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Synthesis of 2-Trifluoromethyl-1,3-oxazolidines as Hydrolytically Stable Pseudoprolines

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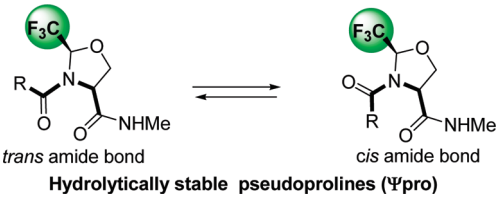

Trifluoromethyl group containing oxazolidines (Fox) are conveniently synthesized by condensation of serine esters with trifluoroacetaldehyde hemiacetal or trifluoroacetone. These oxazolidines can undergo *N*-acylation and amidification reactions and are completely configurationally and hydrolytically stable. Therefore, they can be considered as highly valuable proline surrogates (Tfm-pseudoprolines).

Introduction

The biological activity of peptides is highly dependent on their conformation. Thus, the synthesis of constrained peptides is a challenge for structure−activity relationship studies and the design of new peptides of therapeutic interest. A promising strategy consists of using cyclic amino acids (prolines,[1] pyroglutamic acid[2]...) or pseudopeptides in order to control the *cis*−*trans* isomerization of the amide bond and then the geometry of the peptides. In this context, a very attractive approach involving oxazolidines and thiazolidines synthesized by condensation reactions of serine, threonine, or cysteine with aldehydes, ketones, or their acetals was reported by Mutter et al.[3] These proline surrogates named pseudoprolines (Ψpro) are very attractive tools for peptide synthesis and biological properties. Pseudoprolines are acting as molecular hinges to induce *cis* amide bonds in peptide backbones (Figure 1).[3] For this reason, the pseudoproline strategy has been successfully applied to the synthesis of cyclic peptides.[4] Pseudoprolines are also powerful intermediates for enhancing synthetic efficiency in Fmoc SPPS by temporary disruption of the formation of the secondary structures during the peptide synthesis.[5] Moreover, these pseudoprolines are very interesting tools for investigating the peptides bioactive conformations.[6]

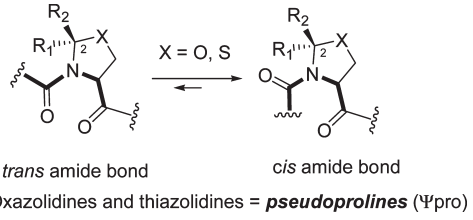

FIGURE 1. Amide isomer equilibrium in pseudoprolines (Ψpro).

A characteristic of the oxazolidine pseudoprolines is their hydrolytic weakness in acidic medium. This can be

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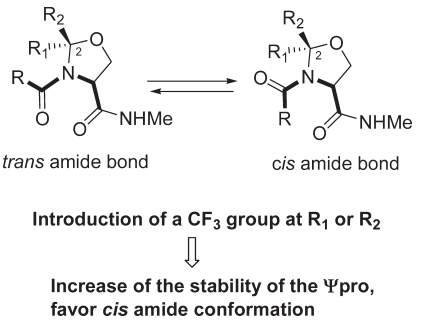

FIGURE 2. CF_3-pseudoprolines (Tfm-Ψpro) containing tripeptide models for amide isomer ratio and stability studies.

considered as an advantage for their use as temporary molecular hinge in peptide synthesis because the pseudoproline cyclic system is hydrolyzed when the peptide is cleaved from the resin to give the target peptide. On the other hand, the acid lability of the oxazolidine ring can be considered as a disadvantage when the expected application is the synthesis of conformationally constrained peptides. This drawback could be partially surmounted by using thiazolidine-type pseudoprolines obtained from cysteine.[7]

It is now well documented that the introduction of fluorine atoms into biomolecules significantly modifies their chemical and biological properties,[8] and a growing number of methods are reported for the synthesis of fluorine-containing compounds.[9] As a new application in peptide and amino acids chemistry, we report here that the introduction of a trifluoromethyl group at the C-2 carbon of the oxazolidine ring of pseudoprolines strongly increased its stability in acidic medium and favor the *cis* amide conformation of tripeptide models (Figure 2). This is mainly due to the strong electron-withdrawing effect of the trifluoromethyl group and its steric hindrance.[10] The tripeptide models represented in Figure 2 were chosen in order to compare the properties of the Tfm-pseudoprolines with unfluorinated pseudoprolines[3a] or prolines reported by other authors.[11]

Moreover, by analogy with trifluoromethyl group containing amino acids (Tfm-AAs) and pseudopeptides,[12] specific effects are expected from the incorporation of Tfm-pseudoprolines into peptides such as increase of the lipophilicity and a better affinity for lipid membranes, better stability toward proteases,[13] particular conformations stabilizations, and better autoassembly.[14] Moreover, the fluorinated pseudoprolines can be used as efficient probes for ^{19}F NMR studies.[15]

Results and Discussion

Synthesis of Tfm-pseudoprolines. In the nonfluorinated series, the main strategy employed for the incorporation of oxazolidine pseudoproline units into a peptide chain is the post-insertion method involving the condensation of aldehydes or ketones or their acetals with preformed serine-based dipeptides or analogues under an acidic catalysis.[3−5,16] The alternative strategy consisting of the *N*-acylation of a free NH oxazolidine was not extensively used because it frequently results in moderate yield and it involves low stability oxazolidines.[17] For the synthesis of the more stable thiazolidine-type pseudoprolines, both methods were reported so far.[18] The synthesis of trifluoromethyl group containing *N*-acylated oxazolidines was at first examined from *N*-acetyl and *N*-Cbz serine esters with trifluoroacetaldehyde ethyl hemiacetal under acidic catalysis according to the post-insertion strategy (Scheme 1). Unfortunately, no reaction occurred under these conditions. The tentative condensation of fluoral hydrate with a preformed Fmoc-Gly-Ser-OMe dipeptide under PTSA or $BF_3 \cdot OEt_2$ activation also failed to give the expected Tfm-pseudoproline containing dipeptide. Therefore, we decided to investigate the two-step strategy involving the synthesis of the oxazolidine ring followed by the *N*-acylation reaction. The targets Tfm-Ψpro esters **1** and **2** were conveniently obtained in satisfactory isolated

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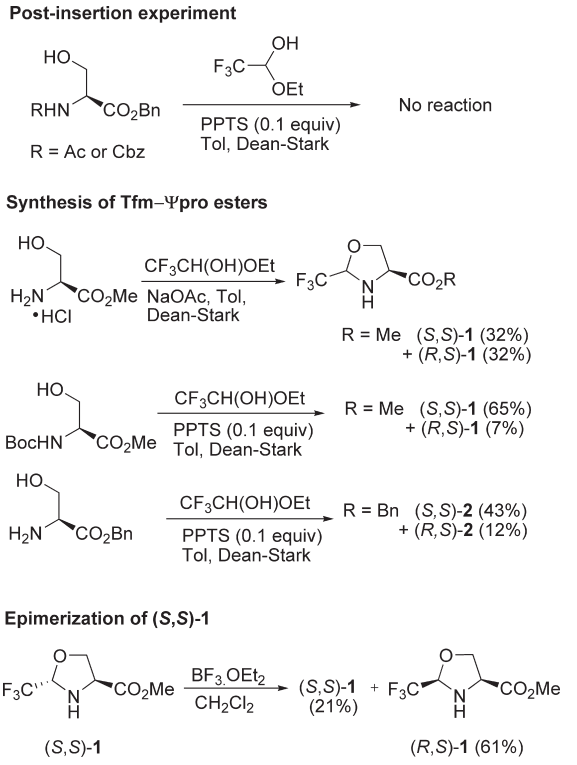
SCHEME 1. Synthesis of Tfm-Ψpro Esters



yields through the condensation reaction of trifluoroacetaldehyde ethyl hemiacetal with serine esters or their *N*-Boc derivatives (Scheme 1). We previously reported that the *N*-Boc protection of the amino alcohol is acting as a temporary protecting group of the nitrogen atom which facilitates the condensation reaction.[19] The ratio of each diastereomer was dependent on the reaction conditions. Starting from the serine methyl ester hydrochloride, the *trans* (*S*,*S*)-**1** and the *cis* (*R*,*S*)-**1** pseudoproline esters were obtained in similar isolated yields (32%).[20] When the reaction was performed from the *N*-Boc-serine methyl ester under acidic catalysis (0.1 equiv PPTS), the most stable *trans* (*S*,*S*)-**1** oxazolidine was obtained as the major compound (65% isolated yield). The isolated diastereomerically pure pseudoproline esters **1** and **2** are extremely stable and can be stored with no trouble. As expected from the strong electron-withdrawing effect of the trifluoromethyl group, there is no epimerization of the C-2 center of the oxazolidine ring through ring-opening and ring-closing equilibrium. In order to have in hand both (*S*,*S*)-**1** and (*R*,*S*)-**1** diastereomers for future studies, we investigated the epimerization of (*S*,*S*)-**1** into (*R*,*S*)-**1**. This was achieved by treating (*S*,*S*)-**1** with $BF_3 \cdot OEt_2$ in dichloromethane. After workup, the (*R*,*S*)-**1** pseudoproline was isolated in 61% yield and proved to remain configurationally stable (Scheme 1).

The absolute configuration of (*S*,*S*)-**1** and (*R*,*S*)-**1** was determined by the presence or the absence of nuclear Overhauser effect between the proton of the C_2 and both the protons of the C_4 and C_5 carbons. To confirm the NMR

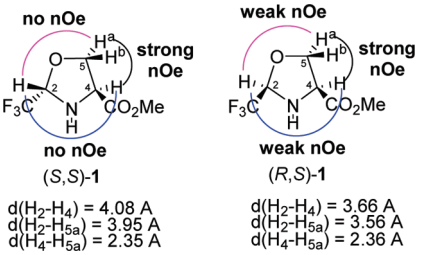
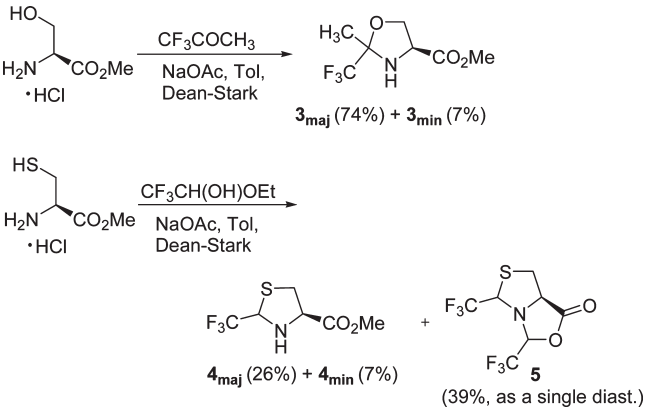


FIGURE 3. Selected NOE identifying the relative configuration of (*S*,*S*)-**1** and (*R*,*S*)-**1**.

SCHEME 2. Synthesis of Tfm-Ψpro Methyl Esters 3 and 4



results obtained with NOESY 2D experiments, the structure of the (*S*,*S*)-**1** and (*R*,*S*)-**1** has been modeled. The theoretical calculations were performed using a semiempirical force field (AM1) and the Hyperchem 5.0 package.[21] The analysis of geometrical data for hydrogen atoms (see Figure 3) measured in the lowest energy equilibrium molecular structure shows that the H_2-H_4 distance in (*S*,*S*)-**1** is larger than H_2-H_4 distance in (*R*,*S*)-**1**. The absence of NOE correlation peaks on the NOESY map for (*S*,*S*)-**1** for this pair of hydrogen is in agreement with this difference in H_2-H_4 distances in both isomers. The same occurrence was observed for the hydrogen pairwise H_2-H_{5a}. For the concerned hydrogen pairs, these NOE results are perfectly consistent with a *cis* and *trans* relationship for (*R*,*S*)-**1** and (*S*,*S*)-**1**, respectively.

