* **2002**, *41*, 9269−9278.

(5) Yu, P. H.; Wright, S.; Fan, E. H.; Lun, Z.-R.; Gubisne-Haberle, D. Physiological and phatological implications of semicarbazide-sensitive amine oxidase. *Biochim. Biophys. Acta* **2003**, *1647*, 193−199 and references therein.

(6) Zorzano, A.; Abella, A.; Marti, L.; Carpene, C.; Palacin, M.; Testar, X. Semicarbazide-sensitive amine oxidase activity exerts insulin-like effects on glucose metabolism and insulin-signaling pathways in adipose cells. *Biochim. Biophys. Acta* **2003**, *1647*, 3−9 and references therein.

(7) 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.

(8) Boomsma, F.; Bhaggoe, U. S.; van der Houwen, A. M. B.; van den Meiracker, A. H. Plasma semicarbazide-sensitive amine oxidas in human (patho)physiology. *Biochim. Biophys. Acta* **2003**, *1647*, 48−54 and references therein.

(9) (a) Lewinsohn, R. Mammalian Monoamine-oxidizing Enzymes with Special Reference to Benzylamine oxidase in Human Tissues. *Brazilian J. Med. Biol. Res.* **1984**, *17*, 223−256. (b) Lizcano, J. M.; Escrich, E.; Ribalta, T.; Muntane, J.; Unzeta, M. Amine Oxidase Activities in Rat Breast Cancer Induced Experimentally with 7,12-Dimethylbenz(α)anthracene. *Biochem. Pharmacol.* **1995**, *42*, 263−269.

(10) (a) 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. (b) Shepard, E. M.; Heather, H.; Juda, G. A.; Dooley, D. M. Inhibition of Six Copper-containing Amine Oxidases by the Antidepressant Drug Tranylcypromine. *Biochim. Biophys. Acta* **2003**, *1647*, 252−259.

(11) Yoshida, S.; Meyer, O. G. J.; Rosen, T. C.; Haufe, G.; Ye, S.; Sloan, M. J.; Kirk, K. L. Fluorinated Phenylcyclopropylamines: Part 1. Synthesis and Effect of Fluorine Substitution at the Cyclopropane Ring on Inhibition of Microbial Tyramine Oxidase. *J. Med. Chem.* **2004**, *47*, 1796−1806.

(12) Meyer, O. G. J.; Fröhlich, R.; Haufe, G. Asymmetric Cyclopropanation of Vinyl Fluorides: Access to Enantiopure Monofluorinated Cyclopropane Carboxylates. *Synthesis* **2000**, 1479−1490.

(13) Haufe, G.; Alvernhe, G.; Laurent, A.; Ernet, T.; Goj, O.; Kröger, S.; Sattler, A. Bromofluorination of alkenes. *Org. Synth.* **1999**, *76*, 159−168.

(14) Eckes, L.; Hanack, M. Herstellung von Vinylfluoriden. *Synthesis* **1978**, 217−218.

(15) Kim, D.; Weinreb, S. M. Elaboration of the Pyridine C−Ring Functionality in Streptonigin Precursor. *J. Org. Chem.* **1978**, *43*, 125−131.

(16) Zhang, X.; Hodgetts, K.; Rachwal, S.; Zhao, H.; Wasley, J. W. F.; Craven, K.; Brodbeck, R.; Kieltyka, A.; Hoffman, D.; Bacolod, M. D.; Girard, B.; Tran, J.; Thurkauf, A. *trans*-1-[(2-Phenylcyclopropyl)methyl]-4-arylpiperazines: Mixed Dopamine D_2/D_4 Receptor Antagonists as Potential Antipsychotic Agents. *J. Med. Chem.* **2000**, *43*, 3923–3932.

(17) White, E. H. The Chemistry of the *N*-Alkyl-*N*-nitrosoamides. *J. Am. Chem. Soc.* **1955**, *77*, 6008–6010.

(18) Schlosser, M. Parametrization of substituents – effect of fluorine and other heteroatoms on OH, NH, and CH acidities. *Angew. Chem.* **1998**, *110*, 1538–1556; *Angew. Chem., Int. Ed.* **1998**, *37*, 1496–1513.

(19) Fuller, R. W.; Molly, B. B. The effect of aliphatic fluorine on amine drugs. *Biochemistry Involving Carbon–Fluorine Bond*; ACS Symposium Series, Vol 28, American Chemical Society: Washington, DC, 1976; pp 77–98.

(20) (a) Moises, H.-W.; Beckmann, H. Antidepressant efficacy of tranylcypromine isomers: a controlled study. *J. Neural Transm.* **1981**, *50*, 185–192. (b) Moises, H.-W.; Beckmann, H. Double-blind study of the antidepressive activity of tranylcypromine isomers. *Arzneim.-Forsch.* **1982**, *32*, 896–897.

(21) Zajoncova, L.; Frebort, I.; Luhova, L.; Sebela, M.; Galuszka, P.; Pec, P. Comparison of kinetic properties of amine oxidases from sainfoin and lentil and immunochemical characterization of copper/quinoprotein amine oxidases. *Biochem. Mol. Biol. Int.* **1999**, *47*, 47–61.

(22) Shepard, E. M.; Smith, J.; Elmore, B. O.; Kuchar, J. A.; Sayre, L. M.; Dooley, D. M. Towards the development of selective amine oxidase inhibitors-Mechanism based inhibition of six copper containing amine oxidases. *Eur. J. Biochem.* **2003**, *269*, 3645–3658.

(23) Yoshida, S.; Rosen, T. C.; Meyer, O. G. J.; Sloan, M. J.; Ye, S.; Haufe, G.; Kirk, K. L. Fluorinated Phenylcyclopropylamines. Part 3: Inhibition of Monoamine Oxidase A and B. *Bioorg. Med. Chem.* **2004**, *12*, 2645–2652.

(24) Ekblom, J. Potential Therapeutic Value of Drugs Inhibiting Semicarbazide-sensitive Amine Oxidase: Vascular Cytoprotection in Diabetes Mellitus. *Pharm. Res.* **1998**, *37*, 87–92.

(25) Boomsma, F.; de Kam, P. J.; Tjeerdsma, G.; van den Meiracker, A. H.; van Veldhuisen, D. J. Plasma Semicarbazide-sensitive Amine Oxidase (SSAO) is an Independent Prognostic Marker for Mortality in Chronic Heart Failure. *Eur. Heart J.* **2000**, *21*, 1859–1863.

(26) Heitz, W.; Knebelkamp, A. Synthesis of fluorostyrenes via palladium catalyzed reactions of aromatic halides with fluoroolefins. *Macromol. Chem., Rapid Commun.* **1991**, *12*, 69–75.

(27) Ernet, T.; Maulitz, A. H.; Würthwein, E.-U.; Haufe, G. Chemical Consequences of Fluorine Substitution. Part 1. Experimental and Theoretical Results on Diels–Alder Reactions of α- and β-Fluorostyrenes. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1929–1938.

(28) 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.

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

JM049957T