Reaction of (Trifluoromethyl)trimethylsilane with Oxazolidin-5-ones: Synthesis of Peptidic and Nonpeptidic Trifluoromethyl Ketones

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Received March 10, 1998

(Trifluoromethyl)trimethylsilane (TMS-CF_3, the Ruppert Reagent) reacts with a variety of amino acid derived *N*-substituted oxazolidin-5-ones in excellent yields. Mild acid hydrolysis of adducts with electron-releasing substituents at C-2 affords *N*-substituted α-amino trifluoromethyl ketones (TFMKs). *N*-CBZ-protected α-amino TFMKs are converted into hitherto unreported hydrochloride salts of α-amino TFMKs by hydrogenolysis. Coupling with amino acid fluorides gives access to peptidic TFMKs which are of utility as protease inhibitors.

Introduction

The incorporation of fluorine into organic molecules as a means of modifying their chemical properties has been exploited in the fields of pharmaceutical, agrochemical, and polymer chemistry.[1] In particular, the biological activity of some fluorinated compounds has led to interest in synthetic procedures for the efficient and selective introduction of fluorine or fluorinated groups.[2]

Fluorination of ketones in the α-position increases the electrophilicity of the carbonyl group.[3] In aqueous solutions α-fluorinated ketones readily form hydrates which have been proposed as mimics for the tetrahedral transition state in peptide bond hydrolysis.[4] Consequently, fluoroketones have been successfully employed as inhibitors of hydrolytic enzymes, including proteases. Although mono[5]- and difluoromethyl[6] ketones are known, trifluoromethyl ketones (TFMKs)[7,8] have been most widely employed as enzyme inhibitors. A likely reason is presumably that the trifluoromethyl moiety can be introduced as an intact group, thus avoiding potentially problematic direct fluorination procedures. Peptidic and nonpeptidic α-amino TFMKs inhibitors are of particular interest due to their structural analogy with the natural protease substrates. TFMKs have been used as inhibitors of a variety of proteolytic enzymes, such as pepsin, angiotensin converting enzyme, carboxypeptidase A,[4] chymotrypsin,[9] human neutrophile elastase,[10] and renin.[11] Nonpeptidic TFMKs have also been shown to exhibit inhibitory activity against metallo-β-lactamases.[12]

Several approaches to α-amino TFMKs have been reported most of which proceed via trifluoromethyl alcohol intermediates. The latter have been obtained by a Henry reaction of nitroalkanes and aldehydes,[9] Curtius rearrangement of an appropriate carboxylic acid azide precursor,[13] or by addition of organometallic trifluoromethyl reagents to α-amino aldehydes.[14] The use of the latter reagents, however, is complicated by the instability of the trifluoromethyl anion toward loss of fluoride and generation of difluorocarbene.[15] A general disadvantage of the synthetic approach *via* α-amino trifluoromethyl alcohols is the need for a final oxidation step to convert the trifluoromethyl alcohol to the desired ketone. Presently, this can only be achieved under mild conditions using the relatively expensive Dess−Martin periodinane reagent.[16] The development of synthetic procedures avoiding trifluoromethyl alcohols as intermediates is therefore of interest. Such an approach was first used by Kolb et al. who employed a modified Dakin−West reaction in a direct synthesis of α-amino TFMKs from amino acid derived oxazolones.[17] *N,N*-Dialkylated α-amino TFMKs have been obtained by opening of trifluoromethyl epoxy ethers with secondary amines.[18] Recently, Katzenellenbogen and Derstine described an approach employing trifluoromethyl imidazolines as latent forms of TFMKs. Despite the good overall yields, the scope of

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S0022-3263(98)00443-5 CCC: $15.00
Published on Web 07/07/1998

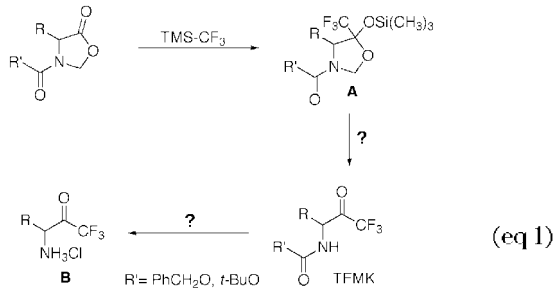
their procedure is limited by the fact that only glycine and phenylglycine derived α-amino TFMKs are accessible.[19]

We have reported a synthesis of *N*-protected α-amino TFMKs based on the addition of (trifluoromethyl)trimethylsilane (TMS-CF_3, the Ruppert Reagent)[20] to *N*-protected oxazolidin-5-ones which are readily available from optically active amino acids.[21] Mild hydrolysis of the initially formed adducts afforded α-amino TFMKs directly, thus avoiding the final oxidation step. Here, we report the experimental details of our approach and its extension to the synthesis of peptidic TFMKs via hydrochloride salts of α-amino TFMKs which have not been previously described.