As an exploratory study, the synthesis of disubstituted oxazolidines was also investigated by mean of the condensation of the serine methyl ester hydrochloride with trifluoroacetone. The expected pseudoprolines **3** were obtained in good yields (Scheme 2). The major diastereomer of **3** was isolated in 74% yield.[22] A preliminary experiment showed that trifluoromethyl group containing thiazolidines can also be obtained by the condensation of the cysteine methyl ester with trifluoroacetaldehyde ethyl hemiacetal. Unfortunately, the expected pseudoprolines **4** were obtained in low yields (33%) with the undesired bicyclic compound **5** (Scheme 2).

The unprotected Tfm-pseudoprolines (*S*,*S*)-**6** and (*R*,*S*)-**6** were very conveniently obtained through saponification of the corresponding methyl esters (*S*,*S*)-**1** and (*R*,*S*)-**1** in, respectively, 52% and 68% yield (Scheme 3). Due to the

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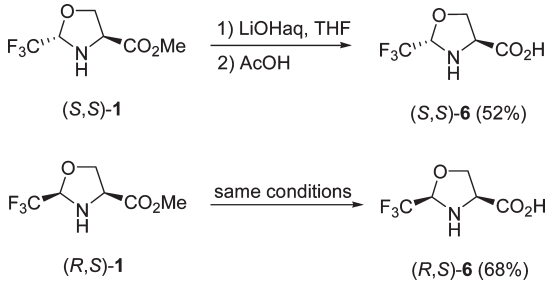
(20) Both diastereomers are very conveniently separated by silica gel chromatography because of high R_f values differences.

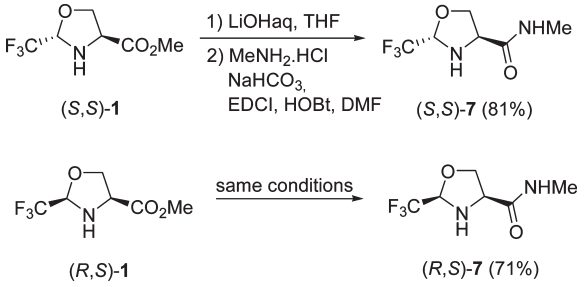
(21) HyperChem is a registered trademark of Hypercube, Inc.

(22) The absolute configurations of **3** and **4** could not be assigned.

SCHEME 3. Synthesis of Tfm-Ψpro 6



SCHEME 4. Synthesis of Tfm-Ψpro *N*-Methylamides 7

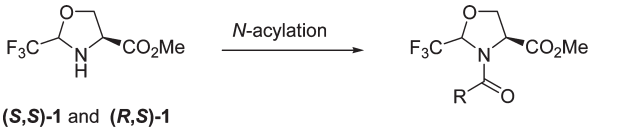


electron-withdrawing effect of the trifluoromethyl group, these oxazolidines are very stable toward ring-opening and can be considered as valid δ-trifluoromethylated proline surrogates.

Synthesis of Tfm-pseudoproline-Based Peptide Models. In order to anticipate the coupling reaction of an amino acid at the *C*-terminal position of the Tfm-Ψpro **6**, the synthesis of the corresponding *N*-methyl amides **7** was investigated. The amide synthesis was achieved from the Tfm-Ψpro methyl esters **1** in a two-step procedure involving the saponification of the ester function followed by the amidification reaction with methylamine using standard peptide bond formation conditions (Scheme 4). Starting from the esters (*S*,*S*)-**1** and (*R*,*S*)-**1**, the *N*-methylamides (*S*,*S*)-**7** and (*R*,*S*)-**7** were obtained in, respectively, 81% and 71% yields. It should be noticed that the amidification reaction can be performed without prerequisite protection of the oxazolidine amino group. Because of the deactivation of this nitrogen atom by the trifluoromethyl group, the diketopiperazine formation side reaction is avoided. The coupling reaction occurred without any epimerization at the C-2 or the C-4 centers. Therefore, the Tfm-pseudoprolines could be useful configurationally stable surrogates of substituted prolines at the *N*-terminal position of peptides.

In order to probe the peptide coupling reactions on the deactivated nitrogen atom in the α position of the trifluoromethyl group and to study *cis*/*trans* amide equilibrium, the *N*-acylation of the Tfm-pseudoproline methyl esters **1** was achieved (Table 1). Because of the dramatic decrease of the nucleophilicity of the amino group in the α-position of the

TABLE 1. Acylation Reactions of Tfm-Ψpro Esters (*S*,*S*)-1 and (*R*,*S*)-1



entry	starting material	acylation conditions	product	yield[a] (%)
1	(*S*,*S*)-**1**	AcCl, Pyr.	R = Me, (*S*,*S*)-**8**	74
2	(*S*,*S*)-**1**	Ac_2O	R = Me, (*S*,*S*)-**8**	84
3	(*S*,*S*)-**1**	Ac_2O, cat I_2	R = Me, (*S*,*S*)-**8**	85
4	(*R*,*S*)-**1**	Ac_2O	R = Me, (*R*,*S*)-**8**	79
5	(*R*,*S*)-**1**	Ac_2O, cat I_2	R = Me, (*R*,*S*)-**8**	86
6	(*S*,*S*)-**1**	$(EtCO)_2O$	R = Et, (*S*,*S*)-**9**	65
7	(*S*,*S*)-**1**	EtCOCl, Pyr.	R = Et, (*S*,*S*)-**9**	97
8	(*R*,*S*)-**1**	$(EtCO)_2O$	R = Et, (*R*,*S*)-**9**	89
9	(*R*,*S*)-**1**	PhCOCl	R = Ph, (*R*,*S*)-**10**	96
10	(*R*,*S*)-**1**	PhCOCl, Pyr.	R = Ph, (*R*,*S*)-**10**	99
11	(*S*,*S*)-**1**	PhCOCl[b]	R = Ph, (*R*,*S*)-**10**	90
12	(*S*,*S*)-**1**	PhCOCl, Et_3N	R = Ph, **10**[c]	60[c]

[a]Isolated yield. [b]When the reaction was performed in the presence of pyridine, (*S*,*S*)-**1** was converted into (*S*,*S*)-**10** with a 20% conversion. [c]54:46 mixture of (*R*,*S*)-**10** and (*S*,*S*)-**10**.

trifluoromethyl group,[23] strong electrophiles such as acyl halides or acid anhydrides have to be used.[24] The *N*-acetylation of the (*S*,*S*)-**1** or the (*R*,*S*)-**1** oxazolidines was conveniently achieved in good yields using acetyl chloride in the presence of pyridine or using acetic anhydride (Table 1, entries 1−5). In the acetyl anhydride conditions, the yield was increased by using an iodine catalysis (Table 1, entry 5).[25] Under all conditions, the acetylation reaction occurred without any epimerization. The *trans*-(*S*,*S*)-**1** and the *cis*-(*R*,*S*)-**1** oxazolidines gave the *trans*-(*S*,*S*)-**8** and the *cis*-(*R*,*S*)-**8** *N*-acetylated oxazolidines, respectively. The *N*-propanoylation of (*S*,*S*)-**1** and (*R*,*S*)-**1** occurred in a similar manner to give (*S*,*S*)-**9** and (*R*,*S*)-**9** (Table 1, entries 6−8). The *N*-benzoylation of the *cis*-(*R*,*S*)-**1** oxazolidine into *cis*-(*R*,*S*)-**10** was performed in very high yields (96−99%) using benzoyl chloride neat or in the presence of pyridine (Table 1, entries 9 and 10). The *trans*-(*S*,*S*)-**1** oxazolidine presented a different behavior when it reacted with benzoyl chloride. When the reaction was carried out with neat benzoyl chloride, epimerization occurred and the *cis*-(*R*,*S*)-**10** was obtained in 90% yield (Table 1, entry 11). When the reaction was performed in the presence of pyridine, preventing the epimerization of the oxazolidine ring, the conversion of *trans*-(*S*,*S*)-**1** into *trans*-(*S*,*S*)-**10** was very low (20%). The benzoylation reaction of *trans*-(*S*,*S*)-**1** with benzoyl chloride in the presence of triethylamine gave a 54:46 mixture of (*R*,*S*)-**10** and (*S*,*S*)-**10** in 60% yield (Table 1, entry 12). These results suggest that the C-2 epimerization of the *trans*-(*S*,*S*)-**1** oxazolidine into the less hindered and more reactive *cis*-(*R*,*S*)-**1** oxazolidine is concomitant to the benzoylation reaction when the reaction is carried out in acidic conditions.[26]

In a similar manner, the major diastereomer of the Ψ(^{CF3,CH3}Pro) methyl ester $\mathbf{3_{maj}}$ was submitted to the *N*-acylation reaction with acetic anhydride in the presence of iodine to give the corresponding *N*-acetylated pseudoproline methyl ester **11** in 55% yield. The yield is lower than in the case of the monosubstituted Tfm-pseudoprolines because of the

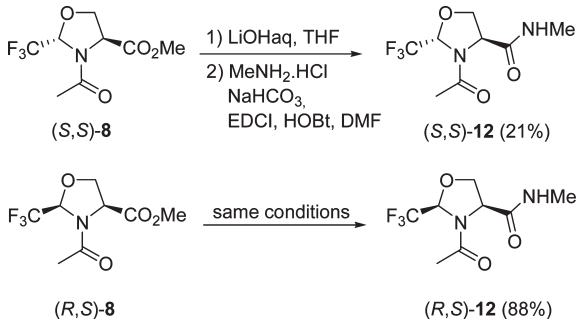
(23) Schlosser, M. *Angew. Chem., Int. Ed.* **1998**, *110*, 1496–1513.

(24) For examples of peptides coupling at the *N*-terminal position of α-Tfm-amino acids, see: (a) Koksch, B.; Quaedflieg, P. J. L. M.; Michel, T.; Burger, K.; Broxterman, Q. B.; Schoemaker, H. E. *Tetrahedron: Asymmetry* **2004**, *15*, 1401–1407. (b) Dal Pozzo, A.; Ni, M.; Muzi, L.; Caporale, A.; de Castiglione, R.; Kaptein, B.; Broxterman, Q. B.; Formaggio, F. *J. Org. Chem.* **2002**, *67*, 6372–6375. (c) Chaume, G.; Lensen, N.; Caupene, C.; Brigaud, T. *Eur. J. Org. Chem.* **2009**, 5717–5724.

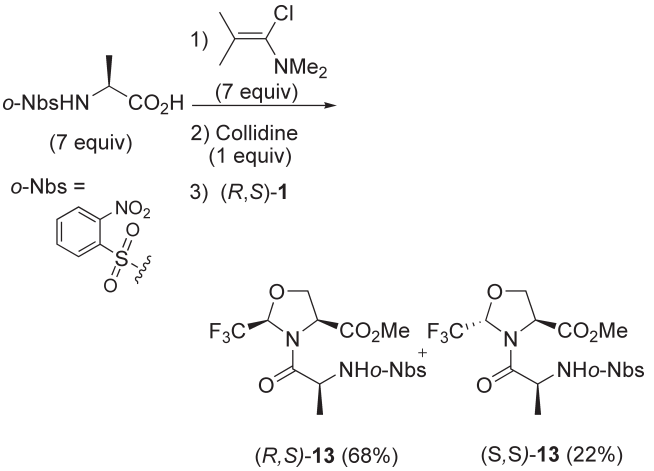
(25) (a) Philippe, C.; Milcent, T.; Nguyen Thi Ngoc, T.; Crousse, B.; Bonnet-Delpon, D. *Eur. J. Org. Chem.* **2009**, *71*, 5215–5223. (b) Varala, R.; Nuvula, S.; Adapa, S. R. *J. Org. Chem.* **2006**, *71*, 8283–8286.

(26) Ando, W.; Igarashi, Y.; Huang, L. *Chem. Lett.* **1987**, 1361–1364.

