

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

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A series of para-substituted diastereopure *cis*- and *trans*-2-fluoro-2-arylcylopropylamines 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-arylcylopropylamine 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-phenylcylopropylamine and by a factor of 90 compared to tranlycypromine. Activity also was strongly dependent on the absolute configuration. The (1*S*,2*S*)-enantiomer of 2-fluoro-2-phenylcylopropylamine was an excellent inhibitor of tyramine oxidase whereas the (1*R*,2*R*)-enantiomer was essentially devoid of activity.

### Introduction

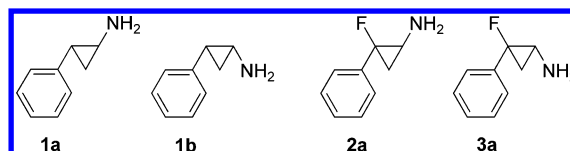
Monoamine oxidases, prevalent in mammals, plants and both prokaryotic and eukaryotic microorganisms, catalyze the oxidation of amines to aldehydes. They have been classified into two groups, copper- (EC 1.4.3.6) and flavin-containing amine oxidases (EC 1.4.3.4).<sup>1</sup>

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.<sup>2</sup> 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,<sup>4</sup> an important example of which has been identified as 2,4,5-trihydroxyphenylalanine quinone (TPQ), elaborated from a tyrosine precursor in the polypeptide chain.<sup>3</sup> 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.<sup>4</sup>

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.<sup>5</sup> Stimulation of these enzymes correlates with an increased glucose uptake.<sup>6</sup> 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.<sup>7</sup> Yu et al. have proposed that metabolites of CAO-catalyzed deaminations could be implicated in certain diseases.<sup>5</sup> In fact, elevated CAO-activity was found for patients with diabetes mellitus and vascular diseases.<sup>8</sup> Amine oxidases are also implicated in the formation of vascular plaques linked to congestive heart failure.<sup>9</sup>

Because of the diverse physiological role of CAOs, selective inhibitors of these enzymes have potential as useful pharmacological and medicinal agents. Tranlycypromine (**1a**, *trans*-2-phenylcylopropylamine), an analogue of amine substrates of CAOs, was demonstrated to be a potent inhibitor of the enzymes.<sup>10</sup> 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-phenylcylopropylamine (**2a**) is an excellent inhibitor of commercially available tyramine oxidase from *Arthrobacter* sp. Inhibition was reversible and competitive, and the IC<sub>50</sub> was 10 times lower than that of the nonfluorinated parent, tranlycypromine (**1a**). In this study, we also confirmed earlier reports that the commercial enzyme is a copper-containing amine oxidase (CAO).<sup>11</sup>



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

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<sup>||</sup> X-ray analysis.

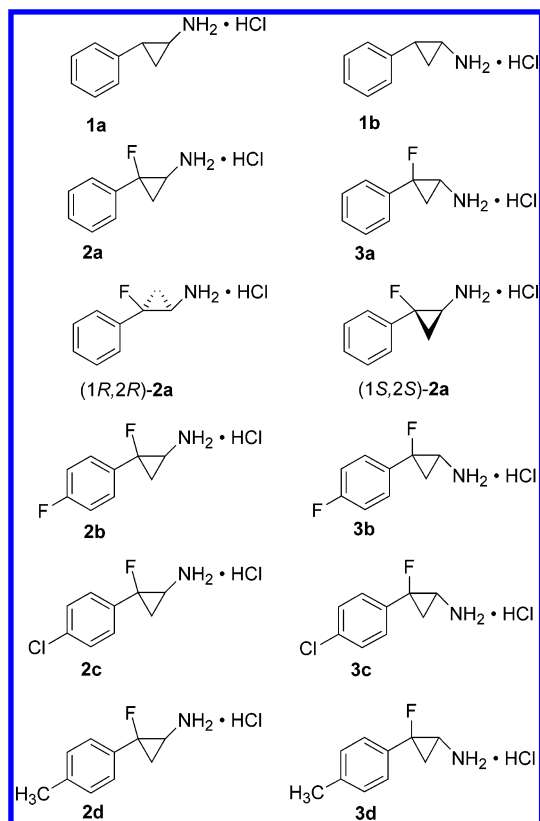


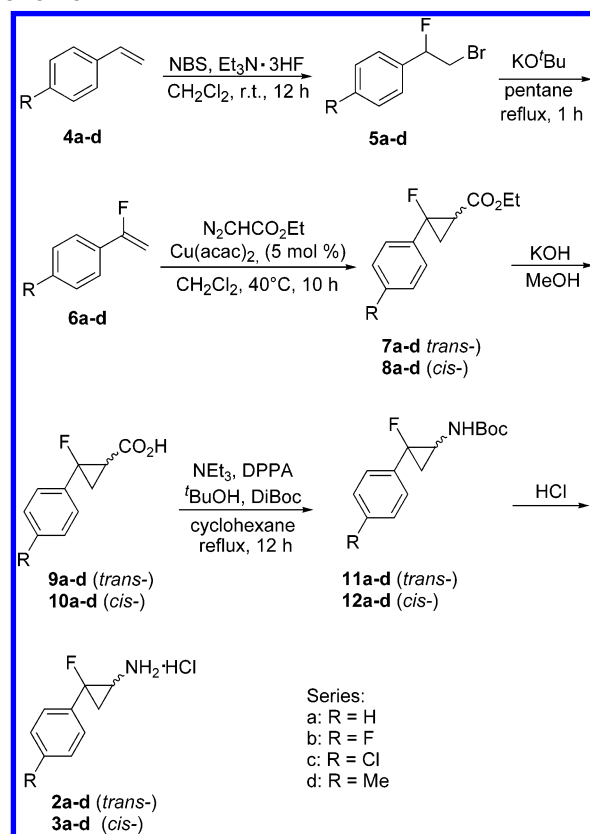
Figure 1. Compounds used in this study.

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**<sup>12</sup> 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<sup>13</sup> produced 2-bromo-1-fluoro-1-(4-(para-substituted-phenyl))ethanes **5b–d**. Base-catalyzed elimination of HBr analogous to a known procedure<sup>14</sup> gave the corresponding 1-fluorostyrenes **6b–d**. Subsequent Cu(acac)<sub>2</sub>-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**

## Scheme 1

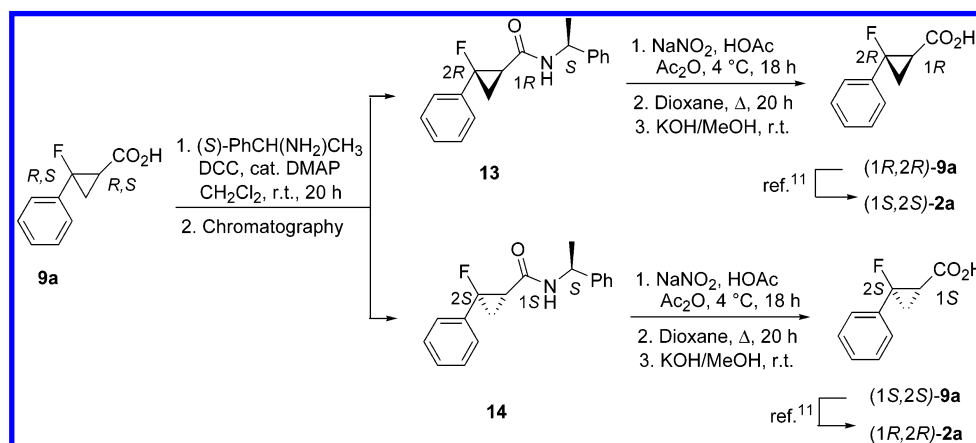


were subjected to Curtius rearrangement<sup>15</sup> to give the carbamates **11b–d** and **12b–d**. Acid-catalyzed hydrolysis converted these carbamates to the target para-substituted 2-aryl-2-fluorocyclopropylamines **2b–d** and **3b–d** (Scheme 1). In addition to spectroscopic data, X-ray structural analysis of **9b**, **10b** and **10c** confirmed *cis*/*trans* configurations at the three-membered ring (Supporting Information).