Results and Discussion

TMS-CF_3 is an efficient trifluoromethylating reagent of carbonyl compounds in the presence of catalytic amounts of nucleophilic initiators, such as fluoride ion or alkoxides.[22] It is commercially available and stable for several weeks. Prompted by a report that TMS-CF_3 adds efficiently to five- and six-membered lactones,[23] we investigated the reaction of oxazolidin-5-ones with this reagent. Initially, we envisaged trifluoromethylated ketals **A** as precursors of α-amino TFMKs (eq 1). Variation of the *N*-protecting group (different amide or urethane substituents) should give access to a variety of nonpeptidic TFMKs. Furthermore, deprotection of suitably *N*-protected TFMKs should yield hydrochloride salts **B**, potentially useful for the synthesis of peptidic TFMKs.

1. Reaction of TMS-CF_3 with C-2 Unsubstituted Oxazolidin-5-ones. *N*-CBZ-Protected oxazolidin-5-ones **1**−**3** (see Table 1) were prepared by Ben-Ishai's procedure.[24] It was hoped that the hydrolytically "stable" CBZ-group would allow a stepwise deprotection procedure in which the *N*-CBZ protected TFMKs could be obtained by acid hydrolysis. Subsequently, hydrogenolysis should give access to hydrochloride salts **B** (eq 1).



(eq 1)

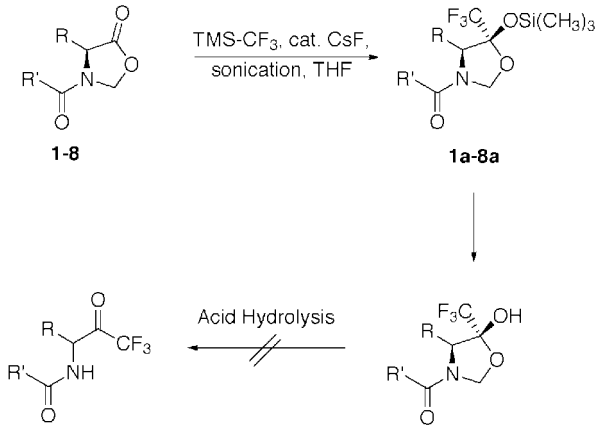
When oxazolidin-5-one **1** was treated with TMS-CF_3 and catalytic amounts of TBAF trihydrate (~1 mol %) adduct **1a** was obtained in moderate yield. Replacement of TBAF trihydrate with cesium fluoride and sonication resulted in a substantial improvement, and adducts **1a**−**3a** were isolated in good to excellent yields (Scheme 1 and Table 1). The reaction tolerated a variety of substituents in the C-4 position of the oxazolidin-5-ones, including functionalized ones (see entry III in Table 1). The products were isolated as single diastereomers as analyzed by ^1H, ^{19}F, and ^{13}C NMR spectroscopy. Single-crystal X-ray analysis of **1a** showed that trifluoromethylation had taken place anti to the benzyl group in the C-4 position.[21] Disappointingly, attempts to cleave the five-membered ring hydrolytically failed and led either to recovery of starting material or intractable mixtures of products. Since it was expected that harsh acidolytic conditions would lead to fragmentation of the CBZ protecting group, the nitrogen protecting group was changed from CBZ to BOC in an attempt to effect a one-step removal of the protecting group and cleavage of the hemiketal. *N*-BOC-protected oxazolidin-5-ones **4**−**8** were prepared by a minor modification of the literature procedure.[24] Reaction with TMS-CF_3 afforded adducts **4a**−**8a** in yields comparable to those obtained for the *N*-CBZ-protected oxazolidin-5-ones using catalytic amounts of cesium fluoride with sonication (Table 1). However, although treatment of a solution of adduct **4a** with concentrated hydrochloric acid for several days led to disappearance of the starting material by ^1H and ^{19}F NMR analyses, we were unable to characterize the products.

Table 1. Reaction of TMS-CF_3 with C-2 Unsubstituted Oxazolidin-5-ones

entry	oxazol	R	R′	yield[a]
I	**1**	$PhCH_2$	$PhCH_2O$	**1a**: 95%
II	**2**	Me	$PhCH_2O$	**2a**: 69%
III	**3**	$MeO_2C(CH_2)_2$	$PhCH_2O$	**3a**: 73%
IV	**4**	$PhCH_2$	*t*-BuO	**4a**: 98%
V	**5**	Me	*t*-BuO	**5a**: 85%
VI	**6**	$(Me)_2CH$	*t*-BuO	**6a**: 84%
VII	**7**	$(Me)_2CHCH_2$	*t*-BuO	**7a**: 95%
VIII	**8**	$PhCH_2SCH_2$	*t*-BuO	**8a**: 77%

[a] Products were obtained as single diastereomers by ^1H, ^{19}F, and ^{13}C NMR analyses.