SCHEME 5. Synthesis of Tfm-Ψpro *N*-Methylamides 12



SCHEME 6. Peptide Coupling Reaction with the Nitrogen Atom of a Tfm-pseudoproline



increased steric hindrance at the C-2 position of the oxazolidine ring. The synthesis of the *N*-acetylated CF_3-pseudoprolines containing tripeptide models (*S*,*S*)-**12** and (*R*,*S*)-**12** was achieved through the saponification reactions of the methyl esters (*S*,*S*)-**8** and (*R*,*S*)-**8** followed by their amidification reaction with methylamine (Scheme 5). This strategy proved to be more satisfactory than the acetylation of the pseudoproline amides (*S*,*S*)-**7** and (*R*,*S*)-**7**, which gave side products resulting from the acetylation reaction on both oxazolidine and amide nitrogen atoms.

In order to anticipate the use of Tfm-pseudoprolines in peptide chemistry, a preliminary experiment of peptide coupling of *o*-Nbs-Ala-OH with the nitrogen atom of the pseudoproline (*R*,*S*)-**1** was investigated (Scheme 6). Because of the strong deactivation of the amino group of the Tfm-pseudoproline, a highly electrophilic amino acid halide[27] (7 equiv) was required to achieve the peptide coupling in a good yield (90%). The expected (*R*,*S*)-**13** dipeptide was obtained in 68% isolated yield with the (*S*,*S*)-**13** diastereomer (22% isolated yield).

***Cis*/*Trans* Amide Isomer Ratio Determination.** As expected, all the new synthesized *N*-acylated Tfm-pseudoprolines were obtained as *cis*/*trans* amide isomers.[28] For each diastereoisomer of pseudoprolines **7**, **8**, **9**, **11**, and **12**, the *cis*/*trans* amide conformer ratio was determined by ^1H and ^{13}C-{^1H} NMR measurements in $CDCl_3$ according to the work previously reported by Lubell et al.[11] The ratio of *cis*/*trans* amide conformers was determined by ^1H and ^{19}F NMR integration. The assignments of the isomers' geometry were performed by the comparison of the ^{13}C chemical shifts of the α, *β*, and *γ* carbons of the *cis* and the *trans* isomers. On the ^{13}C NMR spectra, the α- and *β*-carbon signals of the *trans* isomers should appear upfield compared to the α- and *β*-carbon signals of the *cis* isomers. On the other hand, the *δ*-carbon signals of the *trans* isomers should appear downfield compared to the *δ*-carbon signals of the *cis* isomers. (Table 2). The average 40:60 *cis*/*trans* amide ratio observed is consistent with literature data obtained with similar structures in the proline[11] and the unfluorinated pseudoproline series.[3]

Stability Study of Tfm-pseudoprolines. In order to demonstrate the great increased of stability of the Tfm-pseudoprolines toward acid-mediated ring-opening, the pseudopeptides **8**, **11**, and **12** were treated with different acidic media (Table 3). Both diastereomers of the *N*-acetylpseudoproline methyl esters **8** proved to be completely stable under treatment with 5% trifluoroacetic acid in $CDCl_3$ at room temperature after several days (Table 3, entries 1 and 2). The incorporation of the trifluoromethyl group exerts a remarkable stabilization effect since unfluorinated similar pseudoprolines undergo quantitative ring-opening within minutes under these conditions.[5a] Moreover, the *N*-acetylated pseudoproline methyl esters **8** and **11** as well as their methylamide analogues **12** are totally stable under treatment with 90% or 95% TFA/H_2O at room temperature for several hours (Table 3, entries 3−7). These results suggest that, compared to unfluorinated pseudoprolines, Tfm-pseudoprolines would be completely hydrolytically stable under Fmoc/*t*-Bu solid-phase peptide synthesis strategy. It should also be noticed that in opposition to the unfluorinated series[5a] and the unacylated Tfm-pseudoprolines **1** (Scheme 1), Tfm-pseudoprolines are stable toward Lewis acids. The diastereomerically pure *N*-acylated Tfm-pseudoprolines (*S*,*S*)- or (*R*,*S*)-**8** and -**12** do not undergo epimerization or ring-opening when treated with an excess of $BF_3 \cdot OEt_2$ in $CDCl_3$ for several hours. The combined electron-withdrawing effects of the trifluoromethyl group and the acyl group on the nitrogen atom prevent the ring-opening of the oxazolidine ring.

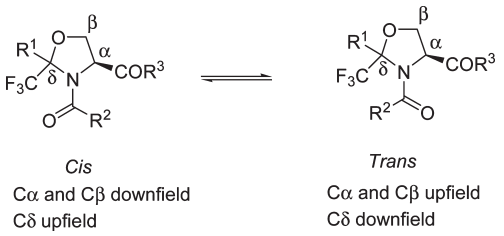
Conclusion

In conclusion, we report that fluorinated oxazolines (Fox) are conveniently synthesized by condensation reaction of serine esters and trifluoroacetaldehyde hemiacetal or trifluoroacetone. These oxazolidines are stabilized toward ring-opening by the trifluoromethyl group and can be considered as pseudoprolines. Despite the great deactivation of their nitrogen atom, these oxazolidines can be efficiently *N*-acylated to give stable pseudoproline-type structures as *cis*/*trans* conformers. The conformational study of the Tfm-pseudoprolines and their *cis*/*trans* isomerization are under investigation and will be reported soon. For future applications in peptide chemistry, it is anticipated that Fox-pseudoprolines would be hydrolytically stable authentic proline surrogates compatible with Fmoc/*t*-Bu SPPS strategy. After removal of the peptide from the resin, the conformational features induced by the trifluoromethyl group

(27) (a) Dal Pozzo, A.; Bergonzi, R.; Ni, M. *Tetrahedron Lett.* **2001**, *42*, 3925–3927. (b) Dal Pozzo, A.; Ni, M.; Muzi, L.; Caporale, A.; de Castiglione, R.; Kaptein, B.; Broxterman, Q. B.; Formaggio, F. *J. Org. Chem.* **2002**, *67*, 6372–6375.

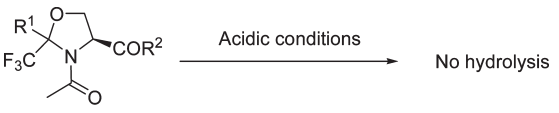
(28) *Cis*/*trans* amide isomers were discriminated from possible diastereomers or side products by coalescence of NMR signals at higher temperature.

TABLE 2. ***Cis*/*Trans* Amide Isomer Ratio of Pseudoprolines 8, 9, 11, and 12 in $CDCl_3$ at 298 K**



				Cα		Cβ		Cδ		
compd	R^1	R^2	R^3	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*/*trans* ratio
(*S*,*S*)-**8** ($CDCl_3$)	H	CH_3	OMe	59.0	58.1	72.1	70.5	84.6	84.8	40:60
(*R*,*S*)-**8** ($CDCl_3$)	H	CH_3	OMe	58.1	56.6	70.5	69.4	84.3	85.5	48:52
(*S*,*S*)-**9** ($CDCl_3$)	H	Et	OMe	58.4	58.2	72.2	70.3	84.4	84.7	40:60
(*R*,*S*)-**9** ($CDCl_3$)	H	Et	OMe	57.4	56.8	70.4	69.0	84.3	84.3	52:48
11 ($CDCl_3$)	CH_3	CH_3	OMe	60.6	60.4	67.5	69.1	91.6	93.9	31:69
(*S*,*S*)-**12** ($CDCl_3$)	H	CH_3	NHMe	60.0	59.0	73.0	71.0	84.1	84.7	40:60
(*R*,*S*)-**12** ($CDCl_3$)	H	CH_3	NHMe	60.0	57.5	71.4	68.7	85.0	85.0	33:66

TABLE 3. Hydrolytic Stability of Tfm-pseudoprolines



8, 11, 12

entry	compd	R^1	R^2	acidic conditions
1	(*S*,*S*)-**8**	H	OMe	5% TFA in $CDCl_3$, rt, 72 h
2	(*R*,*S*)-**8**	H	OMe	5% TFA in $CDCl_3$, rt, 72 h
3	(*S*,*S*)-**8**	H	OMe	90% TFA/H_2O, rt, 4 h
4	(*R*,*S*)-**8**	H	OMe	90% TFA/H_2O, rt, 4 h
5	**11**	CH_3	OMe	90% TFA/H_2O, rt, 5 h
6	(*S*,*S*)-**12**	H	NHMe	95% TFA/H_2O, rt, 5 h
7	(*R*,*S*)-**12**	H	NHMe	95% TFA/H_2O, rt, 5 h

containing pseudoproline would be preserved. The incorporation of Tfm-pseudoprolines into peptide chains is in progress and will be reported in due course.

Experimental Section

Synthesis of Oxazolidine 1−3 and Thiazolidine 4. (4*S*)-2-Trifluoromethyloxazolidine-4-carboxylic Acid Methyl Esters (*S*,*S*)-1 and (*R*,*S*)-1. Representative Procedure from (*S*)-Serine Methyl Ester Hydrochloride. To a solution of (*S*)-serine methyl ester hydrochloride (2.33 g, 15.0 mmol) in toluene (5 mL) at 0 °C were added sodium acetate (1.23 g, 15.0 mmol, 1 equiv) and trifluoroacetaldehyde ethyl hemiacetal (3.48 mL, 30.0 mmol, 2 equiv). The resulting mixture was stirred at room temperature for 30 min and warmed to 90 °C for 2 h. Toluene (30 mL) was then added to the reaction mixture, which was warmed to reflux using a Dean−Stark apparatus for 6 h. The reaction mixture was then cooled to 0 °C with an ice bath and filtered, and toluene was evaporated. Purification by silica gel chromatography (90:10 petroleum ether/ethyl acetate) gave of (*S*,*S*)-**1** (945 mg, 32%) as a colorless oil and (*R*,*S*)-**1** (945 mg, 32%) as a white solid.

Representative Procedure from (*S*)-BocNH-serine Ester. To a solution of (*S*)-BocNH-serine methyl ester (490 mg, 2.23 mmol, 1.0 equiv) in toluene (1 mL) at room temperature were added trifluoroacetaldehyde ethyl hemiacetal (311 μL, 2.68 mmol, 1.2 equiv) and pyridinium *p*-toluenesulfonate (PPTS) (112 mg, 0.45 mmol, 0.2 equiv). The resulting mixture was stirred at 90 °C for 1 h. Then, 20 mL of toluene was added, and the reaction mixture was warmed to reflux using a Dean−Stark apparatus for 20 h. The reaction mixture was then cooled to 0 °C with an ice bath and filtered, and toluene was evaporated. The crude residue was purified by silica gel chromatography (90:10 petroleum ether/ethyl acetate) to give (*S*,*S*)-**1** (291 mg, 65%) as a colorless oil and (*R*,*S*)-**1** (33 mg, 7%) as a white solid.

(***S*,*S*)-1:** colorless oil; $R_f = 0.31$ (80:20 cyclohexane/ethyl acetate); $[\alpha]^{23}_D$ −50.4 (*c* 4.95, $CHCl_3$); IR (neat) 3338, 2962, 1740, 1439, 1287, 1223, 1158, 1131, 665 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.28 (m, 1 H, NH), 3.79 (s, 3 H, OMe), 3.83 (ddd, *J* = 7.8, 6.2, 1.0 Hz, 1 H), 4.02 (dd, *J* = 7.8, 6.2 Hz, 1 H), 4.23 (t, *J* = 7.8 Hz, 1 H), 5.04 (q, *J* = 5.7 Hz, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 52.9, 58.5, 69.7, 87.8 (q, *J* = 34.5 Hz), 123.2 (q, *J* = 283.6 Hz), 171.9; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −85.0 (dd, *J* = 5.7, 1.0 Hz); MS (EI) *m*/*z* = 199 [M^+], 140 [$M^+ - CO_2Me$] (100), 130, 112, 92, 70; HRMS (EI) calcd for $C_6H_8F_3NO_3$ 199.0456, found 199.0457.