Analogous to the procedure used for the resolution of the nonfluorinated counterparts<sup>16</sup> the enantiomers of *trans*-2-fluoro-2-phenylcyclopropanecarboxylic acid (**9a**) were separated via diastereomeric 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.<sup>17</sup> Curtius rearrangement and removal of the Boc group with hydrogen chloride as previously reported for the racemic compound<sup>12</sup> 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).

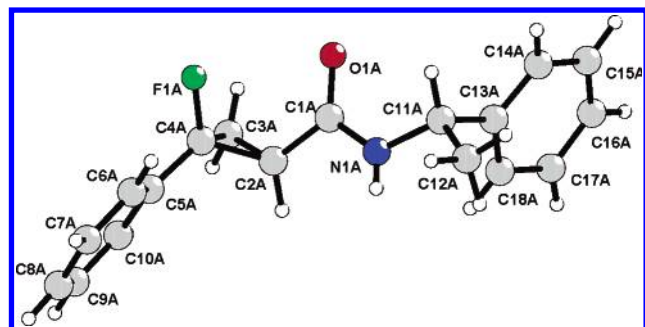
**Influence of Para-Substituents of 2-Fluoro-2-phenylcyclopropylamine on the Inhibition of Microbial Tyramine Oxidase.** The activity of microbial tyramine oxidase from *Arthrobacter* sp. was measured in the presence of different concentrations of the inhibitor. IC<sub>50</sub> values (inhibitor concentration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

## Scheme 2

**Table 1.** IC<sub>50</sub> Values, Inhibition Type and pK<sub>a</sub> Values for Compounds

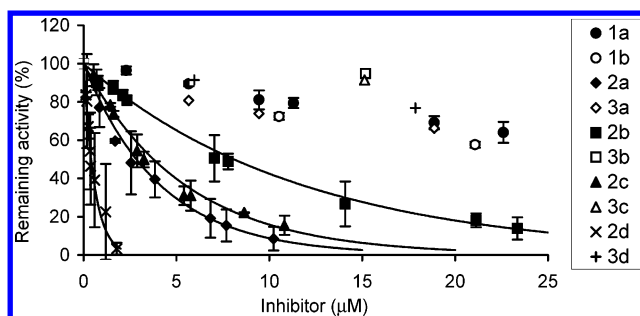
compd	isomer type	NH <sub>2</sub> /F relation	R	pK <sub>a</sub> <sup>a</sup>	IC <sub>50</sub> (μM)	inhibition type
<b>1a</b>	trans		H	8.47	35 ± 6	competitive
<b>1b</b>	cis		H	8.50	33 ± 1	irreversible
<b>2a</b>	trans	cis	H	7.35	3.6 ± 1.5	competitive
<b>2b</b>	trans	cis	F	7.31	8.1 ± 1.6	competitive
<b>2c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

<sup>a</sup> Ionization constants (pK<sub>a</sub>) were determined pH-metric in 0.1 M KNO<sub>3</sub> at 21 °C. <sup>b</sup> 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<sub>50</sub> values together with pK<sub>a</sub> values and inhibition type are summarized in Table 1.

The influence of fluorine substituents on the acidity of neighboring groups is well documented.<sup>18</sup> In one example, Fuller et al. have reported a lowering effect of β-fluorine substitution on the pK<sub>a</sub> of several amine drugs.<sup>19</sup> 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<sub>a</sub> 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<sub>a</sub> value in both stereoisomeric series (cf. compounds

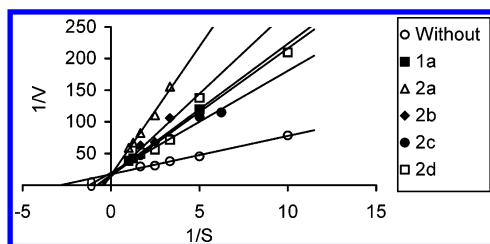
**Figure 3.** Effect of para-substitution of 2-fluoro-2-phenylcyclopropylamines (**2a–d** and **3a–d**) on the inhibition of microbial tyramine oxidase. For comparison the inhibition curves of nonfluorinated phenylcyclopropylamines **1a** and **1b** were added.

**2a** and **2d** or **3a** and **3d**, respectively), while electron-withdrawing substituents lowered the basicity in both series.

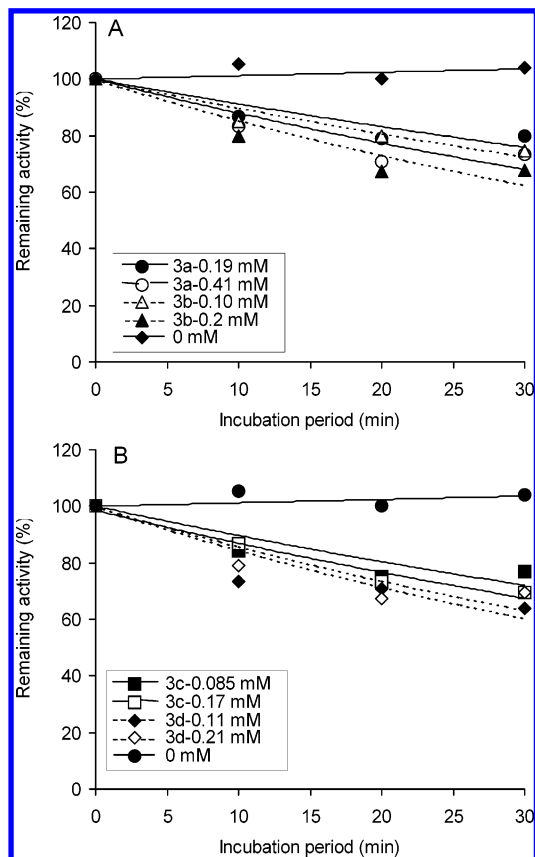
As shown in Figure 3 and Table 1, the diastereomeric nonfluorinated phenylcyclopropylamines, **1a** and **1b**, both inhibited tyramine oxidase and had comparable activity. However, the trans-isomer was a competitive inhibitor, while the cis-isomer was an irreversible inhibitor. The inhibitory potency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

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  $\mu$ M), **2a** (6  $\mu$ M), **2b** (7  $\mu$ M), **2c** (3  $\mu$ M) and **2d** (1  $\mu$ M). 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.



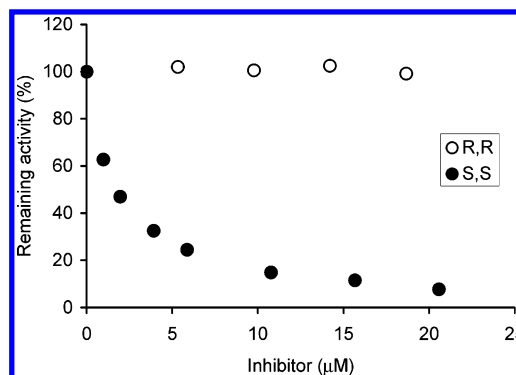
**Figure 5.** Time- and concentration-dependent inactivation of tyramine oxidase by para-substituted *cis*-2-fluoro-2-phenylcyclopropylamines (graph A for **3a** and **3b**, graph B for **3c** and **3d**).

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).