Scheme 1. Addition of TMS-CF_3 to C-2 Unsubstituted Oxazolidin-5-ones 1−8



2. Reaction of TMS-CF_3 with C-2 Substituted Oxazolidin-5-ones. Factors contributing to the failure of the hydrolysis step probably included the difficulty in removing formaldehyde from the reaction mixture, and the exceptional acid stability of the adducts **1a** to **8a** due to the electron-withdrawing effect of the trifluoromethyl

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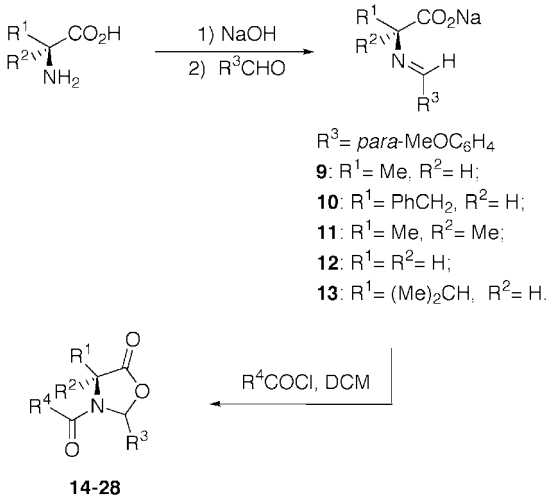
Scheme 2. Synthesis of Oxazolidin-5-ones via Cyclization of Schiff Base Salts



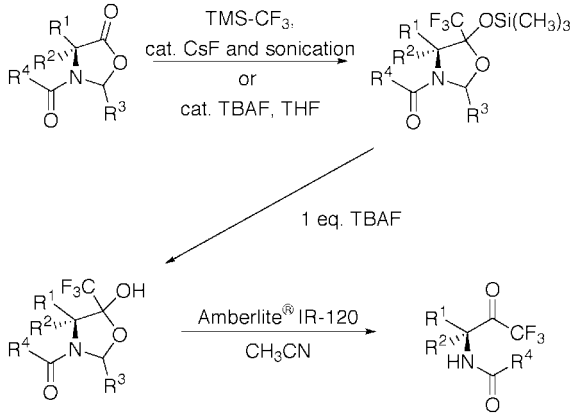
group. It has previously been shown that dimethyl ketals of trifluoromethyl ketones are extremely resistant to acid hydrolysis.[25] Thus, oxazolidin-5-ones bearing electron-releasing substituents, such as *p*-methoxyphenyl, phenyl, or *tert*-butyl in the C-2 position were prepared in the hope of effecting hydrolysis under milder conditions. It was also envisaged that the hydrolysis products (anisaldehyde, benzaldehyde, or pivalaldehyde) would be more easily removed from the reaction mixture than formaldehyde.

N-CBZ-protected and *p*-methoxyphenyl-substituted oxazolidin-5-ones **14**−**16** were obtained by a modification of Hiskey's procedure (Scheme 2).[26] Slow addition (over several hours) of benzyl chloroformate to a suspension of carefully ground amino acid derived Schiff base salts in DCM at −10 to −15 °C (Scheme 2) gave oxazolidin-5-ones **14**−**16** in moderate to good yields. In the cases of *N*-amide-substituted oxazolidin-5-ones **17**−**25**, refluxing a suspension of finely ground Schiff base salt in the presence of the required acid chloride was found to be advantageous over the low-temperature procedure. Phenylalanine-derived Schiff base salt **10** led to the formation of two diastereomers in ratios between 6:1 and 10:1, whereas alanine-derived Schiff base salt **9** underwent ring closure to give mixtures of two diastereomers in ratios between 1:1 and 3:1. Purification was achieved by crystallization from suitable solvents or by flash column chromatography on silica. All oxazolidin-5-ones showed broadened signals in their ^{1}H and ^{13}C NMR spectra, presumably due to hindered conformational interconversion. However, interpretable ^{1}H NMR spectra were obtained at higher temperatures (90 °C) using deuterated toluene as solvent.