(***R*,*S*)-1:** white solid; mp 65 °C; $R_f = 0.10$ (80:20 cyclohexane/ethyl acetate); $[\alpha]^{23}_D$ −17.61 (*c* 4.9, $CHCl_3$); IR (neat) 3309, 1737, 1462, 1285, 1231, 1156, 1127, 669 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.18 (m, 1 H, NH), 3.71 (s, 3 H, OMe), 4.08 (ddq, *J* = 6.5, 6.0, 0.7 Hz, 1 H), 4.11 (t, *J* = 6.0 Hz, 1 H), 4.15 (ddq, *J* = 6.5, 6.0, 1.1 Hz, 1 H), 4.89 (q, *J* = 5.2 Hz, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 52.6, 58.6, 68.8, 87.6 (q, *J* = 34.5 Hz), 122.9 (q, *J* = 283.6 Hz), 171.1; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −84.1 (ddd, *J* = 5.2, 1.1, 0.7 Hz); MS (EI) *m*/*z* = 199 [M^+], 140 [$M^+ - CO_2Me$] (100), 130, 112, 92, 70; HRMS (EI) calcd for $C_6H_8F_3NO_3$ 199.0456; found 199.0458.

(4*S*)-2-Trifluoromethyloxazolidine-4-carboxylic Acid Benzyl Esters (*S*,*S*)-2 and (*R*,*S*)-2. (*S*,*S*)-**2** and (*R*,*S*)-**2** were prepared according to the same procedure from (*S*)-serine benzyl ester (716 mg, 3.67 mmol, 1.0 equiv) in toluene (12 mL), trifluoroacetaldehyde ethyl hemiacetal (447 μL, 3.85 mmol, 1.05 equiv), and PPTS (92 mg, 0.37 mmol, 0.1 equiv). The resulting mixture was stirred at 90 °C for 1 h and then warmed to reflux using a Dean−Stark apparatus for 3 h. Purification by silica gel chromatography (85:15 cyclohexane/ethyl acetate) gave (*S*,*S*)-**2** (431 mg, 43%) as a colorless oil and (*R*,*S*)-**2** (119 mg, 12%) as a white solid.

(***S*,*S*)-2:** $R_f = 0.66$ (70:30 cyclohexane/ethyl acetate); $[\alpha]^{26}_D$ −39.8 (*c* 1.08, $CHCl_3$); IR (neat) 3333, 3036, 2958, 1738, 1285, 1131 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.39 (dd, *J* = 8.2, 7.3 Hz, 1 H, NH), 3.82 (dd, *J* = 7.8, 6.4 Hz, 1 H), 4.09 (ddd, *J* = 7.8, 7.3, 6.4 Hz, 1 H), 4.26 (t, *J* = 7.8 Hz, 1 H), 5.07 (dq, *J* = 8.2, 5.5 Hz, 1 H), 5.17 (d, *J* = 11.9 Hz, 1 H), 5.21 (d, *J* = 11.9 Hz, 1 H), 7.31−7.41 (m, 5 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 58.6, 67.8, 69.6, 87.7 (q,

J = 34.5 Hz), 123.2 (q, J = 283.7 Hz), 128.4, 128.7, 128.8, 134.7, 171.2; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −85.0 (d, J = 5.5 Hz); HRMS (EI) calcd for $C_{12}H_{12}F_3NO_3$ 275.0769, found 275.0777.

(***R,S*)-2:** white solid; mp 96−98 °C; R_f = 0.34 (70:30 cyclohexane/ethyl acetate); $[\alpha]^{22}_D$ −31.4 (*c* 0.8, $CHCl_3$); IR (neat) 3315, 2962, 2902, 1741, 1290, 1135 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (m, 1 H, NH), 4.10−4.20 (m, 3 H), 4.91 (dq, J = 7.8, 5.0 Hz, 1 H), 5.18 (s, 2 H), 7.34−7.37 (m, 5 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 58.8, 67.5, 68.9, 87.8 (q, J = 34.5 Hz), 122.8 (q, J = 283.7 Hz), 128.4, 128.6, 128.7, 135.0, 170.4; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −84.1 (d, J = 5.0 Hz); HRMS (EI) calcd for $C_{12}H_{12}F_3NO_3$ 275.0769, found 275.0760.

Lewis Acid Epimerization Procedure. To a stirred solution of pure (*S*,*S*)-**1** (912 mg, 4.58 mmol, 1.0 equiv) in dichloromethane (10 mL) at 0 °C was added $BF_3\cdot OEt_2$ complex (610 μL, 4.80 mmol, 1.05 equiv). The mixture was stirred for 8 h at room temperature. Subsequently, 5 mL of brine was added to the reaction mixture, and the product was extracted with dichloromethane (3 × 5 mL) and then dried over $MgSO_4$. Purification by flash chromatography (80:20 cyclohexane/ethyl acetate) gave 193 mg (21%) of (*S*,*S*)-**1** as colorless oil and 553 mg (61%) of (*R*,*S*)-**1** as a white solid.

(4*S*)-2-Trifluoromethyl-2-methyloxazolidine-4-carboxylic Acid Methyl Ester (3). The compound **3** was prepared from (*S*)-serine methyl ester hydrochloride (450 mg, 2.89 mmol) in toluene (1 mL), sodium acetate (237 mg, 2.89 mmol, 1 equiv), and trifluoroacetone (517 μL, 5.78 mmol, 2 equiv). The resulting mixture was stirred at room temperature for 6 h, and 6 mL of toluene was added to the reaction mixture which was warmed to reflux using a Dean−Stark apparatus for 18 h. Purification by silica gel chromatography (70:30 pentane/ether) gave $\mathbf{3_{maj}}$ (453 mg, 74%) as a colorless oil and $\mathbf{3_{min}}$ (44 mg, 7%) as a colorless oil.

Major diastereomer ($\mathbf{3_{maj}}$): colorless oil; R_f = 0.9 (7:3 pentane/Et_2O); $[\alpha]^{28}_D$ −33.3 (*c* 5.1, $CHCl_3$); IR (neat) 3325, 2959, 1741, 1438, 1220, 1153, 1101, 1034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (d, J = 1.0 Hz, 3 H), 3.00 (d, J = 6.4 Hz, 1 H, NH), 3.80 (s, 3 H, OMe), 3.90 (ddq, J = 8.2, 6.9, 1.0 Hz, 1 H), 4.10 (ddd, J = 8.2, 6.9, 6.4 Hz, 1 H), 4.31 (t, J = 8.2 Hz, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 19.7, 52.8, 59.5, 70.1, 94.6 (q, J = 30.7 Hz), 124.6 (q, J = 286.6 Hz), 172.4; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −85.9 (s); MS (EI) m/z = 198 [$M^+ - CH_3$], 154 [$M^+ - CO_2Me$] (100), 144, 126, 84; HRMS (EI) calcd for $C_7H_{10}F_3NO_3$ 213.0613, found 213.0623.

Minor diastereomer ($\mathbf{3_{min}}$): colorless oil; R_f = 0.16 (7:3 pentane/Et_2O); $[\alpha]^{27}_D$ −19.3 (*c* 3.4, $CHCl_3$); IR (neat): 3360, 3000, 2958, 1741, 1438, 1224, 1153, 1104, 1039 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (d, J = 0.9 Hz, 3 H), 2.89 (d, J = 6.9 Hz, 1 H, NH), 3.78 (s, 3 H, OMe), 4.16−4.32 (m, 3 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 20.6, 52.6, 59.1, 69.3, 94.0 (q, J = 30.7 Hz), 124.4 (q, J = 287.5 Hz), 171.2; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −85.5 (s); MS (EI) m/z = 198 [$M^+ - CH_3$], 154 [$M^+ - CO_2Me$] (100), 144, 126, 84; HRMS (EI) calcd for $C_7H_{10}F_3NO_3$ 213.0613, found 213.0616.

(4*R*)-2-Trifluoromethylthiazolidine-4-carboxylic Acid Methyl Ester (4). Compound **4** was prepared from (*R*)-cysteine methyl ester hydrochloride (1.54 g, 9.0 mmol) in toluene (5 mL), sodium acetate (738 mg, 9.0 mmol, 1 equiv), and trifluoroacetaldehyde ethyl hemiacetal (2.10 mL, 18.0 mmol, 2 equiv). The resulting mixture was stirred at room temperature for 30 min and then warmed to reflux using a Dean−Stark apparatus for 16 h. Purification by silica gel chromatography (90:10 cyclohexane/ethyl acetate) gave $\mathbf{4_{min}}$ (140 mg, 7%) as an orange oil, $\mathbf{4_{maj}}$ (491 mg, 26%) as an orange oil, and the bicyclic side product **5** as a white solid (977 mg, 39%).

$\mathbf{4_{maj}}$: orange oil; R_f = 0.06 (90:10 cyclohexane/ethyl acetate); $[\alpha]^{22}_D$ −31.9 (*c* 1.05, $CHCl_3$); IR (neat) 3352, 2956, 1788, 1737, 1438, 1148, 1111 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.8 (m, 1 H, NH), 3.11 (dd, J = 10.5, 9.2 Hz, 1 H), 3.27 (dd, J = 10.5, 6.0 Hz, 1 H), 3.80 (s, 3 H, OMe), 4.07 (dd, J = 9.2, 6.0 Hz, 1 H), 4.89 (q, J = 6.0 Hz, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 35.7, 52.7, 65.2, 66.5 (q, J = 33.5 Hz), 124.4 (q, J = 277.9 Hz), 170.5; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −78.0 (d, J = 6.0 Hz); HRMS (EI) calcd for $C_6H_8F_3NSO_2$ 215.0228, found 215.0225.

$\mathbf{4_{min}}$: colorless oil; R_f = 0.14 (90:10 cyclohexane/ethyl acetate); $[\alpha]^{22}_D$ −81.6 (*c* 1.15, $CHCl_3$); IR (neat) 3333, 2958, 2853, 1788, 1737, 1438, 1145, 1111 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97 (dd, J = 10.5, 6.9 Hz, 1 H), 3.20 (m, 1 H, NH), 3.41 (dd, J = 10.5, 6.4 Hz, 1 H), 3.81 (s, 3 H, OMe), 4.12 (dd, J = 6.9, 6.4 Hz, 1 H), 4.89 (q, J = 6.0 Hz, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 36.8, 52.9, 64.2, 66.5 (q, J = 34.5 Hz), 124.8 (q, J = 278.8 Hz), 171.6; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −79.5 (d, J = 6.9 Hz); HRMS (EI) calcd for $C_6H_8F_3NSO_2$ 215.0228, found 215.0228.

Bicyclic side product (5): white solid; mp 70−74 °C; R_f = 0.47 (9:1 cyclohexane/ethyl acetate); $[\alpha]^{22}_D$ −39.0 (*c* 2.45, $CHCl_3$); IR (neat) 2954, 1802, 1267, 1157, 1112, 998, 881 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 (dquint, J = 12.4, 1.9 Hz, 1 H), 4.38 (dd, J = 12.4, 7.8, 1.0 Hz, 1 H), 4.38 (dd, J = 7.8, 1.9 Hz, 1 H), 4.79 (qd, J = 7.2, 1.0 Hz, 1 H), 5.32 (q, J = 4.5 Hz, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 34.8, 64.6, 74.6 (q, J = 34.5 Hz), 91.7 (q, J = 37.4 Hz), 120.8 (q, J = 282.7 Hz), 123.8 (q, J = 279.8 Hz), 171.4; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −79.7 (dd, J = 7.2, 1.9 Hz), −85.7 (d, J = 4.5 Hz); MS (EI) m/z = 281 [M^+], 237 [$M^+ - CO_2$], 212 [$M^+ - CF_3$] (100), 184, 149, 123, 109, 69; HRMS (EI) calcd for $C_7H_5F_6NSO_2$ 280.9945, found 280.9958.