Clinical studies with the enantiomers of tranylcypromine, which in practice is administered in racemic form, have shown that only the (1*S*,2*R*)-(+)-enantiomer



**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.

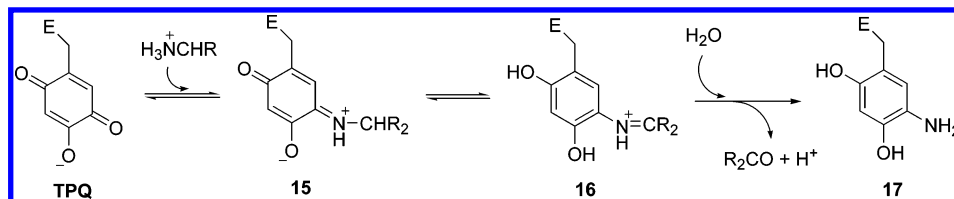
produces an improvement of the symptoms of depression, while the (1*R*,2*R*)-(-)-isomer is ineffective. Differences concerning the general state of being of patients were not detected.<sup>20</sup>

## Discussion

In this study, we found that para-substitution of the aromatic ring of 2-fluoro-2-aryl cyclopropylamines 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,<sup>11</sup> 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.<sup>4c</sup> CAO has a copper ion and an organic cofactor, TPQ, in its active site.<sup>4c</sup> 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.<sup>4e</sup>

was described.<sup>10a</sup> 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 different influence of the  $\alpha$ -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  $\alpha$ -carbon is necessary.<sup>4e</sup> 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.<sup>11</sup> 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**.<sup>4e</sup> 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,<sup>21</sup> to be expected if the inhibition is occurring at a site apart from the binding site. Since the tranlycypromine 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**). Tranlycypromine (**1a**) is a competitive inhibitor of CAO. However, CAO is not inhibited by the (1*R*,2*S*)-(-)-enantiomer (*trans*-configuration) of tranlycypromine.<sup>10</sup> Crystallographic studies have shown that the (1*S*,2*R*)-(+)-enantiomer of tranlycypromine forms an adduct with *Escherichia coli* CAO.<sup>10a</sup> Similar enantioselectivity of tranlycypromine (**1a**) was reported in the

inhibition of *Arthobacter globiformis* CAO.<sup>10b</sup> The authors suspected steric exclusion of (1*R*,2*S*)-(-)-tranlycypromine 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.<sup>22</sup>

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).<sup>23</sup> The diastereoisomeric tranlycypromines **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  $\mu$ M), while lower or equal activity was observed in the *cis*-series, **3a** (65 or 19  $\mu$ M). 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  $\mu$ M) 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  $\mu$ M) 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  $\mu$ M.<sup>11</sup>) 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,<sup>24</sup> in congestive heart failure,<sup>25</sup> and Alzheimers disease<sup>7</sup> may be responsible for vascular deterioration in these patients. In clinical approaches based on CAO inhibition, selectivity over MAO inhibition would be quite important.<sup>24</sup>

## Experimental Section

**General Methods.** <sup>1</sup>H (300 MHz), <sup>13</sup>C (75 MHz) and <sup>19</sup>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<sub>3</sub> or CFCl<sub>3</sub>. 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.<sup>12–14</sup> 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,<sup>13</sup> to an ice cooled solution of 4-methylstyrene (**4d**) (9.45 g, 80.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (80 mL) were added  $\text{Et}_3\text{N}\cdot 3\text{HF}$  (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  $\text{NH}_4\text{OH}$ . After separation of the phases, the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (600 mL) and the combined organic layers were washed with 0.1 M HCl (600 mL), 5%  $\text{NaHCO}_3$  and  $\text{H}_2\text{O}$  (200 mL). The phases were dried ( $\text{MgSO}_4$ ), 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**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.36 (3 H, s,  $\text{CH}_3$ ), 3.60 (1 H, ddd,  $J = 4.3$  Hz,  $J = 11.2$  Hz,  $J = 26.7$  Hz,  $\text{CH}_2$ ), 3.69 (1 H, ddd,  $J = 7.9$  Hz,  $J = 11.2$  Hz,  $J = 15.3$  Hz,  $\text{CH}_2$ ), 5.57 (1 H, ddd,  $J = 4.3$  Hz,  $J = 7.9$  Hz,  $J = 46.9$  Hz,  $\text{CH}$ ), 7.13–7.25 (4 H, m, aromatic);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.6 (q,  $\text{CH}_3$ ), 34.2 (dt,  $J = 29.3$  Hz,  $\text{CH}_2$ ), 92.8 (dd,  $J = 178.0$  Hz,  $\text{CHF}$ ), 125.7 (dd,  $J = 5.1$  Hz, aromatic), 129.4 (d, aromatic), 134.2 (d,  $J = 20.3$  Hz, aromatic), 139.2 (s, aromatic);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  –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)  $\nu$  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. ( $\text{C}_9\text{H}_{10}\text{BrF}$ ) C, H. The  $^1\text{H}$  NMR chemical shifts are in good agreement with those of a 100 MHz spectrum described in the literature.<sup>26</sup>

**(1-Fluorovinyl)-4-methylbenzene (6d).** Analogous to a published procedure,<sup>14</sup> under ice cooling,  $\text{KO}^t\text{Bu}$  (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%  $\text{NaHCO}_3$  (300 mL), 0.05 M HCl (150 mL) and  $\text{H}_2\text{O}$  (300 mL) and then dried ( $\text{MgSO}_4$ ). 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;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.34 (3 H, s,  $\text{CH}_3$ ), 4.76 (1 H, dd,  $J = 3.3$  Hz,  $J = 17.9$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 4.94 (dd,  $J = 3.3$  Hz,  $J = 49.8$  Hz, 1 H,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 7.14 (2 H, dd,  $J = 8.0$  Hz,  $J = 0.7$  Hz, aromatic), 7.42 (2 H, d,  $J = 8.0$  Hz, aromatic);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.2 (q,  $\text{CH}_3$ ), 88.5 (dt,  $J = 22.9$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 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, CF);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  –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. ( $\text{C}_9\text{H}_9\text{F}$ ) C, H. The  $^1\text{H}$  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,  $\text{Cu}(\text{acac})_2$  (24 mg, 0.09 mmol) was dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (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.<sup>27</sup> The mixture was heated to reflux, and a solution of ethyl diazoacetate (513 mg, 4.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (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  $\text{CH}_2\text{Cl}_2$  (150 mL). After the solution was washed with saturated  $\text{Na}_2\text{CO}_3$  and  $\text{H}_2\text{O}$

(300 mL), the organic portion was dried ( $\text{MgSO}_4$ ) 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/ $\text{CH}_2\text{Cl}_2$ , 2:1). The esters **7b** or **8b** were isolated as colorless oils.

**Data for 7b:** (Yield: 233 mg, 33%)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.28 (3 H, t,  $J = 7.2$  Hz,  $\text{CH}_3$ ), 1.57 (1 H, ddd,  $J = 7.0$  Hz,  $J = 9.3$  Hz,  $J = 10.5$  Hz,  $\text{CH}_\text{X}$ ), 2.14 (1 H, ddd,  $J = 3.2$  Hz,  $J = 7.7$  Hz,  $J = 9.3$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.21–2.32 (1 H, m,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 4.18–4.28 (2 H, m,  $\text{OCH}_2$ ), 7.00–7.33 (4 H, m, aromatic);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.1 (q,  $\text{CH}_3$ ), 18.4 (dt,  $J = 12.7$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 28.6 (dd,  $J = 12.7$  Hz,  $\text{CH}_\text{X}$ ), 61.1 (t,  $\text{OCH}_2$ ), 80.4 (ds,  $J = 227.6$  Hz, CF), 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-CF), 167.5 (ds,  $J = 2.5$  Hz, C=O);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  –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)  $\nu$  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. ( $\text{C}_{12}\text{H}_{12}\text{F}_2\text{O}_2$ ) C, H, N.