Upon addition of TMS-CF_3 to C-2 substituted oxazolidin-5-one **15** using CsF with sonication TLC analysis indicated substantial decomposition of starting material. The use of catalytic amounts of a solution of TBAF in THF (Scheme 3) was found to be superior with *N*-CBZ substituted oxazolidin-5-ones **14**−**16** reacting smoothly with TMS-CF_3 (entries I to III in Table 2).[27]

The reaction of *N*-acylated C-2 substituted oxazolidin-5-ones **17**−**25** and **27** was clearly influenced by steric

Scheme 3. Addition of TMS-CF_3 to C-2 Substituted Oxazolidin-5-ones 14−28



constraints. Thus, *N*-benzoyl-substituted oxazolidin-5-one **17** (entry IV in Table 2) and *N*-phenoxyacetyl-substituted **21** with a benzyl group in the C-4 position (entry VIII in Table 2) did not react with TMS-CF_3. In contrast, oxazolidin-5-ones **18** (entry V in Table 2) and **22** with the sterically less demanding methyl substituent at C-4 (entry IX in Table 2) gave adducts **18a** and **22a** in good yields, suggesting the more bulky benzyl group at C-4 prevents addition of TMS-CF_3 to oxazolidin-5-ones **17** and **21** (vide infra). C-4 Dimethylated oxazolidin-5-ones **20** (entry VII in Table 2) and **23** (entry X in Table 2) afforded adducts **20a** and **23a** in good yield. The C-4 substituent influenced the diastereoselectivity of the trifluoromethyl group addition to the oxazolidin-5-ones: while a benzyl group in the C-4 position led to the formation of products with high diastereomeric excess (entry II in Table 2), considerably lower selectivities were observed for oxazolidin-5-ones bearing the smaller methyl group in that position (entries V and IX in Table 2). *N*-Acylated adducts **17a**−**25a** and **27a** were generally less stable toward aqueous workup and chromatography on silica than the corresponding *N*-CBZ substituted adducts **14a**−**16a**, **26a**, and **28a**. *N*-Acetyl-substituted adducts **24a** and **25a** appeared particularly labile and could not be isolated by column chromatography on silica gel, but ^{1}H and ^{19}F NMR analysis of the crude reaction mixture suggested their formation.

The trifluoromethyl ketals were desilylated using 1 equiv of TBAF solution (Table 3). *N*-CBZ-protected trifluoromethyl hemiketals **14b**−**16b** (top three entries in Table 3) were unstable toward loss of anisaldehyde and hydrolyzed without isolation by stirring in acetonitrile with strongly acidic ion-exchange resin (Amberlite IR-120 Plus) for 48 to 72 h at 40−45 °C to give TFMKs **14c**−**16c** as mixtures of the ketone and hydrate forms.[28] *N*-Acylated hemiketals **18b**−**23b** were found to cleave more readily than the *N*-urethane-substituted ones, and hydrolysis was usually complete within 6 to 12 h. However, isolation of the TFMKs and separation from anisaldehyde, the byproduct of the hydrolysis reaction, was difficult, and significant losses of material were observed when purification by column chromatography

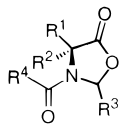
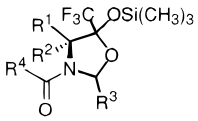
(25) Simmons, H. E.; Wiley: D. W. *J. Am. Chem. Soc.* **1960**, *82*, 2288−2296.

(26) Hiskey, R. G.; Jung, J. M. *J. Am. Chem. Soc.* **1963**, *85*, 578−582.

(27) Different batches of commercially available TBAF solution in THF were found to be of varying efficiency as initiator of the trifluoromethylation. Best results were obtained using an "old bottle" of the reagent.

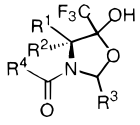
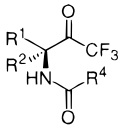
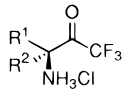
(28) Exemplary experimental data for **15b** is included in the Experimental Section.

Table 2. Reaction of TMS-CF_3 with C-2 Substituted Oxazolidin-5-ones (Ar = *p*-$MeOC_6H_4$)

Entry		R^1	R^2	R^3	R^4	
I	**14**	Me	H	Ar	$PhCH_2O$	**14a**: 92%
II	**15**	$PhCH_2$	H	Ar	$PhCH_2O$	**15a**: 91%
III	**16**	$(Me)_2CH$	H	Ar	$PhCH_2O$	**16a**: 86%
IV	**17**	$PhCH_2$	H	Ar	Ph	no reaction
V	**18**	Me	H	Ar	Ph	**18a**: 94%
VI	**19**	H	H	Ar	Ph	**19a**: unstable
VII	**20**	Me	Me	Ar	Ph	**20a**: 72%
VIII	**21**[a]	$PhCH_2$	H	Ar	$PhOCH_2$	no reaction
IX	**22**[a]	Me	H	Ar	$PhOCH_2$	**22a**: 85%[a]
X	**23**	Me	Me	Ar	$PhOCH_2$	**23a**: 75%
XI	**24**	$PhCH_2$	H	Ar	Me	**24a**: unstable
XII	**25**	Me	H	Ar	Me	**25a**: unstable
XIII	**26**	$PhCH_2$	H	*t*-Bu	$PhCH_2O$	**26a**: 80%
XIV	**27**[33]	$PhCH_2$	H	*t*-Bu	Ph	**27a**: 71%
XV	**28**[39]	$PhCH_2$	H	Ph	$PhCH_2O$	**28a**: 53%

[a] The experimental details for **21**, **22**, and **22a** have been published elsewhere (see ref 12b).