(2*S*,4*S*)-2-Trifluoromethyloxazolidine-4-carboxylic Acid (*S*,*S*)-6. To a solution of of (*S*,*S*)-**1** (490 mg, 2.46 mmol) in THF (15 mL) at 0 °C was added a 1 M aqueous solution of 2.95 mL of LiOH (2.95 mmol, 1.1 equiv). The reaction mixture was stirred vigorously for 4 h. Subsequently, Et_2O (25 mL) was added, and the reaction mixture was extracted with water (2 × 25 mL). The aqueous layers were combined, and water was removed under reduced pressure to afford of the corresponding lithium carboxylate (470 mg) as a yellow oil which was used in the next step without further purification: ^{1}H NMR (400 MHz, D_2O) δ 3.49 (t, J = 7.8 Hz, 1 H), 3.66 (t, J = 7.8 Hz, 1 H), 4.09 (t, J = 7.8 Hz, 1 H), 5.09 (q, J = 5.9 Hz, 1 H); ^{13}C NMR (100.5 MHz, D_2O) δ 60.5, 70.3, 87.3 (q, J = 34.5 Hz), 123.2 (q, J = 282.8 Hz), 176.5; ^{19}F NMR (376.2 MHz, D_2O) δ −84.6 (d, J = 5.9 Hz). The lithium carboxylate was taken up with 2.7 mL of a 1 M aqueous solution of acetic acid (2.7 mmol, 1.1 equiv). The product was extracted with AcOEt (3 × 5 mL) then dried over $MgSO_4$ to give (*S*,*S*)-**6** (237 mg, 52%) as colorless crystals: mp 69 °C; $[\alpha]^{26}_D$ −26.3 (*c* 1.4, MeOH); IR (neat) 3297, 2921, 2853, 1725, 1425, 1163, 1124, 946, 923 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (dd, J = 7.8, 5.5 Hz, 1 H), 4.17 (dd, J = 7.8, 5.5 Hz, 1 H), 4.35 (t, J = 7.8 Hz, 1 H), 5.11 (q, J = 5.5 Hz, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 58.3, 69.7, 87.6 (q, J = 34.5 Hz), 123.1 (q, J = 283.6 Hz), 175.8; ^{19}F NMR (376.2 MHz,$CDCl_3$) δ −85.0 (d, J = 5.5 Hz); MS (EI) m/z = 155, 140 ($M^+ - CO_2H$) (80), 116 ($M^+ - CF_3$) (100), 112, 92, 70. Anal. Calcd for $C_5H_6F_3NO_3$ (185.03): C, 32.44; H, 3.27; N, 7.57. Found: C, 32.55; H, 3.19; N, 7.53.

(2*R*,4*S*)-2-Trifluoromethyloxazolidine-4-carboxylic Acid (*R*,*S*)-6. To a solution of of (*R*,*S*)-**1** (161 mg, 0.81 mmol) in THF (4.4 mL) at 0 °C was added a 1 M aqueous solution of LiOH (890 μL, 0.89 mmol, 1.1 equiv). The reaction mixture was stirred vigorously for 4 h. Then Et_2O (10 mL) was added, and the reaction mixture was extracted with water (2 × 10 mL). The aqueous layers were combined, and the water was removed under reduced pressure to afford the corresponding lithium carboxylate (106 mg) as a yellow oil which was used in next step without further purification: ^{1}H NMR (400 MHz, D_2O) δ 3.78−3.88 (m, 2 H), 3.97 (m, 1 H), 4.88 (q, J = 5.2 Hz, 1 H); ^{13}C NMR (100.5 MHz, D_2O) δ 60.7, 69.4, 87.2 (q, J = 32.6 Hz), 123.0 (q, J = 282.8 Hz), 178.0; ^{19}F NMR (376.2 MHz, D_2O) δ −83.6 (d, J = 5.2 Hz). The lithium carboxylate was treated with

of a 1 M aqueous solution of acetic acid (890 μL, 0.89 mmol, 1.1 equiv). The product was extracted with AcOEt (3 × 5 mL) and then dried over $MgSO_4$ to give (*R*,*S*)-**6** (101 mg, 68%) as an orange oil: $[\alpha]^{27}_D$ −7.4 (*c* 1.15, MeOH); IR (neat) 3050, 2950, 1558, 1501, 1404, 1340, 1149, 1085, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.25−4.29 (m, 3 H), 5.03 (q, *J* = 5.2 Hz, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 58.5, 69.5, 87.5 (q, *J* = 34.5 Hz), 122.8 (q, *J* = 282.8 Hz), 173.4; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −84.2 (d, *J* = 5.2 Hz); MS (EI) *m*/*z* = 155, 140 [$M^+ - CO_2H$] (80), 116 [$M^+ - CF_3$] (100), 112, 92, 70; HRMS (EI) calcd for $C_5H_6F_3NO_3$ 185.0300; found 185.0300.

(2*S*,4*S*)-2-Trifluoromethyloxazolidine-4-*N*-methylamide (*S*,*S*)-7. To a solution of lithium carboxylate (1.43 g, 7 mmol) prepared from (*S*,*S*)-**1** acording to the previous procedure in DMF (16 mL) were successively added at room temperature methylamine hydrochloride (708 mg, 10.5 mmol, 1.5 equiv), HOBt (945 mg, 7 mmol, 1 equiv), $NaHCO_3$ (1.76 g, 21 mmol, 3 equiv), and EDCI (1.47 g, 0.7.7 mmol, 1.1 equiv). The reaction mixture was stirred overnight at room temperature and then diluted with AcOEt and water. The layers were separated, and the aqueous phase was extracted with AcOEt (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (60:40 AcOEt/cyclohexane) gave (*S*,*S*)-**7** (1.00 g, 81%) as white solid: mp 77−78 °C; R_f = 0.42 (3:7 cyclohexane/ethyl acetate); $[\alpha]^{26}_D$ −50.8 (*c* 0.5, $CHCl_3$); IR (neat) 3325, 3128, 2953, 2886, 1656, 1577, 1138 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.86 (d, *J* = 5.0 Hz, 3 H), 3.28 (t, *J* = 8.3 Hz, 1 H), 3.89 (t, *J* = 7.3 Hz, 1 H), 3.97 (dt, *J* = 8.3, 7.3 Hz, 1 H), 4.19 (t, *J* = 7.3 Hz, 1 H), 5.00 (dq, *J* = 8.3, 5.2 Hz, 1 H), 6.75 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 26.3, 59.4, 70.2, 87.7 (q, *J* = 33.5 Hz), 123.0 (q, *J* = 282.7 Hz), 170.4; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −84.5 (d, *J* = 5.2 Hz); MS (EI) *m*/*z* = 140 [M^+ − CONHMe] (100), 112, 92, 58. Anal. Calcd for $C_6H_9F_3N_2O_2$ (198.06): C, 36.67; H, 4.58; N, 14.14. Found: C, 36.52; H, 4.55; N, 14.03.

(2*R*,4*S*)-2-Trifluoromethyloxazolidine-4-*N*-methylamide (*R*,*S*)-7. To a solution of lithium carboxylate (1.06 g, 5.5 mmol) prepared acording to the previous procedure from (*R*,*S*)-**1** in DMF (16 mL) were successively added at room temperature methylamine hydrochloride (631 mg, 1,7 equiv, 9.3 mmol), HOBt (842 mg, 1.13 equiv, 6.23 mmol), $NaHCO_3$ (1.57 g, 3.4 equiv, 18.7 mmol), and EDCI (1.31 g, 1.2 equiv, 6.8 mmol). The reaction mixture was stirred overnight at room temperature and then diluted with AcOEt and water. The layers were separated, and the aqueous phase was extracted with AcOEt (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (60:40 AcOEt/cyclohexane) gave (*R*,*S*)-**7** (776 mg, 71%) as a white solid: mp 73−75 °C; R_f = 0.13 (3:7 cyclohexane/ethyl acetate); $[\alpha]^{21.4}_D$ −38.8 (*c* 0.66, $CHCl_3$); IR (neat) 3450, 3304, 2936, 1654, 1544, 1414, 1287, 1151, 1126 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.84 (d, *J* = 5.0 Hz, 3 H), 3.32 (t, *J* = 8.7 Hz, 1 H), 4.07 (dt, *J* = 8.7, 8.2 Hz, 1 H), 4.21 (t, *J* = 8.2 Hz, 1 H), 4.29 (t, *J* = 8.2 Hz, 1 H), 5.00 (dq, *J* = 8.7, 5.5 Hz, 1 H), 7.19 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 25.9, 59.6, 70.5, 87.6 (q, *J* = 33.6 Hz), 123.3 (q, *J* = 283.6 Hz), 171.6; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −84.2 (d, *J* = 5.5 Hz); MS (EI) *m*/*z* = 140 [M^+ − C(O)NHMe] (100), 112, 92, 58. Anal. Calcd for $C_6H_9F_3N_2O_2$ (198.06): C, 36.67; H, 4.58; N, 14.14. Found: C, 36.70; H, 4.56; N, 14.36.

Acylation of Oxazolidines 1. Acyl Chloride Procedure. To a stirred solution of oxazolidine **1** (1 equiv) in dichloromethane at 0 °C were successively added pyridine (3 equiv) and acyl chloride (3 equiv). The mixture was stirred for 20 h at room temperature. Dichloromethane was added, and the reaction mixture was washed with brine. The product was extracted with dichloromethane (3×) and then dried over $MgSO_4$. Purification by flash chromatography gave the corresponding acylated oxazolidines **8**−**10** in 74−97% yield.

Acid Anhydride Procedure. A stirred solution of oxazolidine **1** (1 equiv) in acid anhydride (10 equiv) was warmed to 140 °C for 20 h. Upon cooling, excess acid anhydride was removed under vacuum. Purification by flash chromatography gave the corresponding acylated oxazolidines **8** and **9** in 65−89% yield.

Acid Anhydride Procedure with Iodine Catalysis. A solution of oxazolidines **1** (1 equiv) and iodine (0.1 equiv) in acid anhydride (10 equiv) was stirred at room temperature until the reaction was completed as monitored by ^{19}F NMR analysis. Subsequently, dichloromethane was added, and the organic layer was washed with a 1 M aqueous solution of $NaHSO_3$ (3×). The aqueous layer was extracted with dichloromethane (3×), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography gave the corresponding acylated oxazolidines **8** in 85−86% yield.

(2*S*,4*S*)-*N*-Acetyl-2-trifluoromethyloxazolidine-4-carboxylic Acid Methyl Ester (*S*,*S*)-8. The product was prepared by the acyl choride procedure using 89 mg of (*S*,*S*)-**1** (0.44 mmol, 1.0 equiv) in dichloromethane (500 μL), 110 μL of pyridine (1.34 mmol, 3 equiv), and 95 μL of acetyl chloride (1.34 mmol, 3 equiv). Purification by flash chromatography (70:30 cyclohexane/ethyl acetate) gave 78 mg (74%) of acylated oxazolidine (*S*,*S*)-**8** as a 41:59 inseparable mixture of *cis*/*trans* rotational isomers (in $CDCl_3$ at 298 K).

The product was prepared by the acid anhydride procedure using 102 mg of (*S*,*S*)-1 (0.51 mmol, 1.0 equiv) in 480 μL of acetic anhydride (5.1 mmol, 10 equiv). Purification by flash chromatography (70:30 cyclohexane/ethyl acetate) gave 103 mg (84%) of acetylated oxazolidine (*S*,*S*)-**8** as a 40:60 inseparable mixture of *cis*/*trans* rotational isomers (in $CDCl_3$ at 298 K).