**Data for 8b:** (Yield: 206 mg, 30%)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.03 (3 H, t,  $J = 7.2$  Hz,  $\text{CH}_3$ ), 1.78 (1 H, ddd,  $J = 7.5$  Hz,  $J = 10.2$  Hz,  $J = 18.4$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 1.92 (1 H, ddd,  $J = 7.5$  Hz,  $J = 7.5$  Hz,  $J = 12.2$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.54 (1 H, ddd,  $J = 7.5$  Hz,  $J = 10.2$  Hz,  $J = 17.8$  Hz,  $\text{CH}_\text{X}$ ), 3.92 (2 H, q,  $J = 7.0$  Hz,  $\text{OCH}_2$ ), 7.00–7.54 (4 H, m, aromatic);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  13.9 (q,  $\text{CH}_2\text{CH}_3$ ), 16.5 (dt,  $J = 11.4$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 27.7 (dd,  $J = 15.8$  Hz,  $\text{CH}_\text{X}$ ), 60.7 (t,  $\text{CH}_2\text{CH}_3$ ), 82.3 (ds,  $J = 221.1$  Hz, CF), 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-CF), 168.7 (s, C=O);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  –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)  $\nu$  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. ( $\text{C}_{12}\text{H}_{12}\text{F}_2\text{O}_2$ ) 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  $\text{Cu}(\text{acac})_2$  (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/ $\text{Et}_2\text{O}$ , 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%)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.29 (3 H, q,  $J = 7.2$  Hz,  $\text{CH}_2\text{CH}_3$ ), 1.57 (1 H, ddd,  $J = 6.9$  Hz,  $J = 8.8$  Hz,  $J = 10.5$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.15 (ddd,  $J = 7.6$  Hz,  $J = 8.8$  Hz,  $J = 10.5$  Hz, 1 H,  $\text{CH}_\text{X}$ ), 2.25 (1 H, ddd,  $J = 6.9$  Hz,  $J = 7.6$  Hz,  $J = 20.0$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.35 (s, 3 H,  $\text{C}_\text{ar}-\text{CH}_3$ ), 4.18–4.29 (2 H, m,  $\text{CH}_2\text{CH}_3$ ), 7.16–7.25 (4 H, m, aromatic);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.2 (q,  $\text{CH}_2\text{CH}_3$ ), 18.7 (dt,  $J = 12.7$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 21.0 (q,  $\text{C}_\text{ar}-\text{CH}_3$ ), 28.7 (dd,  $J = 12.7$  Hz,  $\text{CH}_\text{X}$ ), 61.1 (t,  $\text{CH}_2\text{CH}_3$ ), 80.9 (ds,  $J = 227.6$  Hz, CF), 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);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  –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)  $\nu$  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<sub>13</sub>H<sub>15</sub>FO<sub>2</sub>) C, H.

**Data for 8d:** (Yield: 420 mg, 19%) <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.03 (3 H, q,  $J$  = 7.2 Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.77 (1 H, ddd,  $J$  = 7.2 Hz,  $J$  = 10.3 Hz,  $J$  = 19.1 Hz, CH<sub>A</sub>H<sub>B</sub>), 1.93 (1 H, ddd,  $J$  = 7.2 Hz,  $J$  = 7.4 Hz,  $J$  = 12.2 Hz, CH<sub>A</sub>H<sub>B</sub>), 2.34 (3 H, d,  $J$  = 1.9 Hz, C<sub>ar</sub>-CH<sub>3</sub>), 2.53 (1 H, ddd,  $J$  = 7.4 Hz,  $J$  = 10.3 Hz,  $J$  = 17.9 Hz, CH<sub>X</sub>), 3.93 (t,  $J$  = 7.2 Hz, 2 H, CH<sub>2</sub>CH<sub>3</sub>), 7.14–7.17 (2 H, m, aromatic), 7.33–7.37 (2 H, m, aromatic); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  13.9 (q, CH<sub>2</sub>CH<sub>3</sub>), 16.5 (dt,  $J$  = 10.2 Hz, CH<sub>A</sub>H<sub>B</sub>), 21.2 (q, C<sub>ar</sub>-CH<sub>3</sub>), 27.7 (dd,  $J$  = 16.5 Hz, CH<sub>X</sub>), 60.6 (t, CH<sub>2</sub>CH<sub>3</sub>), 83.0 (ds,  $J$  = 220.0 Hz, CF), 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); <sup>19</sup>F NMR (CDCl<sub>3</sub>)  $\delta$  -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)  $\nu$  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<sub>13</sub>H<sub>15</sub>FO<sub>2</sub>) 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<sub>2</sub>Cl<sub>2</sub> (25 mL). The organic layer was discarded and the aqueous phase was acidified with concentrated HCl to pH 1 and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  25 mL). The organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) 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<sub>2</sub>Cl<sub>2</sub>/pentane at -20 °C, **9b** as a colorless, crystalline solid (Yield: 290 mg, 95%). Data for **9b**: Mp 114 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.67 (1 H, ddd,  $J$  = 7.2 Hz,  $J$  = 9.3 Hz,  $J$  = 10.6 Hz, CH<sub>X</sub>), 2.16 (1 H, ddd,  $J$  = 7.6 Hz,  $J$  = 9.3 Hz,  $J$  = 11.8 Hz, CH<sub>A</sub>H<sub>B</sub>), 2.30 (1 H, ddd,  $J$  = 7.2 Hz,  $J$  = 7.6 Hz,  $J$  = 19.9 Hz, CH<sub>A</sub>H<sub>B</sub>), 7.04–7.36 (4 H, m, aromatic), 11.30 (1 H, br, COOH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  19.1 (dt,  $J$  = 12.7 Hz, CH<sub>A</sub>H<sub>B</sub>), 28.3 (dd,  $J$  = 11.4 Hz, CH<sub>X</sub>), 81.2 (ds,  $J$  = 228.9 Hz, CF), 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); <sup>19</sup>F NMR (CDCl<sub>3</sub>)  $\delta$  -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<sub>12</sub>H<sub>13</sub>FO<sub>2</sub>) 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<sub>2</sub>Cl<sub>2</sub>/pentane at -20 °C, **10b** as a colorless, crystalline solid (Yield: 167 mg, 93%) Data for **10b**: Mp 98 °C (CH<sub>2</sub>Cl<sub>2</sub>/pentane); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.77–1.93 (2 H, m, CH<sub>A</sub>H<sub>B</sub>), 2.48 (1 H, ddd,  $J$  = 7.5 Hz,  $J$  = 10.0 Hz,  $J$  = 17.4 Hz, CH<sub>X</sub>), 6.90–7.50 (4 H, m, aromatic), 11.06 (s, 1 H, COOH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  17.4 (dt,  $J$  = 10.2 Hz, CH<sub>A</sub>H<sub>B</sub>), 27.5 (dd,  $J$  = 17.8 Hz, CH<sub>X</sub>), 82.9 (ds,  $J$  = 222.6 Hz, CF), 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); <sup>19</sup>F NMR (CDCl<sub>3</sub>)  $\delta$  -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<sub>12</sub>H<sub>13</sub>FO<sub>2</sub>) 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<sub>2</sub>Cl<sub>2</sub>/pentane, **9c** as a colorless, crystalline solid (Yield: 80 mg, 62%). Data for **9c**: Mp 138 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  1.69 (1 H, ddd,  $J$  = 7.4 Hz,  $J$  = 9.3 Hz,  $J$  = 10.6 Hz, CH<sub>A</sub>H<sub>B</sub>), 2.18 (1 H, ddd,  $J$  = 2.5 Hz,  $J$  = 7.6 Hz,  $J$  = 9.3 Hz, CH<sub>X</sub>), 2.33 (1 H, ddd,  $J$  = 7.4 Hz,  $J$  = 7.6 Hz,  $J$  = 20.3 Hz, CH<sub>A</sub>H<sub>B</sub>), 7.25–7.39 (4 H, m, aromatic); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  19.1 (dt,  $J$  = 12.6 Hz, CH<sub>A</sub>H<sub>B</sub>), 28.6 (dd,  $J$  = 11.4 Hz, CH<sub>X</sub>), 80.6 (ds,  $J$  = 228.9 Hz, CF), 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); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 188.30 MHz)  $\delta$  -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)  $\nu$  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<sub>10</sub>H<sub>8</sub>ClFO<sub>2</sub>) 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<sub>2</sub>Cl<sub>2</sub>/pentane, **10c** as a colorless, crystalline solid (Yield: 188 mg, 92%). Data for **10c**: Mp 103 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  1.83–2.04 (2 H, m, CH<sub>A</sub>H<sub>B</sub>), 2.52 (ddd,  $J$  = 7.6 Hz,  $J$  = 10.1 Hz,  $J$  = 17.6 Hz, 1 H, CH<sub>X</sub>), 7.32–7.39 (4 H, m, aromatic); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  17.3 (dt,  $J$  = 10.4 Hz, CH<sub>A</sub>H<sub>B</sub>), 27.6 (dd,  $J$  = 17.3 Hz, CH<sub>X</sub>), 82.8 (ds,  $J$  = 222.0 Hz, CF), 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); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 188.30 MHz)  $\delta$  -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)  $\nu$  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<sub>10</sub>H<sub>8</sub>ClFO<sub>2</sub>) 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<sub>2</sub>Cl<sub>2</sub>/pentane (1:4), **9d** as a white, amorphous solid (Yield: 335 mg, 75%). Data for **9d**: Mp 112 °C (CH<sub>2</sub>Cl<sub>2</sub>/pentane); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.66 (1 H, ddd,  $J$  = 6.9 Hz,  $J$  = 9.1 Hz,  $J$  = 10.5 Hz, CH<sub>X</sub>), 2.16 (1 H, ddd,  $J$  = 7.6 Hz,  $J$  = 9.1 Hz,  $J$  = 10.3 Hz, CH<sub>A</sub>H<sub>B</sub>), 2.29 (1 H, ddd,  $J$  = 6.9 Hz,  $J$  = 7.6 Hz,  $J$  = 20.0 Hz, CH<sub>A</sub>H<sub>B</sub>), 2.36 (s, CH<sub>3</sub>), 7.17–7.25 (4 H, m, aromatic), 11.29 (1 H, br, CO<sub>2</sub>H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  19.2 (dt,  $J$  = 12.7 Hz, CH<sub>A</sub>H<sub>B</sub>), 21.1 (q, CH<sub>3</sub>), 28.4 (dd,  $J$  = 11.4 Hz, CH<sub>X</sub>), 81.6 (ds,  $J$  = 230.2 Hz, CF), 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); <sup>19</sup>F NMR (CDCl<sub>3</sub>)  $\delta$  -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)  $\nu$  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<sub>11</sub>H<sub>11</sub>FO<sub>2</sub>) 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  $\text{CH}_2\text{Cl}_2$ /pentane (1:10), 212 mg (74%) of **10d** was isolated as white, amorphous solid. Data for **10d**: Mp 86 °C ( $\text{CH}_2\text{Cl}_2$ /pentane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.79 (1 H, ddd,  $J = 7.2$  Hz,  $J = 10.0$  Hz,  $J = 18.8$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 1.87 (ddd,  $J = 7.2$  Hz,  $J = 7.4$  Hz,  $J = 12.9$  Hz, 1 H,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.34 (3 H, s,  $\text{CH}_3$ ), 2.46 (1 H, ddd,  $J = 7.4$  Hz,  $J = 10.0$  Hz,  $J = 17.6$  Hz,  $\text{CH}_\text{X}$ ), 7.11–7.32 (4 H, m, aromatic), 11.04 (1 H, br,  $\text{CO}_2\text{H}$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.3 (dt,  $J = 10.2$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 21.2 (q,  $\text{CH}_3$ ), 27.4 (dd,  $J = 17.8$  Hz,  $\text{CH}_\text{X}$ ), 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);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -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)  $\nu$  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. ( $\text{C}_{11}\text{H}_{11}\text{FO}_2$ ) C, H.