Table 3. Hydrolysis of Trifluoromethyl Hemiketals (Ar = *p*-$MeOC_6H_4$)

	R^1	R^2	R^3	R^4		
14b	Me	H	Ar	$PhCH_2O$	**14c**	**14d**
15b	$PhCH_2$	H	Ar	$PhCH_2O$	**15c**	**15d**
16b	$(Me)_2CH$	H	Ar	$PhCH_2O$	**16c**	**16d**
18b	Me	H	Ar	Ph	**18c**	
19b	H	H	Ar	Ph	**19c**	
20b	Me	Me	Ar	Ph	**20c**	
22b	Me	H	Ar	$PhOCH_2$	**22c**[a]	
23b	Me	Me	Ar	$PhOCH_2$	**23c**	
27b	$PhCH_2$	H	*t*-Bu	Ph	**27c**	

[a] The experimental details **22c** have been published elsewhere (see ref 12b).

on silica was attempted. Isolated yields ranged from 35 to 68%, and whenever possible TFMKs were best purified by crystallization. Since ^{19}F and ^1H NMR analyses indicated completion of the hydrolysis reaction, the relatively low yields obtained represent difficulties in isolating the compounds rather than a limitation of our procedure.

To circumvent the problematic formation of anisaldehyde, addition of TMS-CF_3 to C-2 *tert*-butyl-substituted oxazolidin-5-ones was investigated (pivalaldehyde has a boiling point of 74 °C and is therefore easier to remove from crude reaction mixtures). Oxazolidin-5-ones **26** and **27** were obtained as above (Scheme 2, entries XIII and XIV in Table 2) following the literature procedure for **27**.[29] Addition of TMS-CF_3 to *N*-benzoyl-substituted **27** proceeded in good yield. After desilylation of **27a**,

(29) Seebach, D.; Fadel, A. *Helv. Chim. Acta* **1985**, *68*, 1243−1250.

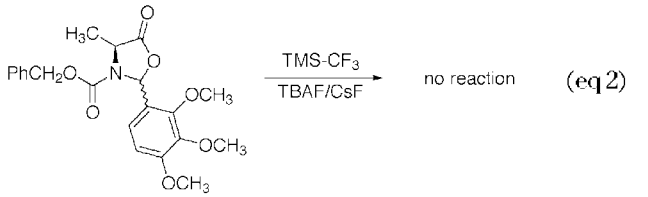
Table 4. Hydration of TFMKs

entry	TFMK	solvent	δ_k[a]	δ_h[a]	ratio k:h
I	**19c**	$CDCl_3$	−79.1	−85.6	1:10
		$(CD_3)_2CO$		−85.7	only h
II	**18c**	$CDCl_3$	−76.4	−82.2	2:1
		$(CD_3)_2CO$		−82.6	only h
III	**20c**	$CDCl_3$	−73.0	−79.8	10:1
		$(CD_3)_2CO$	−73.9		only k
IV	**27c**	$CDCl_3$	−76.2	−82.5	1.5:1
		$(CD_3)_2CO$	−76.8	−82.7	<1:10

[a] ^{19}F NMR (235.19 MHz), k = ketone, h = hydrate.

hydrolysis occurred rapidly and isolation of TFMK **27c** was facilitated by the volatility of trimethylacetaldehyde (pivalaldehyde). Trifluoromethylation of *N*-urethane-protected **28** to give **28a** proceeded in considerably better yield using cesium fluoride with sonication than TBAF as initiator. **26a** was readily desilylated, but, somewhat surprisingly, hydrolysis conditions as before (Amberlite, CH_3CN, Scheme 3) failed and it was not possible to cleave the ring to give the desired TFMK under other mild conditions (dilute acid).

Trimethoxy-substituted oxazolidin-5-one **29** was prepared, anticipating that acid hydrolysis would occur more rapidly than for the *p*-methoxyphenyl-substituted adducts. Cyclization of the intermediate Schiff base salt gave **29**, albeit in poorer yield than the corresponding C-2 *p*-methoxyphenyl-substituted oxazolidin-5-ones. However, attempted trifluoromethylation of **29** using either TBAF/TMS-CF_3 or CsF/TMS-CF_3 was unsuccessful (eq 2). C-2 *p*-methoxyphenyl-substituted **14**, however, was



(eq 2)

29

readily converted into adduct **14a** (entry I in Table 2). These results were interpreted as further evidence for the importance of steric factors in the trifluoromethyl group transfer to oxazolidin-5-ones (vide infra).