The product was prepared by the acid anhydride procedure with iodine catalysis using 875 mg of (*S*,*S*)-**1** (4.39 mmol, 1.0 equiv), 111 mg iodine (0.44 mmol, 0.1 equiv), and 4.1 mL of acetic anhydride (44.0 mmol, 10 equiv). The reaction was completed in 18 h at room temperature. Purification by flash chromatography (70:30 cyclohexane/ethyl acetate) gave 898 mg (85%) of acetylated oxazolidine (*S*,*S*)-**8** as a 39:61 inseparable mixture of *cis*/*trans* rotational isomers (in $CDCl_3$ at 298 K): colorless oil; R_f = 0.17 (70:30 cyclohexane/ethyl acetate); $[\alpha]^{22}_D$ −53.8 (*c* 1.7, $CHCl_3$); IR (neat) 2960, 1749, 1678, 1384, 1342, 1281, 1206, 1175, 1147, 1118, 943, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 298 K) (*trans* rotational isomer) δ 2.21 (s, 3 H), 3.78 (s, 3 H), 4.24 (d, *J* = 9.6 Hz, 1 H), 4.50 (dd, *J* = 9.6, 8.2 Hz, 1 H), 4.55−4.65 (m, 1 H), 5.60 (q, *J* = 4.6 Hz, 1 H); (*cis* rotational isomer) δ 2.06 (s, 3 H), 3.85 (s, 3 H), 4.38 (d, *J* = 7.8 Hz, 1 H), 4.55−4.65 (m, 2 H), 5.87 (q, *J* = 4.6 Hz, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$, 298 K) (*trans* rotational isomer) δ 22.3, 52.7, 58.1, 70.5, 84.8 (q, *J* = 35.4 Hz), 122.9 (q, *J* = 287.5 Hz), 168.9, 169.9; (*cis* rotational isomer) δ 22.7, 53.3, 59.0, 72.1, 84.6 (q, *J* = 34.5 Hz), 122.9 (q, *J* = 287.5 Hz), 170.0, 170.2; ^{19}F NMR (376.2 MHz, $CDCl_3$, 298 K) (*trans* rotational isomer) δ −81.7 (d, *J* = 4.6 Hz); (*cis* rotational isomer) −81.4 (d, *J* = 4.6 Hz); MS (EI) *m*/*z* = 241 [M^+], 182 [$M^+ - CO_2Me$] (50), 172, 140 (100), 130, 112; HRMS (EI) calcd for $C_8H_{10}F_3NO_4$ 241.0562, found 241.0561.

(2*R*,4*S*)-*N*-Acetyl-2-trifluoromethyloxazolidine-4-carboxylic Acid Methyl Ester (*R*,*S*)-8. The product was prepared by the acid anhydride procedure using 100 mg of (*R*,*S*)-**1** (0.50 mmol, 1.0 equiv) in 470 μL of acetic anhydride (5.0 mmol, 10 equiv). Purification by flash chromatography (70:30 cyclohexane/ethyl acetate) gave 96 mg (79%) of acetylated oxazolidine (*R*,*S*)-8 as a 48:52 inseparable mixture of *cis*/*trans* rotational isomers (in $CDCl_3$ at 298 K).

The product was prepared by the acid anhydride procedure with iodine catalysis using 910 mg of (*R*,*S*)-**1** (4.57 mmol, 1.0 equiv), 114 mg of iodine (0.46 mmol, 0.1 equiv), and 4.3 mL of acetic anhydride (45.7 mmol, 10 equiv). The reaction was completed in 18 h at room temperature. Purification by flash chromatography (70:30 cyclohexane/ethyl acetate) gave 953 mg

(86%) of acetylated oxazolidine (*R*,*S*)-**8** as a 45:55 inseparable mixture of *cis*/*trans* rotational isomers (in $CDCl_3$ at 298 K): colorless oil; R_f = 0.16 (70:30 cyclohexane/ethyl acetate); $[\alpha]^{29}_D$ −62.9 (*c* 4.8, $CHCl_3$); IR (neat) 2959, 1751, 1681, 1438, 1390, 1349, 1285, 1212, 1148, 1121, 956, 845, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 298 K) (*trans* rotational isomer) δ 2.22 (s, 3 H), 3.78 (s, 3 H), 4.37 (m, 1 H), 4.50 (m, 1 H), 5.00 (m, 1 H), 5.53 (m, 1 H); (*cis* rotational isomer) δ 2.22 (s, 3 H), 3.83 (s, 3 H), 4.43−4.58 (m, 2 H), 4.72 (m, 1 H), 5.92 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$, 298 K) (*trans* rotational isomer) δ 22.2, 52.8, 56.6, 69.4, 85.5 (q, J = 34.5 Hz), 122.8 (q, J = 286.6 Hz), 169.0, 170.1; (*cis* rotational isomer) δ 22.2, 53.1, 58.1, 70.5, 84.3 (q, J = 37.4 Hz), 122.8 (q, J = 286.6 Hz), 169.0, 170.1; ^{19}F NMR (376.2 MHz, $CDCl_3$, 298 K) (*trans* rotational isomer) δ −82.0 (s); (*cis* rotational isomer) δ −82.2 (s); ^1H NMR (400 MHz, $CDCl_3$, 323 K) (single rotational isomer) δ 2.19 (s, 3 H), 3.79 (s, 3 H), 4.36−4.52 (m, 2 H), 4.85 (m, 1 H), 5.73 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$, 323 K) (single rotational isomer) δ 22.0, 52.8, 57.5, 69.9, 84.8, 122.7 (q, J = 286.6 Hz), 168.9; ^{19}F NMR (376.2 MHz, $CDCl_3$, 323 K) (single rotational isomer) δ −81.8 (s); MS (EI) m/z = 242 [M^+ + H], 182 [$M^+ - CO_2Me$] (50), 172, 140 (100), 130, 112. Anal. Calcd for $C_8H_{10}F_3NO_4$ (241.06): C, 39.84; H, 4.18; N, 5.81. Found: C, 40.08; H, 4.21; N, 5.82.

(2*S*,4*S*)-*N*-Propionyl-2-trifluoromethyloxazolidine-4-carboxylic Acid Methyl Ester (*S*,*S*)-9. The product was prepared by the acyl choride procedure using 150 mg of (*S*,*S*)-**1** (0.75 mmol, 1.0 equiv) in dichloromethane (500 μL), 182 μL of pyridine (2.26 mmol, 3 equiv), and 196 μL of propionyl chloride (2.26 mmol, 3 equiv). Purification by flash chromatography (70:30 cyclohexane/ethyl acetate) gave 187 mg (97%) of acylated oxazolidine (*S*,*S*)-**9** as a 40:60 inseparable mixture of *cis*/*trans* rotational isomers (in $CDCl_3$ at 298 K).

The product was prepared by the acid anhydride procedure using 493 mg of (*S*,*S*)-**1** (2.47 mmol, 1.0 equiv) in 3.2 mL of propionic anhydride (24.7 mmol, 10 equiv). Purification by flash chromatography (80:20 cyclohexane/ethyl acetate) gave 432 mg (65%) of acylated oxazolidine (*S*,*S*)-**9** as a 40:60 inseparable mixture of *cis*/*trans* rotational isomers (in $CDCl_3$ at 298 K): white solid; mp 36−37 °C; R_f = 0.21 (80:20 cyclohexane/ethyl acetate); $[\alpha]^{28}_D$ −50.4 (*c* 2.85, $CHCl_3$); IR (neat) 2987, 2951, 1741, 1685, 1359, 1275, 1177, 1142, 1114, 991, 939, 846 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 298 K) (*trans* rotational isomer) δ 1.12−1.23 (m, 3 H), 2.37 (m, 1 H), 2.47 (m, 1 H), 3.78 (s, 3 H), 4.22 (d, J = 8.7 Hz, 1 H), 4.49 (t, J = 8.7 Hz, 1 H), 4.59 (m, 1 H), 5.64 (q, J = 4.6 Hz, 1 H); (*cis* rotational isomer) δ 1.12−1.23 (m, 3 H), 2.15 (m, 1 H), 2.26 (m, 1 H), 3.83 (s, 3 H), 4.37 (m, 1 H), 4.52−4.66 (m, 2 H), 5.89 (q, J = 4.1 Hz, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$, 298 K) (*trans* rotational isomer) δ 8.7, 27.8, 52.8, 58.2, 70.3, 84.7 (q, J = 35.5 Hz), 122.9 (q, J = 288.5 Hz), 170.1, 172.5; (*cis* rotational isomer) δ 8.7, 28.5, 53.3, 58.4, 72.2, 84.4 (q, J = 36.4 Hz), 122.9 (q, J = 288.5 Hz), 170.4, 173.6; ^{19}F NMR (376.2 MHz, $CDCl_3$, 298 K) (*trans* rotational isomer) δ −81.6 (d, J = 4.6 Hz); (*cis* rotational isomer): δ −81.4 (d, J = 4.1 Hz); ^1H NMR (400 MHz, $CDCl_3$, 323 K) (single rotational isomer) δ 1.18 (td, J = 7.0, 2.5 Hz, 3 H), 2.20−2.50 (m, 2 H), 3.79 (s, 3 H), 4.26 (m, 1 H), 4.50 (m, 1 H), 4.58 (m, 1 H), 5.66 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$, 323 K) (single rotational isomer) δ 8.7, 28.1, 52.9, 58.5, 70.8 and 72.1, 84.9 (q, J = 30.7 Hz), 123.1 (q, J = 288.5 Hz), 170.2, 172.8 and 173.1; ^{19}F NMR (376.2 MHz, $CDCl_3$, 323 K) (single rotational isomer) δ −81.8 (s); MS (EI) m/z = 255 [M^+], 196 [$M^+ - CO_2Me$] (70), 186, 140, 130, 57 (100); HRMS (EI) calcd for $C_9H_{12}F_3NO_4$ 255.0718, found 255.0726.

(2*R*,4*S*)-*N*-Propionyl-2-trifluoromethyloxazolidine-4-carboxylic Acid Methyl Ester (*R*,*S*)-9. The product was prepared by the acid anhydride procedure using 115 mg of (*R*,*S*)-**1** (0.57 mmol, 1.0 equiv) in 740 μL of propionic anhydride (5.7 mmol, 10 equiv). Purification by flash chromatography (90:10 cyclohexane/ethyl acetate) gave 130 mg (89%) of acylated oxazolidine (*R*,*S*)-**9** as a 52:48 inseparable mixture of *cis*/*trans* rotational isomers (in $CDCl_3$ at 298 K): colorless oil; R_f = 0.14 (80:20 cyclohexane/ethyl acetate); $[\alpha]^{28}_D$ −63.3 (*c* 5.0, $CHCl_3$); IR (neat): 2922, 2853, 1751, 1681, 1175, 1211, 1148, 1116, 684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 298 K) (*trans* rotational isomer) δ 1.19 (t, J = 7.0 Hz, 3 H), 2.29−2.54 (m, 2 H), 3.80 (s, 3 H), 4.30−4.54 (m, 2 H), 4.97 (m, 1 H), 5.58 (m, 1 H); (*cis* rotational isomer) δ 1.19 (t, J = 7.0 Hz, 3 H), 2.29−2.54 (m, 2 H), 3.80 (s, 3 H), 4.30−4.54 (m, 2 H), 4.70 (m, 1 H), 5.97 (m, 1 H); ^{13}C NMR ($CDCl_3$, 298 K) (*trans* rotational isomer) δ 8.4, 27.4, 52.9, 56.8, 69.0, 84.3, 122.6 (q, J = 286.6 Hz), 169.0, 172.3; (*cis* rotational isomer) δ 8.4, 27.4, 52.9, 57.4, 70.4, 84.3, 122.6 (q, J = 286.6 Hz), 169.0, 173.0; ^{19}F NMR ($CDCl_3$, 298 K) (*trans* rotational isomer): δ −81.9 (s); (*cis* rotational isomer): δ −82.2 (s); ^1H NMR ($CDCl_3$, 323 K) (single rotational isomer) δ 1.19 (t, J = 7.3 Hz, 3 H), 2.41 (q, J = 7.3 Hz, 2 H), 3.79 (s, 3 H), 4.41 (t, J = 8.7 Hz, 1 H), 4.46 (t, J = 8.7 Hz, 1 H), 4.85 (m, 1 H), 5.75 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$, 323 K) (single rotational isomer) δ 8.4, 27.4, 52.7, 57.3, 69.8, 84.8 (q, J = 36.4 Hz), 122.8 (q, J = 286.6 Hz), 169.0, 172.7; ^{19}F NMR (376,2 MHz, $CDCl_3$, 323 K) (single rotational isomer) δ −81.7 (s); MS (EI) m/z = 256 [MH^+], 196 [$M^+ - CO_2Me$] (70), 186, 140, 130, 57 (100). Anal. Calcd for $C_9H_{12}F_3NO_4$ (255.07): C, 42.36; H, 4.74; N, 5.49. Found: C, 42.48; H, 4.55; N, 5.49.