**(1R,2R)-(+)- and (1S,2S)-(-)-(2-Fluoro-2-phenyl)cyclopropanecarboxylic (S)-(1-Phenylethyl)amide (13 and 14).** To a solution of *trans*-( $\pm$ )-(2-fluoro-2-phenyl)cyclopropanecarboxylic acid (**9a**) prepared as described before<sup>12</sup> (360 mg, 2.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (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/ $\text{Et}_2\text{O}$ , 1:1) and purified further by recrystallization from  $\text{Et}_2\text{O}$ /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);  $[\alpha]^{20}_\text{D} +146.5$  ( $c = 1.0$ ,  $\text{CHCl}_3$ , 99% d.s.);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.50 (3 H, d,  $J = 6.9$  Hz,  $\text{CH}_3$ ), 1.53 (ddm,  $J = 7.2$  Hz,  $J = 10.5$  Hz, 1 H,  $\text{CH}_\text{X}$ ), 1.98–2.06 (1 H, dm,  $J = 7.9$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.21 (1 H, ddd,  $J = 7.4$  Hz,  $J = 7.9$  Hz,  $J = 20.5$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 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);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  18.4 (dt,  $J = 11.4$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 21.7 (q,  $\text{CH}_3$ ), 31.0 (dd,  $J = 12.7$  Hz,  $\text{CH}_\text{X}$ ), 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);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -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)  $\nu$  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. ( $\text{C}_{18}\text{H}_{18}\text{FNO}$ ) C, H, N.

**Data for (-)-14:** (Yield: 172 mg, 35%) Mp 149 °C (ethyl acetate);  $[\alpha]^{20}_\text{D} -182.3$  ( $c = 1.0$ ,  $\text{CHCl}_3$ , >99% d.s.);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.41–1.51 (1 H, m,  $\text{CH}_\text{X}$ ), 1.44 (3 H, d,  $J = 6.9$  Hz,  $\text{CH}_3$ ), 1.91–1.99 (1 H, m,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.21 (ddd,  $J = 7.4$  Hz,  $J = 7.4$  Hz,  $J = 20.7$  Hz, 1 H,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 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);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  18.4 (dt,  $J = 11.4$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 21.8 (q,  $\text{CH}_3$ ), 31.0 (dd,  $J = 11.4$  Hz,  $\text{CH}_\text{X}$ ), 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);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -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)  $\nu$  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. ( $\text{C}_{18}\text{H}_{18}\text{FNO}$ ) C, H, N. The structure of (-)-**14** was confirmed by X-ray structural analysis (Figure 2 and Supporting Information).

**(1R,2R)-(+)-2-Fluoro-2-phenylcyclopropanecarboxylic Acid (1R,2R)-(+)-9a.** The procedure developed by White<sup>17</sup> was followed. To a solution of (+)-**13** (306 mg, 1.08 mmol) in a mixture of  $\text{Ac}_2\text{O}$  (3.7 mL) and  $\text{AcOH}$  (0.6 mL) was added  $\text{NaNO}_2$  (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  $\text{H}_2\text{O}$  (10 mL). The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (75 mL), and the combined organic layers were washed with 5%  $\text{Na}_2\text{CO}_3$  and  $\text{H}_2\text{O}$  (25 mL) and dried ( $\text{Na}_2\text{SO}_4$ ). 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  $\text{H}_2\text{O}$  (15 mL) was added. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (20 mL) and then acidified with concentrated HCl to pH 1. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (100 mL), the combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), and all volatiles were removed under vacuum. After recrystallization from  $\text{CH}_2\text{Cl}_2$ /pentane (**1R,2R**)-(+)-**9a** was isolated as white powder (Yield: 100 mg, 51%). Data for (**1R,2R**)-(+)-**9a**:  $[\alpha]^{20}_\text{D} +293.5$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

**(1S,2S)-(-)-2-Fluoro-2-phenylcyclopropanecarboxylic Acid (1S,2S)-(-)-9a.** Using the same procedure as above, hydrolysis of (-)-**14** (126 mg, 0.445 mmol) gave, after recrystallization from  $\text{CH}_2\text{Cl}_2$ /pentane as a white powder (Yield: 63 mg, 79%). Data for (**1S,2S**)-(-)-**9a**:  $[\alpha]^{20}_\text{D} -292.9$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ).