NMR spectra in $CDCl_3$ or $(CD_3)_2CO$ indicated that the synthetic TFMKs existed as mixtures of the hydrate and ketone form (see Experimental Section). Table 4 summarizes the observed ketone/hydrate ratios of *N*-benzoyl-substituted TFMKs. Assignment of ketone and hydrate was based on their respective shifts in the ^{19}F NMR spectrum according to a literature reference.[17a] The NMR solvents deuterated chloroform and acetone were used as purchased from the supplier without any attempt to remove residual water. As expected on the basis of the anticipated higher water content of deuterated acetone, spectra run in this solvent showed generally larger amounts of the hydrate form. These results suggest that the degree of substitution of the α-carbon influences the ratio of ketone to hydrate. Thus, C-2-unsubstituted **19c** exists almost exclusively in the hydrate form either in deuterated acetone or in deuterated chloroform (entry I, Table 4). In contrast, C-4 methyl-substituted **18c** forms a mixture of ketone and hydrate as a solution in $CDCl_3$ in which the former predominates (entry II, Table 4). Similar results are obtained with a benzyl group as α-substituent (entry IV, Table 4). A quaternary center in the α-position to the carbonyl group favors formation of the ketone in both solvents (entry III, Table 4). Furthermore, it appears that there is a correlation between the chemical shift of the signals for the trifluoromethyl group in the ^{19}F NMR and the degree of substitution of the carbon in the α-position. A downfield shift both for the ketone and the hydrate was observed from secondary (entry I, Table 4) to quaternary centers (entry III, Table 4).

3. Mechanistic Considerations. Prakash and Krishnamurti have reported that five- and six-membered (ring) lactones are the only known carboxylic acid derivatives which react smoothly and in good yields with TMS-CF_3.[23] Simple esters seem to be unreactive toward TMS-CF_3 while acid chlorides lead to the formation of complex product mixtures.[23] These differences in reactivity may be attributed to two effects: On one hand the mesomerically stabilizing alkoxy substituent decreases the reactivity of alkyl esters toward nucleophilic attack by TMS-CF_3; on the other the electron-withdrawing effect of the halogen atoms renders acid halides so reactive that controlled addition cannot occur. Thus, the high-yielding addition of TMS-CF_3 to five- and six-membered ring lactones, and the both structurally and electronically related oxazolidin-5-ones, may reflect their intermediate reactivity as electrophiles toward TMS-CF_3 relative to acid halides and to esters.

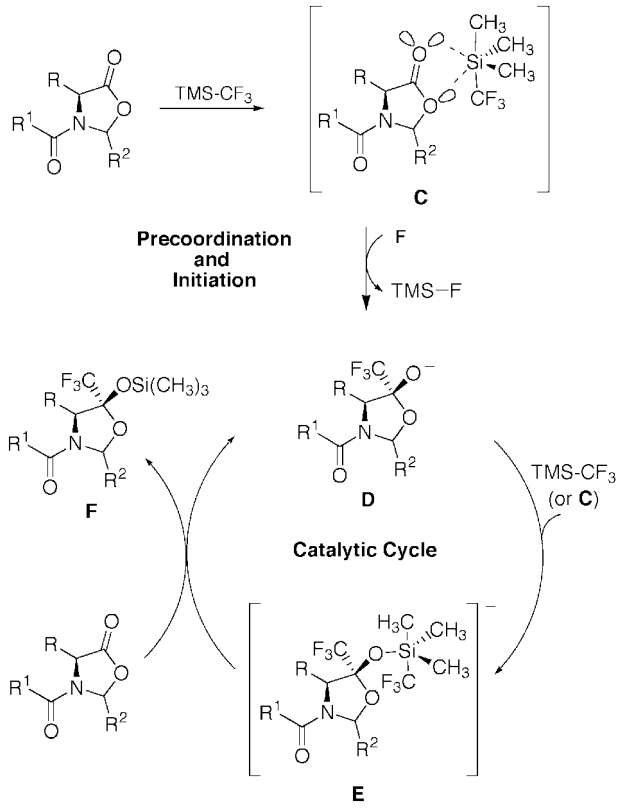
An interesting feature of the reaction of TMS-CF_3 oxazolidin-5-ones is the observed diastereoselectivity of the reaction: Trifluoromethylation of C-2 unsubstituted oxazolidin-5-ones with cesium fluoride and sonication afforded the adducts as single diastereomers (see Table 1). In the trifluoromethylation of C-2 *p*-methoxyphenyl-substituted oxazolidin-5-ones using a TBAF−THF solution (as initiator) the steric bulk of the C-4 substituent appears to influence the diastereoselectivity of the reaction.