***N*-Benzoyl-2-trifluoromethyloxazolidine-4-carboxylic Acid Methyl Ester 10. (2*R*,4*S*)-*N*-Benzoyl-2-trifluoromethyloxazolidine-4-carboxylic Acid Methyl Ester (*R*,*S*)-10.** The product was prepared by the acyl chloride procedure using 213 mg of (*R*,*S*)-**1** (1.07 mmol, 1.0 equiv) in dichloromethane (1.3 mL), 260 μL of pyridine (3.21 mmol, 3 equiv), and 373 μL of benzoyl chloride (3.21 mmol, 3 equiv). Purification by flash chromatography (80:20 cyclohexane/ethyl acetate) gave 321 mg (99%) of benzoylated oxazolidine (*R*,*S*)-**10** as a colorless oil.

A stirred solution of 98 mg of (*R*,*S*)-**1** (0.49 mmol, 1.0 equiv) in 60 μL of benzoyl chloride (0.51 mmol, 1.05 equiv) at room temperature was warmed to 100 °C for 1 h. The reaction mixture was then cooled to room temperature, and the resulting crude was directly purified by flash chromatography (80:20 cyclohexane/ethyl acetate) to give 143 mg (96%) of benzoylated oxazolidine (*R*,*S*)-**10** as a colorless oil.

A stirred solution of 300 mg of (*S*,*S*)-**1** (1.5 mmol, 1.0 equiv) in 184 μL of benzoyl chloride (1.58 mmol, 1.05 equiv) at room temperature was warmed to 100 °C for 1 h. The reaction mixture was then cooled to room temperature, and the resulting crude was directly purified by flash chromatography (90:10 cyclohexane/ethyl acetate) to give 412 mg (90%) of benzoylated oxazolidine (*R*,*S*)-**10** as a colorless oil.

(*R*,*S*)-10: colorless oil; R_f = 0.21 (80:20 cyclohexane/ethyl acetate); $[\alpha]^{28}_D$ −44.4 (*c* 6.8, $CHCl_3$); IR (neat) 2959, 1746, 1670, 1447, 1361, 1284, 1178, 1146 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3 H), 4.30 (t, J = 8.7 Hz, 1 H), 4.50 (dd, J = 8.7, 4.1 Hz, 1 H), 4.86 (m, 1 H), 5.94 (m, 1 H), 7.44 (t, J = 7.8 Hz, 2 H), 7.51 (t, J = 7.8 Hz, 1 H), 7.61 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 52.9, 58.9, 69.9, 85.1 (q, J = 35.5 Hz), 122.4 (q, J = 285.6 Hz), 127.2, 128.7, 131.3, 134.1, 169.2, 171.3; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −81.2 (s); MS (EI) m/z = 303 [M^+], 234, 105 (100), 77. Anal. Calcd for $C_{13}H_{12}F_3NO_4$ (303.07): C, 51.49; H, 3.99; N, 4.62. Found: C, 51.42; H, 3.99; N, 4.62.

(2*S*,4*S*)-*N*-Benzoyl-2-trifluoromethyloxazolidine-4-carboxylic Acid Methyl Ester (*S*,*S*)-10. To a stirred solution of 106 mg of (*S*,*S*)-**1** (0.53 mmol, 1.0 equiv) in THF (3.5 mL) were successively added 148 μL of Et_3N (1.06 mmol, 2.0 equiv) and 123 μL of benzoyl chloride (1.06 mmol, 2.0 equiv) at room temperature. The reaction mixture was warmed to reflux for 18 h, cooled to room temperature, and evaporated. The resulting crude was purified by flash chromatography (90:10 petroleum ether/ethyl acetate) to give 45 mg (28%) of (*S*,*S*)-**10** and 52 mg (32%) of (*R*,*S*)-**10**.

(*S,S*)-**10:** white solid; mp 93−94 °C; R_f = 0.42 (75:25 cyclohexane/ethyl acetate); $[\alpha]^{25}_D$ −173.3 (*c* 0.95, $CHCl_3$); IR (neat) 3009, 2961, 2924, 2857, 1742, 1677, 1181, 1147, 1104, 1059, 844, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.55 (s, 3 H), 4.34 (d *J* = 9.2 Hz, 1 H), 4.63 (dd, *J* = 9.2, 7.3 Hz, 1 H), 4.75 (d, *J* = 7.3 Hz, 1 H), 6.14 (m, 1 H), 7.42 (t, *J* = 6.9 Hz, 2 H), 7.49 (t, *J* = 6.9 Hz, 1 H), 7.58 (d, *J* = 6.9 Hz, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 53.0, 60.2, 72.2, 84.8 (q, *J* = 36.4 Hz), 123.0 (q, *J* = 288.5 Hz), 127.6, 128.6, 131.5, 134.7, 169.8, 170.8; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −82.5 (s); MS (EI) *m*/*z* = 303 [M^+], 244, 234, 105 (100), 77; HRMS (EI) calcd for $C_{13}H_{12}F_3NO_4$ 303.0718, found 303.0729.

Acylation of Oxazolidines 3_{maj}. (4*S*)-*N*-Acetyl-2-trifluoromethyl-2-methyloxazolidine-4-carboxylic Acid Methyl Ester (11). The product was prepared by the acid anhydride procedure using 244 mg of the diastereomer $\mathbf{3_{maj}}$ (1.14 mmol, 1.0 equiv), 29 mg of iodine (0.11 mmol, 0.1 equiv), and 1.1 mL of acetic anhydride (11.44 mmol, 10 equiv). The reaction was completed in 40 h at room temperature. Purification by flash chromatography (70:30 cyclohexane/ethyl acetate) gave 161 mg (55%) of the *N*-acetylated oxazolidine **11** as a 31:69 inseparable mixture of *cis*/*trans* rotational isomers (in $CDCl_3$ at 298 K): colorless oil; R_f = 0.33 (75:25 cyclohexane/ethyl acetate); $[\alpha]^{26}_D$ −31.2 (*c* 0.95, $CHCl_3$); IR (neat) 2959, 2922, 1749, 1685, 1380, 1341, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (*trans* rotational isomer) δ 1.90 (s, 3 H), 2.07 (s, 3 H), 3.85 (s, 3 H), 4.26 (dquint, *J* = 9.2, 1.4 Hz, 1 H), 4.41 (ddq, *J* = 9.2, 6.9, 1.4 Hz, 1 H), 4.58 (dd, *J* = 6.9, 1.4 Hz, 1 H); (*cis* rotational isomer) δ 1.93 (s, 3 H), 2.27 (s, 3 H), 3.78 (s, 3 H), 4.10 (dquint, *J* = 9.4, 1.4 Hz, 1 H), 4.34 (ddq, *J* = 9.4, 7.3, 1.4 Hz, 1 H), 4.77 (dd, *J* = 7.3, 1.4 Hz, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) (*trans* rotational isomer) δ 18.4, 24.1, 53.2, 60.4, 69.1, 93.9 (q, *J* = 31.6 Hz), 123.9 (q, *J* = 291.4 Hz), 168.3, 170.6; (*cis* rotational isomer) δ 20.3, 22.3, 52.7, 60.6, 67.5, 91.6 (q, *J* = 31.6 Hz), 124.1 (q, *J* = 290.4 Hz), 168.8, 170.6; ^{19}F NMR (376.2 MHz, CDCl) (*trans* rotational isomer) δ −80.9 (d, *J* = 1.4 Hz); (*cis* rotational isomer) δ −82.0 (d, *J* = 1.4 Hz); MS (EI) *m*/*z* = 255 [M^+], 154 (100), 126, 69; HRMS (EI) calcd for $C_9H_{12}F_3NO_4$ 255.0718, found 255.0720.

Synthesis of *N*-Acetyl-2-trifluoromethyloxazolidine-4-*N*-methylamides (12). (2*S*,4*S*)-*N*-Acetyl-2-trifluoromethyloxazolidine-4-*N*-methylamide (*S,S*)-12. To a solution of 638 mg of (*S*,*S*)-**8** (2.65 mmol) in THF (15 mL) at 0 °C was added a 1 M aqueous solution of 2.91 mL of LiOH (2.91 mmol, 1.1 equiv). The reaction mixture was stirred vigorously for 4 h. Subsequently, Et_2O (10 mL) was added, and the reaction mixture was extracted with water (2 × 10 mL). Aqueous layers were combined, and water was removed under reduced pressure to afford 616 mg of the corresponding lithium carboxylate as a 78:22 inseparable mixture of rotational isomers (in D_2O at 298 K) directly used in next step without further purification: ^1H NMR (400 MHz, D_2O) (minor rotational isomer) δ 2.03 (s, 3 H), 4.22 (dd, *J* = 8.2, 2.3 Hz, 1 H), 4.34−4.44 (m, 2 H), 5.82 (q, *J* = 4.1 Hz, 1 H); (major rotational isomer) δ 1.88 (s, 3 H), 4.15 (dd, *J* = 7.8, 1.4 Hz, 1 H), 4.34−4.44 (m, 2 H), 5.72 (q, *J* = 5.2 Hz, 1 H); ^{13}C NMR (100.5 MHz, D_2O) (minor rotational isomer) δ 21.9, 60.2, 72.1, 84.5 (q, *J* = 35.5 Hz), 123.0 (q, *J* = 274 Hz), 172.1, 176.5; (major rotational isomer) δ 22.3, 61.1, 73.4, 84.2 (q, *J* = 37.4 Hz), 122.9 (q, *J* = 277 Hz), 174.3, 176.7; ^{19}F NMR (376.2 MHz, D_2O) (minor rotational isomer) δ −81.6 (d, *J* = 4.1 Hz); (major rotational isomer) δ −81.2 (d, *J* = 5.2 Hz).

To a solution of lithium carboxylate (373 mg, 1.60 mmol) in DMF (8 mL) were successively added at room temperature methylamine hydrochloride (162 mg, 1,5 equiv, 2.40 mmol), HOBt (216 mg, 1 equiv, 1.60 mmol), $NaHCO_3$ (403 mg, 3 equiv, 4.80 mmol), and EDCI (338 mg, 1.1 equiv, 1.76 mmol). The reaction mixture was stirred overnight at room temperature and then diluted with AcOEt and water. The layers were separated, and the aqueous phase was extracted with AcOEt (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (96:4 dichloromethane/methanol) gave 80 mg (21%) of oxazolidine (*S*,*S*)-**12** as a 40:60 inseparable mixture of *cis*/*trans* rotational isomers (in $CDCl_3$ at 298 K): white solid; mp 198−203 °C; R_f = 0.38 (96:4 ethyl acetate/methanol); $[\alpha]^{25}_D$ −10.3 (*c* 0.85, MeOH); IR (neat) 3245, 3099, 2925, 1669, 1648, 1582, 861 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 298 K) (*trans* rotational isomer) δ 2.21 (s, 3 H), 2.86 (d, *J* = 4.8 Hz, 3 H); 4.30−4.45 (m, 3 H), 5.62 (q, *J* = 4.8 Hz, 1 H), 5.84 (m, 1 H); (*cis* rotational isomer) δ 2.10 (s, 3 H), 2.90 (d, *J* = 4.8 Hz, 3 H), 4.30−4.45 (m, 2 H), 4.59 (t, *J* = 7.8 Hz, 1 H), 5.84 (m, 1 H), 5.98 (q, *J* = 5.2 Hz, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$, 233 K) (*trans* rotational isomer) δ 22.9, 26.7, 59.0, 71.0, 84.7 (q, *J* = 34.5 Hz), 122.7 (q, *J* = 288.5 Hz), 169.3, 169.6; (*cis* rotational isomer) δ 23.2, 26.8, 60.0, 73.0, 84.1 (q, *J* = 34.5 Hz), 122.5 (q, *J* = 288.5 Hz), 168.9, 169.7; ^{19}F NMR (376.2 MHz, $CDCl_3$, 298 K) (*trans* rotational isomer) δ −81.3 (d, *J* = 4.8 Hz); (*cis* rotational isomer) δ −80.5 (d, *J* = 5.2 Hz); MS (EI) *m*/*z* = 240 [M^+], 183 (100), 140, 58; HRMS (EI) calcd for $C_8H_{11}F_3N_2O_3$ 240.0722, found 240.0718.