**General Procedure for Curtius Degradation of 2-Fluoro-2-phenylcyclopropanecarboxylic Acids.** The corresponding 2-fluoro-2-aryl cyclopropanecarboxylic acid (1.25 mmol), anhydrous  $\text{NEt}_3$  (152 mg, 1.5 mmol), anhydrous  $\text{tBuOH}$  (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 ( $\text{Boc}_2\text{O}$ ) (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,  $\text{H}_2\text{O}$ , sat.  $\text{NaHCO}_3$  and brine (20 mL). Unreacted  $\text{Boc}_2\text{O}$  was removed by bulb-to-bulb distillation. The carbamates were isolated by silica gel chromatography.

***tert*-Butyl *trans*-( $\pm$ )-[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;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.39 (1 H, ddd,  $J = 6.0$  Hz,  $J = 8.1$  Hz,  $J = 21.7$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 1.47 (9 H, s,  $\text{CH}_3$ ), 1.46–1.56 (1 H, m,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.93 (br s, 1 H,  $\text{CH}_\text{X}$ ), 4.98 (1 H, br s, NH), 7.02–7.08 (2 H, m, aromatic), 7.32–7.39 (2 H, m, aromatic);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.4 (dt,  $J = 11.4$  Hz,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 28.3 (q,  $\text{CH}_3$ ), 33.5 (dm,  $J = 10.2$  Hz,  $\text{CH}_\text{X}$ ), 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);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -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)  $\nu$  3370 (s), 3093 (s), 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. ( $\text{C}_{14}\text{H}_{17}\text{F}_2\text{NO}_2$ ) 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  $-20^{\circ}\text{C}$ . Data for **12b**: Mp  $131^{\circ}\text{C}$  (ethyl acetate/pentane);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.25–1.39 (1 H, m,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 1.32 (9 H, s,  $\text{CH}_3$ ), 1.75 (1 H, ddd,  $J = 8.2\text{ Hz}$ ,  $J = 9.7\text{ Hz}$ ,  $J = 21.5\text{ Hz}$ ,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 3.25–3.30 (1 H, m,  $\text{CH}_\text{X}$ ), 4.38 (1 H, br s,  $\text{NH}$ ), 7.03–7.09 (2 H, m, aromatic), 7.35–7.45 (2 H, m, aromatic);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.8–18.2 (mt,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 28.1 (q,  $\text{CH}_3$ ), 33.8–34.1 (md,  $\text{CH}_\text{X}$ ), 79.9 (s, O-C), 80.8 (ds,  $J = 217.4\text{ Hz}$ , CF), 115.2 (dd,  $J = 21.6\text{ Hz}$ , aromatic), 129.0–129.8 (m, aromatic), 155.7 (s, C=O), 162.8 (ds,  $J = 246.7\text{ Hz}$ , aromatic);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -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)  $\nu$  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. ( $\text{C}_{14}\text{H}_{17}\text{F}_2\text{NO}_2$ ) 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  $-20^{\circ}\text{C}$ . Data for **11c**: Mp  $141^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.35–1.53 (2 H, m,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 1.47 (9 H, s,  $\text{CH}_3$ ), 2.94 (1 H, br s,  $\text{CH}_\text{X}$ ), 4.92 (1 H, br s,  $\text{NH}$ ), 7.25–7.36 (4 H, m, aromatic);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.9 (dt,  $J = 14.4\text{ Hz}$ ,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 28.3 (q,  $\text{CH}_3$ ), 34.0 (dd,  $J = 9.2\text{ Hz}$ ,  $\text{CH}_\text{X}$ ), 78.5 (ds,  $J = 218.3\text{ Hz}$ , 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);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -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)  $\nu$  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. ( $\text{C}_{14}\text{H}_{17}\text{ClFNO}_2$ ) 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  $-20^{\circ}\text{C}$ . Data for **12c**: Mp  $147^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.25–1.46 (1 H, m,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 1.31 (9 H, s,  $\text{CH}_3$ ), 1.77 (1 H, ddd,  $J = 8.2\text{ Hz}$ ,  $J = 9.6\text{ Hz}$ ,  $J = 21.5\text{ Hz}$ ,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 3.22–3.30 (1 H, m,  $\text{CH}_\text{X}$ ), 4.39 (1 H, br s,  $\text{NH}$ ), 7.30–7.45 (4 H, m, aromatic);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  18.3 (br m,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 28.0 (q,  $\text{CH}_3$ ), 34.4 (br s,  $\text{CH}_\text{X}$ ), 80.1 (s, C-O), 80.7 (ds,  $J = 216.4\text{ Hz}$ , CF), 128.4 (d, aromatic), 132.5 (ds,  $J = 20.3$ , aromatic), 134.3 (ds,  $J = 6.4\text{ Hz}$ , aromatic), 155.6 (s, C=O);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -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)  $\nu$  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. ( $\text{C}_{14}\text{H}_{17}\text{ClFNO}_2$ ) 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  $-20^{\circ}\text{C}$ . Data for **11d**: Mp  $98^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.37 (1 H, ddd,  $J = 6.1\text{ Hz}$ ,  $J = 8.1\text{ Hz}$ ,  $J = 22.2\text{ Hz}$ ,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 1.47 (9 H, s, C-( $\text{CH}_3$ )<sub>3</sub>), 1.54 (1 H, ddd,  $J = 8.1\text{ Hz}$ ,  $J = 8.3\text{ Hz}$ ,  $J = 12.7\text{ Hz}$ ,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.35 (3 H, s,  $\text{CH}_3$ ), 2.95 (br s, 1 H,  $\text{CH}_\text{X}$ ), 4.95 (1 H, br s,  $\text{NH}$ ), 7.15–7.25 (4 H, m, aromatic);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.9 (dt,  $J = 11.4\text{ Hz}$ ,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 21.1 (q, C-( $\text{CH}_3$ )<sub>3</sub>), 28.3 (q,  $\text{CH}_3$ ), 33.6 (dm,  $\text{CH}_\text{X}$ ), 79.1 (ds,  $J = 218.7\text{ Hz}$ , CF), 79.9 (s, C-O), 125.4 (dd,  $J = 5.1\text{ Hz}$ , aromatic), 129.1 (d, aromatic), 134.4 (ds,  $J = 19.1\text{ Hz}$ , aromatic), 138.0 (s, aromatic), 156.3 (s, C=O);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -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)  $\nu$  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. ( $\text{C}_{15}\text{H}_{20}\text{FNO}_2$ ) 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  $-20^{\circ}\text{C}$ . Data for **12d**: Mp  $125^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.34 (10 H, s,  $\text{CH}_\text{A}\text{H}_\text{B}$  and C-( $\text{CH}_3$ )<sub>3</sub>), 1.74 (1 H, ddd,  $J = 8.6\text{ Hz}$ ,  $J = 9.1\text{ Hz}$ ,  $J = 21.5\text{ Hz}$ ,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 2.37 (3 H, s,  $\text{CH}_3$ ), 3.20–3.36 (1 H, m,  $\text{CH}_\text{X}$ ), 4.18 (1 H, br s,  $\text{NH}$ ), 7.18–7.32 (4 H, m, aromatic);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  18.4 (dt,  $J = 11.9\text{ Hz}$ ,  $\text{CH}_\text{A}\text{H}_\text{B}$ ), 21.1 (q, C-( $\text{CH}_3$ )<sub>3</sub>), 28.1 (q,  $\text{CH}_3$ ), 33.9 (dm,  $\text{CH}_\text{X}$ ), 79.8 (s, C-O), 81.1 (ds,  $J = 216.1\text{ Hz}$ , CF), 127.3 (dm, aromatic), 129.1 (d, aromatic), 130.6 (ds,  $J = 22.0\text{ Hz}$ , aromatic), 138.5 (ds,  $J = 8.2\text{ Hz}$ , aromatic), 155.8 (s, C=O);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -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)  $\nu$  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. ( $\text{C}_{15}\text{H}_{20}\text{FNO}_2$ ) 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**:  $\alpha_\text{D}^{20}$  -89.3 ( $c = 1.0$ ,  $\text{CHCl}_3$ ),  $> 98\%$  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**:  $\alpha_\text{D}^{20}$  +89.9 ( $c = 1.0$ ,  $\text{CHCl}_3$ ),  $> 98\%$  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  $\text{Et}_2\text{O}$  (40 mL), and the product was purified by recrystallization from  $\text{MeOH/Et}_2\text{O}$ .