The diastereoselectivity of nucleophilic addition to carbonyl groups in cyclic (and acyclic) systems depends on the size of the incoming nucleophile and the steric environment of the carbonyl group. Both ab initio calculations and empirical studies suggest that the trifluoromethyl group is comparable in size to an isopropyl group using a half-sphere approximation.[30] Therefore, a significant degree of diastereoselectivity in the trifluoromethylation of carbonyl groups with adjacent chiral carbon atoms might be expected. Krishnamurti et al., however, reported that trifluoromethylation of 2-methyl cyclohexanone affords a 3:2 mixture of diastereomers suggesting that the steric bulk of the reagent alone cannot account for the highly diastereoselective trifluoromethylation of oxazolidin-5-ones.[23]

A mechanistic proposal for the trifluoromethylation of oxazolidin-5-ones with TMS-CF_3 is shown in Scheme 4: Precoordination of TMS-CF_3 to the oxazolidin-5-one substrate activates the carbonyl group toward nucleophilic attack and may lead to the formation of a complex such as **C**. Attack by fluoride initiates the nucleophilic transfer of a trifluoromethyl group to the oxazolidin-5-one with concomitant formation of fluorotrimethylsilane. Trifluoromethyl-substituted **D** enters into an autocatalytic cycle in which **D** attacks another molecule of TMS-CF_3 (or **C**) to yield sterically demanding ate-complex **E**.

(30) Nagai, T.; Nishioka, G.; Koyama, M.; Ando, A.; Miki, T.; Kumadaki, I. *Chem. Pharm. Bull.* **1991**, *39*, 233−235.

Scheme 4. Proposed Mechanism for the Addition of TMS-CF_3 to Oxazolidin-5-ones



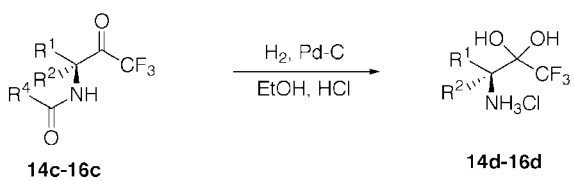
Transfer of the trifluoromethyl unit to another substrate molecule gives the product **F** and regenerates **D**. The mechanism proposed in Scheme 4 is analogous to that suggested for the trifluoromethylation of ketones and aldehydes with TMS-CF_3 and accounts for the characteristic features of this reaction: the need for only catalytic amounts of fluoride and the formation of fluorotrimethylsilane.[22] The ultimate driving force of the trifluoromethyl group transfer is the stability of the Si−F and the Si−O bonds, respectively. Precoordination of TMS-CF_3 to the substrate as invoked in Scheme 4 may provide an additional explanation for the increased reactivity of lactones toward TMS-CF_3 in comparison to esters. The Lewis basicity of the oxygen lone pairs in lactones is greater than in open chain esters, which adopt preferentially an s-trans-conformation resulting in optimal mesomeric resonance stabilization of the carbonyl group. This stereoelectronically stabilizing $(n_O)-(\sigma_{C-O}^*)$ interaction is not possible in the five-membered lactone ring which enforces a cisoid conformation.[31] Hence, precoordination and the resulting activation to nucleophilic attack are more likely to occur in lactones. The stereoselectivity observed in the trifluoromethylation of oxazolidin-5-ones may be explained by the steric constraints of the relatively tight complex **C** and/or encumbered ate-complex **E**. Supporting evidence for this hypothesis comes from Krishnamurti's observation that trifluoromethylation of 2-methyl cyclohexanone occurs with poor diastereoselectivity.[23] In comparison to lactones, cyclic ketones lack the additional interaction between silicon and oxygen which is invoked here to provide a possible rationale for the stereoselective transfer.

(31) *Stereoelectronic Effects in Organic Chemistry;* Deslongchamps, P., Eds.; Pergamon Press: New York, 1983.