(2*R*,4*S*)-*N*-acetyl-2-trifluoromethyloxazolidine-4-*N*-methylamide (*R,S*)-12. To a solution of 953 mg of (*R*,*S*)-**8** (3.95 mmol) in THF (20 mL) at 0 °C was added a 1 M aqueous solution of 4.35 mL of LiOH (4.35 mmol, 1.1 equiv). The reaction mixture was stirred vigorously for 2 h. Subsequently, Et_2O (15 mL) was added, and the reaction mixture was extracted with water (2 × 15 mL). Aqueous layers were combined, and water was removed under reduced pressure to afford 819 mg of the corresponding lithium carboxylate as a 75:25 inseparable mixture of rotational isomers (in D_2O at 298 K) directly used in the next step without further purification: ^1H NMR (400 MHz, D_2O) (major rotational isomer) δ 1.95 (s, 3 H), 4.12 (ddq, *J* = 8.2, 6.9, 1.4 Hz, 1 H), 4.39 (ddq, *J* = 8.7, 8.2, 1.4 Hz, 1 H), 4.52 (dd, *J* = 8.7, 6.9 Hz, 1 H), 5.69 (q, *J* = 5.5 Hz, 1 H); (minor rotational isomer) δ 2.00 (s, 3 H), 4.03 (ddq, *J* = 8.2, 4.1, 1.4 Hz, 1 H), 4.33 (ddq, *J* = 8.7, 8.2, 1.4 Hz, 1 H), 5.04 (dd, *J* = 8.7, 4.1 Hz, 1 H), 5.73 (q, *J* = 5.2 Hz, 1 H); ^{19}F NMR (376.2 MHz, D_2O) (Major rotational isomer) δ −81.5 (dt, *J* = 5.5, 1.4 Hz); (minor rotational isomer) δ −81.4 (dt, *J* = 5.2, 1.4 Hz).

To a solution of lithium carboxylate (819 mg, 3.51 mmol) in DMF (7 mL) were successively added at room temperature methylamine hydrochloride (356 mg, 1,5 equiv, 5.27 mmol), HOBt (474 mg, 1 equiv, 3.51 mmol), $NaHCO_3$ (885 mg, 3 equiv, 10.54 mmol), and EDCI (741 mg, 1.1 equiv, 3.86 mmol). The reaction mixture was stirred overnight at room temperature and then diluted with AcOEt and water. The layers were separated, and the aqueous phase was extracted with AcOEt (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (96:4 dichloromethane/methanol) gave 739 mg (88%) of oxazolidine (*R*,*S*)-**12** as a 33:66 inseparable mixture of *cis*/*trans* rotational isomers (in $CDCl_3$ at 298 K): colorless oil; R_f = 0.50 (96:4 ethyl acetate/methanol); $[\alpha]^{25}_D$ −60.3 (*c* 0.9, $CHCl_3$); IR (neat) 3291, 3080, 2917, 1666, 1542, 1052, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 298 K) (*trans* rotational isomer) δ 2.25 (bs, 3 H), 2.82 (bs, 3 H), 4.20−4.95 (m, 3 H), 5.68 (bs, 1 H), 6.92 (bs, 1 H); (*cis* rotational isomer) δ 2.25 (bs, 3 H), 2.82 (bs, 3 H); 4.20−4.95 (m, 3 H), 5.84 (bs, 1 H), 7.21 (bs, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$, 298 K) (*trans* rotational isomer) δ 22.0, 25.9, 57.5, 68.7, 85.0 (bs), 122.4 (q, *J* = 286.6 Hz), 168.4, 171.1; (*cis* rotational isomer) δ 22.0, 25.9, 60.0, 71.4, 85.0 (bs), 122.4 (q, *J* = 286.6 Hz), 168.4, 171.1; ^{19}F NMR (376.2 MHz, $CDCl_3$, 298 K) (*trans* rotational isomer) δ −82.0 (s); (*cis* rotational isomer) δ −81.1 (s); ^1H NMR (400 MHz, $CDCl_3$, 323 K) (single rotational isomer) δ 2.23 (bs, 3 H), 2.82 (bs, 3 H), 4.42 (bs, 1 H), 4.56 (bs, 1 H), 4.77 (bs, 1 H), 5.72 (bs, 1 H), 6.86 (bs, 1 H); ^1H NMR (400 MHz, DMSO-d_6, 298 K) (*trans*

rotational isomer) δ 2.05 (bs, 3 H), 2.64 (bs, 3 H), 4.17 (bs, 1 H), 4.42 (bs, 1 H), 4.77 (bs, 1 H), 5.83 (bs, 1 H), 8.0 (bs, 1 H); (*cis* rotational isomer) δ 2.15 (bs, 3 H), 2.61 (bs, 3 H); 4.17 (bs, 1 H), 4.42 (bs, 1 H), 4.70 (bs, 1 H), 6.10 (bs, 1 H), 7.73 (bs, 1 H); ^{13}C NMR (100.5 MHz, DMSO-d_6, 298 K) (*trans* rotational isomer) δ 22.4, 25.8, 59.5, 71.2, 84.2 (q, J = 32.6 Hz), 123.0 (q, J = 285.6 Hz), 168.4, 171.2; (*cis* rotational isomer) δ 22.4, 25.8, 58.1, 69.6, 85.0 (q, J = 34.5 Hz), 123.1 (q, J = 286.6 Hz), 168.4, 170.5; ^{1}H NMR (400 MHz, DMSO-d_6, 363 K) (single rotational isomer) δ 2.38 (bs, 3 H), 2.92 (bs, 3 H), 4.48 (t, J = 7.3 Hz, 1 H), 4.69 (t, J = 7.3 Hz, 1 H), 5.01 (t, J = 7.3 Hz, 1 H), 6.19 (q, J = 5.0 Hz, 1 H), 7.93 (bs, 1 H); MS (EI) m/z = 240 [M$^+$], 183 (100), 140; HRMS (EI) calcd for $C_8H_{11}F_3N_2O_3$ 240.0722, found 240.0719.

Synthesis of *o*-Nbs-Ala-Ser($\Psi^{CF3,H}$pro)-OMe (13). To a suspension of *o*-Nbs-L-alanine (1.3 g, 4.74 mmol, 7.0 equiv) in DCM (4.8 mL) under argon at 0 °C was added 1-bromo-*N*,*N*-2-trimethyl-1-propenylamine (628 μL, 4.74 mmol, 7.0 equiv). The resulting solution was stirred at 0 °C until the disappearance of the precipitate (usually 20 min). The total conversion of the acids to chlorides was checked by TLC after quenching. When the conversion was complete, the solution of amino acid chloride was added via cannula to a neat mixture of (*R*,*S*)-**1** pseudoproline (135 mg, 0.68 mmol, 1.0 equiv) and collidine (0.68 mmol, 1.0 equiv) at 0 °C. The temperature was allowed to warm to room temperature, and the solution was concentrated twice using a stream of argon. After 24 h, the resulting mixture was diluted with DCM and quenched with a saturated aqueous solution of $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with DCM (3 ×). The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude 73:27 mixture of diastereomers was purified by flash chromatography (70:30 cyclohexane/ethyl acetate) to give 70 mg (22%) of the minor (*S*,*S*)-**13** diastereomer and 210 mg (68%) of the major (*R*,*S*)-**13** diastereomer as a 47:53 inseparable mixture of *cis*/*trans* rotational isomers in $CDCl_3$.

(***R*,*S*)-13 major diastereomer:** white solid; mp 182−183 °C; R_f = 0.30 (60:40 cyclohexane/ethyl acetate); $[\alpha]^{24.0}_D$ −122.5 (*c* 1.8, $CHCl_3$); IR (neat) 3300, 3107, 1730, 1677, 1535, 1440, 1154 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) (*trans* rotational isomer) δ 1.27 (d, J = 5.5 Hz, 3 H), 3.67 (bs, 3 H), 4.13−4.68 (m, 3 H), 4.86−5.00 (m, 1 H), 6.08−6.21 (m, 1 H), 7.75−7.95 (m, 2 H), 7.98−8.10 (m, 2 H), 8.62−8.78 (m, 1 H); (*cis* rotational isomer): δ 1.27 (d, J = 5.5 Hz, 3 H), 3.67 (bs, 3 H), 4.13−4.68 (m, 3 H), 5.15−5.27 (m, 1 H), 5.80−5.92 (m, 1 H), 7.75−7.95 (m, 2 H), 7.98−8.10 (m, 2 H), 8.98−9.12 (m, 1 H); ^{13}C NMR (100.5 MHz, DMSO-d_6, 298 K) (*trans* rotational isomer) δ 18.3, 50.9, 52.6, 56.9, 69.8, 83.7 (q, J = 36.4 Hz), 122.3 (q, J = 279.9 Hz), 124.3, 129.5, 132.6, 133.1, 134.2, 147.3, 168.8, 170.8; (*cis* rotational isomer) δ 19.3, 51.9, 52.6, 57.8, 70.7, 84.7 (q, J = 36.4 Hz), 122.3 (q, J = 279.9 Hz), 124.3, 129.5, 132.6, 133.5, 133.8, 147.3, 168.7, 170.8; ^{19}F NMR (376.2 MHz, DMSO-d_6, 298 K) (*trans* rotational isomer) δ −80.9 (s); (*cis* rotational isomer) δ −81.7 (s); ^{1}H NMR (400 MHz, DMSO-d_6, 363 K) (single rotational isomer) δ 1.31 (d, J = 6.9 Hz, 3 H), 3.71 (s, 3 H), 4.32−4.51 (m, 3 H), 5.01−5.10 (m, 1 H), 5.89−5.99 (m, 1 H), 7.84−7.92 (m, 2 H), 7.94−8.00 (m, 1 H), 8.06−8.11 (m, 1 H), 8.38−8.52 (m, 1 H); ^{13}C NMR (100.5 MHz, DMSO-d_6, 363 K) (single rotational isomer) δ 17.6, 50.2, 52.0, 56.5, 68.9, 83.6 (q, J = 35.5 Hz), 122.1 (q, J = 287.5 Hz), 123.9, 129.2, 132.1, 133.2, 133.6, 147.0, 168.1, 170.3; ^{19}F NMR (376.2 MHz, DMSO-d_6, 363 K) (single rotational isomer) δ −80.7 (s). Anal. Calcd for $C_{15}H_{16}F_3N_3O_8S$ (455.06): C, 39.56; H, 3.54; N, 9.23. Found: C, 39.45; H, 3.47; N, 8.99.

(*S*,*S*)-13 minor diastereomer: colorless oil; R_f = 0.41 (50:50 cyclohexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$, 323 K) (single rotational isomer) δ 1.43 (d, J = 6.9 Hz, 3 H), 3.82 (s, 3 H), 4.43 (dq, J = 8.7, 6.9 Hz, 1 H), 4.57 (d, J = 6.4 Hz, 2 H), 5.16 (t, J = Hz, 6.4 Hz, 1 H), 5.56 (q, J = 5.0 Hz, 1 H), 6.15 (d, J = 8.7 Hz, 1 H), 7.70−7.75 (m, 2 H), 7.88−7.92 (m, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$, 323 K) (single rotational isomer) δ 18.7, 51.3, 53.4, 57.2, 70.4, 84.0 (q, J = 36.4 Hz), 122.4 (q, J = 286.6 Hz), 125.8, 129.6, 133.0, 134.1, 134.3, 147.4, 168.7, 171.2; ^{19}F NMR (376.2 MHz, $CDCl_3$, 323 K) (single rotational isomer) δ −82.3 (d, J = 5.0 Hz).

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Supporting Information Available: General experimental information and proton, fluorine, and carbon NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.