**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  $\text{P}_2\text{O}_5$  under vacuum. The product was purified by recrystallization from  $\text{MeOH/Et}_2\text{O}$ .

**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<sub>2</sub>O, **2b** was isolated as a white solid (Yield: 68 mg, 83%). Data for **2b**: Mp. > 160 °C (decomp). <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>, 400 MHz) δ 1.79–1.86 (2 H, m, CH<sub>A</sub>H<sub>B</sub>), 3.05–3.09 (1 H, m, CH<sub>X</sub>), 4.84 (3 H, s, NH<sub>3</sub><sup>+</sup>), 7.16–7.20 (2 H, m, aromatic), 7.50–7.53 (2 H, m, aromatic); <sup>13</sup>C NMR (methanol-*d*<sub>4</sub>, 100.63 MHz) δ 17.8 (dt, *J* = 12.4 Hz, CH<sub>A</sub>H<sub>B</sub>), 32.5 (dd, *J* = 10.4 Hz, CH<sub>X</sub>), 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, <sup>4</sup>*J* = 3.2 Hz, *J* = 21.3 Hz, aromatic), 164.9 (dds, <sup>5</sup>*J* = 2.2 Hz, *J* = 247.5 Hz, aromatic); <sup>19</sup>F NMR (Methanol-*d*<sub>4</sub>) 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<sub>9</sub>H<sub>10</sub>ClF<sub>2</sub>N) 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<sub>2</sub>O, **2c** was isolated as a white solid (Yield: 104 mg, 93%). Data for **3b**: Mp 155 °C (decomp); <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>) δ 1.78 (1 H, ddd, *J* = 6.0 Hz, *J* = 9.5 Hz, *J* = 10.0 Hz, CH<sub>A</sub>H<sub>B</sub>), 1.95 (1 H, ddd, *J* = 9.5 Hz, *J* = 10.0 Hz, *J* = 20.0 Hz, CH<sub>A</sub>H<sub>B</sub>), 3.40 (1 H, ddd, *J* = 6.0 Hz, *J* = 10.0 Hz, *J* = 13.9 Hz, CH<sub>X</sub>), 4.78 (3 H, s, NH<sub>3</sub><sup>+</sup>), 7.23–7.29 (2 H, m, aromatic), 7.67–7.72 (2 H, m, aromatic); <sup>13</sup>C NMR (methanol-*d*<sub>4</sub>) δ 16.4 (dt, *J* = 14.0 Hz, CH<sub>A</sub>H<sub>B</sub>), 32.9 (dd, *J* = 21.6 Hz, CH<sub>X</sub>), 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); <sup>19</sup>F NMR (methanol-*d*<sub>4</sub>) 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<sub>9</sub>H<sub>10</sub>ClF<sub>2</sub>N) 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); <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>) δ 0.64–0.73 (2 H, m, CH<sub>A</sub>H<sub>B</sub>), 1.90–1.95 (1 H, m, CH<sub>X</sub>), 3.17 (3 H, s, NH<sub>3</sub><sup>+</sup>), 6.25–6.32 (4 H, m, aromatic); <sup>13</sup>C NMR (methanol-*d*<sub>4</sub>) δ 17.9 (dt, *J* = 12.7 Hz, CH<sub>A</sub>H<sub>B</sub>), 32.5 (dd, *J* = 10.2 Hz, CH<sub>X</sub>), 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); <sup>19</sup>F NMR (methanol-*d*<sub>4</sub>) 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<sub>9</sub>H<sub>10</sub>Cl<sub>2</sub>FN) 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<sub>2</sub>O (1:3) **3c** was isolated as a white solid (Yield: 61 mg, 80%). Data for **3c**: Mp > 145 °C (decomp); <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>) δ 1.80 (1 H, ddd, *J* = 6.2 Hz, *J* = 6.2 Hz, *J* = 9.3 Hz, CH<sub>A</sub>H<sub>B</sub>), 1.96 (1 H, ddm, *J* = 6.2 Hz, *J* = 19.8 Hz, CH<sub>A</sub>H<sub>B</sub>), 3.41 (1 H, ddd, *J* = 6.2 Hz, *J* = 10.1 Hz, *J* = 14.0 Hz, CH<sub>X</sub>), 4.77 (3 H, s, NH<sub>3</sub><sup>+</sup>), 7.52–7.65 (4 H, m, aromatic); <sup>13</sup>C NMR (methanol-*d*<sub>4</sub>) δ 16.0 (dt, *J* = 12.7 Hz, CH<sub>A</sub>H<sub>B</sub>), 32.7 (dd, *J* = 22.9 Hz, CH<sub>X</sub>), 79.6 (ds, *J* = 221.3 Hz, CF), 130.5 (d, aromatic), 132.2 (ds, *J* = 5.1, aromatic), 137.7 (s, aromatic); <sup>19</sup>F NMR (methanol-*d*<sub>4</sub>) 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<sub>9</sub>H<sub>10</sub>Cl<sub>2</sub>FN) 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<sub>2</sub>O **2d** was isolated as a white solid (Yield: 36 mg, 89%). Data for **2d**: Mp > 166 °C (decomp). <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>) δ 1.72–1.82 (2 H, m, CH<sub>A</sub>H<sub>B</sub>), 2.36 (3 H, s, CH<sub>3</sub>), 2.98–3.04 (1 H, m, CH<sub>X</sub>), 4.78 (3 H, br s, NH<sub>3</sub><sup>+</sup>), 7.23–7.34 (4 H, m, aromatic); <sup>13</sup>C NMR (methanol-*d*<sub>4</sub>) δ 17.9 (dt, *J* = 12.7 Hz, CH<sub>A</sub>H<sub>B</sub>), 21.5 (q, CH<sub>3</sub>), 32.5 (dd, *J* = 10.2 Hz, CH<sub>X</sub>), 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); <sup>19</sup>F NMR (methanol-*d*<sub>4</sub>) 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<sub>10</sub>H<sub>13</sub>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); <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>) δ 1.74 (1 H, ddd, *J* = 6.0 Hz, *J* = 9.8 Hz, *J* = 10.0 Hz, CH<sub>A</sub>H<sub>B</sub>), 1.90 (1 H, ddd, *J* = 9.8 Hz, *J* = 9.8 Hz, *J* = 19.6 Hz, CH<sub>A</sub>H<sub>B</sub>), 2.39 (3 H, s, CH<sub>3</sub>), 3.36 (1 H, ddd, *J* = 6.0 Hz, *J* = 9.8 Hz, *J* = 13.8 Hz, CH<sub>X</sub>), 4.78 (3 H, s, NH<sub>3</sub><sup>+</sup>), 7.34 (2 H, d, *J* = 7.9 Hz, aromatic), 7.52 (2 H, d, *J* = 7.9 Hz, aromatic); <sup>13</sup>C NMR (methanol-*d*<sub>4</sub>) δ 15.9 (dt, *J* = 14.0 Hz, CH<sub>A</sub>H<sub>B</sub>), 21.4 (q, CH<sub>3</sub>), 32.5 (dd, *J* = 21.6 Hz, CH<sub>X</sub>), 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, <sup>5</sup>*J* = 2.5 Hz, aromatic); <sup>19</sup>F NMR (methanol-*d*<sub>4</sub>) 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<sub>10</sub>H<sub>13</sub>ClFN·1/3H<sub>2</sub>O) C, H, N.

**(1R,2R)-(-)-2-Fluoro-2-phenylcyclopropylamine Hydrochloride [(1R,2R)-(-)-2a].** Using the general procedure for deprotection with THF/HCl, (1R,2R)-(-)-**2a** was synthesized from (1R,2R)-(-)-**11a** (29 mg, 0.155 mmol). After recrystallization from methanol/Et<sub>2</sub>O, (1R,2R)-(-)-**2a** (17 mg, 58%) was isolated as a white solid. Data for (1R,2R)-(-)-**2a**: [α]<sub>D</sub><sup>20</sup> -70.9 (c = 1.0, MeOH).

**(1S,2S)-(+)-2-Fluoro-2-phenylcyclopropylamine Hydrochloride [(1S,2S)-(+)-2a].** Using the general procedure for deprotection with THF/HCl, (1S,2S)-(+)-**2a** was synthesized from (1S,2S)-(+)-**11a** (40 mg, 0.159 mmol). After recrystallization from methanol/Et<sub>2</sub>O, (1S,2S)-(+)-**2a** was isolated as a white solid (Yield: 26 mg, 87%). Data for (1S,2S)-(+)-**2a**: [α]<sub>D</sub><sup>20</sup> +70.2 (c = 1.0, MeOH).

**X-ray Data. trans-(±)-2-Fluoro-2-(4-fluorophenyl)cyclopropanecarboxylic Acid (9b).** Formula C<sub>10</sub>H<sub>8</sub>F<sub>2</sub>O<sub>2</sub>, *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, β = 94.04(1)°, *V* = 886.1(2) Å<sup>3</sup>, ρ<sub>calcd</sub> = 1.486 g cm<sup>-3</sup>, μ = 11.32 cm<sup>-1</sup>, empirical absorption correction via ψ scan data (0.765 ≤ *T* ≤ 0.895), *Z* = 4, monoclinic, space group *P*2<sub>1</sub>/*n* (No. 14), λ = 1.54178 Å, *T* = 223 K, ω/2θ scans, 1849 reflections collected (±*h*, +*k*, +*l*), [(sin θ)/λ] = 0.62 Å<sup>-1</sup>, 1803 independent (*R*<sub>int</sub> = 0.028) and 1593 observed reflections [*I* ≥ 2 σ(*I*)], 129 refined parameters, *R* = 0.037, *wR*<sup>2</sup> = 0.111, max. residual electron density 0.21 (−0.20) e Å<sup>-3</sup>, hydrogens calculated and refined as riding atoms.

**cis-(±)-2-Fluoro-2-(4-fluorophenyl)cyclopropanecarboxylic Acid (10b).** Formula C<sub>10</sub>H<sub>8</sub>F<sub>2</sub>O<sub>2</sub>, *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, β = 109.78(2)°, *V* = 889.6(4) Å<sup>3</sup>, ρ<sub>calcd</sub> = 1.480 g cm<sup>-3</sup>, μ = 11.28 cm<sup>-1</sup>, empirical absorption correction via ψ

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

**trans-(±)-2-(4-Chlorophenyl)-2-fluorocyclopropanecarboxylic Acid (9c).** Formula  $\text{C}_{10}\text{H}_8\text{ClFO}_2$ ,  $M = 214.61$ , colorless crystal  $0.25 \times 0.20 \times 0.03 \text{ mm}$ ,  $a = 9.294(2)$ ,  $b = 22.969(5)$ ,  $c = 9.916(2) \text{ \AA}$ ,  $\beta = 111.28(2)^\circ$ ,  $V = 1972.5(7) \text{ \AA}^3$ ,  $\rho_{\text{calcd}} = 1.445 \text{ g cm}^{-3}$ ,  $\mu = 33.46 \text{ cm}^{-1}$ , empirical absorption correction via  $\psi$  scan data ( $0.488 \leq T \leq 0.906$ ),  $Z = 8$ , monoclinic, space group  $P2_1/n$  (No. 14),  $\lambda = 1.54178 \text{ \AA}$ ,  $T = 223 \text{ K}$ ,  $\omega/2\theta$  scans, 3114 reflections collected ( $\pm h, -k, -l$ ),  $[(\sin \theta)/\lambda] = 0.62 \text{ \AA}^{-1}$ , 2931 independent ( $R_{\text{int}} = 0.027$ ) and 1262 observed reflections [ $I \geq 2 \sigma(I)$ ], 255 refined parameters,  $R = 0.065$ ,  $wR^2 = 0.142$ , max. residual electron density  $0.38 (-0.37) \text{ e \AA}^{-3}$ , hydrogens calculated and refined as riding atoms.

**(1S,2S)-(-)-(2-Fluoro-2-phenyl)cyclopropanecarboxylic (S)-(1-Phenylethyl)amide (14).** Formula  $\text{C}_{18}\text{H}_{18}\text{FNO}_2$ ,  $M = 283.33$ , colorless crystal  $0.70 \times 0.10 \times 0.10 \text{ mm}$ ,  $a = 9.762(1)$ ,  $b = 12.912(1)$ ,  $c = 24.489(1) \text{ \AA}$ ,  $V = 3086.8(4) \text{ \AA}^3$ ,  $\rho_{\text{calcd}} = 1.219 \text{ g cm}^{-3}$ ,  $\mu = 6.75 \text{ cm}^{-1}$ , empirical absorption correction via SORTAV ( $0.649 \leq T \leq 0.936$ ),  $Z = 8$ , orthorhombic, space group  $P2_12_12_1$  (No. 19),  $\lambda = 1.54178 \text{ \AA}$ ,  $T = 223 \text{ K}$ ,  $\omega$  and  $\varphi$  scans, 14575 reflections collected ( $\pm h, \pm k, \pm l$ ),  $[(\sin \theta)/\lambda] = 0.59 \text{ \AA}^{-1}$ , 4056 independent ( $R_{\text{int}} = 0.119$ ) and 2536 observed reflections [ $I \geq 2 \sigma(I)$ ], 390 refined parameters,  $R = 0.069$ ,  $wR^2 = 0.190$ , max. residual electron density  $0.54 (-0.22) \text{ e \AA}^{-3}$ , 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.<sup>28</sup> The activity of tyramine oxidase was measured spectrophotometrically using benzylamine as a substrate as already reported.<sup>11</sup>

**Observation of Time-Dependent Inhibition.** The experiments were carried out by the previously described method of Kitz and Wilson<sup>29</sup> as follows. The incubation of tyramine oxidase with compound was carried out at  $25^\circ\text{C}$  in  $0.125 \text{ mL}$  of  $0.1 \text{ M}$  potassium phosphate (pH 7.2) containing  $0.021 \mu\text{g}$  of tyramine oxidase,  $6\%$  of dimethyl sulfoxide, and different concentrations of inhibitor. Aliquots ( $20 \mu\text{L}$ ) were taken out periodically from the mixture, and diluted with  $0.48 \text{ mL}$  of assay solution followed by the observation of the increase of absorbance at  $250 \text{ nm}$  as described above.

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**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 (1S,2S)-(-)-(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>.

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