The lack of reactivity of oxazolidin-5-ones **17** and **21** (entries IV and VIII in Table 2) and **29** can be rationalized on the basis of steric crowding due to the presence of sterically demanding substituents. *N*-Amide-substituted oxazolidin-5-ones **17** and **21** have three aromatic rings close to the oxazolidin-5-one. The importance of steric factors is borne out by the fact that *N*-benzoyl-4-methyl-substituted oxazolidin-5-one **18** yields the addition product **18a** in good yield (entry V in Table 2). Similarly, oxazolidin-5-one **15** with a CBZ-group in the 3-position which has the aromatic system further away from the oxazolidin-5-one ring reacts almost quantitatively with TMS-CF_3. The trimethoxyphenyl substituent in **29** is presumably sterically so demanding that trifluoromethylation cannot occur, despite a small C-4 substituent (methyl).[32]

4. Peptidic Trifluoromethyl Ketones. Previous routes to peptidic trifluoromethyl ketones proceed either via trifluoromethyl alcohols[14,17c,33] or imidazolines[19] as latent TFMK precursors. Hydrochloride salts of α-amino TFMKs which can be coupled with amino acid derivatives to give peptidic trifluoromethyl ketones have not been described. Since such an approach avoids the problematic oxidation of trifluoromethyl alcohols, we investigated the use of *N*-CBZ protected TFMKs **14c**−**16c** as potential precursors of the corresponding hydrochloride salts.

Treatment of *N*-CBZ-protected α-amino TFMK **15c** under standard hydrogenolysis conditions afforded a white solid in 90% yield which was assigned as monomeric hydrochloride salt **15d** on the basis of its spectroscopic data (^{1}H, ^{13}C, and ^{19}F NMR, mass-spectrum). The ^{19}F NMR showed a single signal at $\delta = -81.7$ ppm (235.19 MHz, D_2O) supporting the proposed monomeric structure. This value corresponds to the shift of a TFMK hydrate.[17a] Evidence for hydration was also obtained from analysis of its ^{13}C NMR spectrum which showed one quartet with a coupling constant of $J_{C-F} = 32$ Hz at $\delta = 92.4$ ppm (125.7 MHz, D_2O) for C-2. The optical rotation of (*S*)-phenylalanine-derived hydrochloride salt **15d** was determined as a solution in 1 N hydrochloric acid and the value of $[\alpha]^{20}_D = -37.0$ ($c = 1.0$, 1 N HCl) was found to be stable over several days. Attempts to purify crude **15d** via base extraction followed by reacidification led to total loss of material. This was probably due to the hydrophilicity of the intermediate free α-amino TFMK hydrate. Trifluoromethyl ketone hydrochloride salts **14d** and **16d** were obtained from *N*-CBZ protected TFMKs **14c** and **16c** following the same procedure (eq 3 and Table 3) and in similar yields. Addition of TMS-CF_3 to

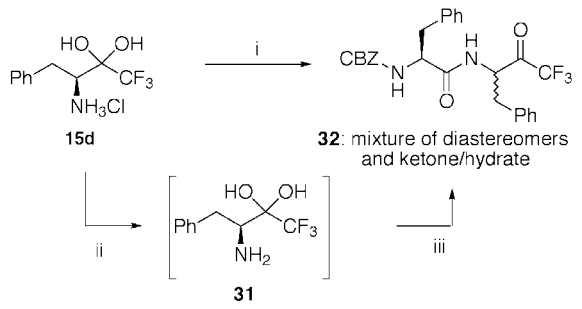


oxazolidin-5-ones, hydrolysis of the adducts, and hydrogenolytic removal of the CBZ-group could be carried out in a one-pot procedure. Hydrogenolysis of the crude

(32) Evidence supporting the steric demand of the trimethoxyphenyl substituent was also obtained from the ^{1}H NMR spectrum of **29** which showed extremely broadened signals.

(33) Skiles, J. W.; Fuchs, V.; Miao, C.; Sorcek, R.; Grozinger, K. G.; Mauldin, S. C.; Vitous, J.; Mui, P. W.; Jacober, S.; Chow, G.; Matteo, M.; Skoog, M.; Weldon, S. M.; Possanza, G.; Keirns, J.; Letts, G.; Rosenthal, A. S. *J. Med. Chem.* **1992**, *35*, 641−662.

Scheme 5. Synthesis of Peptidic Trifluoromethyl Ketones

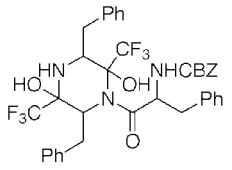


Reagents and conditions: (i) *N*-CBZ-PheCOF, pyridine, DCM, 35%; (ii) Et_3N, THF, 0°C; (iii) EtOCOCl, Et_3N, THF, 30%.

hydrolysis mixture followed by removal of solvents in vacuo afforded a gum-like yellow-brown substance. Trituration with chloroform/diethyl ether caused the hydrochloride salt to precipitate. The overall yields of the one-pot procedure were lower than the combined optimized yields of the individual steps, but still satisfactory. Attempts to hydrogenate desilylated adducts directly without hydrolysis led to intractable mixtures of products from which the desired hydrochloride salts could only be isolated in poor yields.

Initially, the coupling of hydrochloride salts of α-amino TFMKs to activated amino acid derivatives to give peptidic TFMKs was attempted using the mixed anhydride method for activation of the amino acid component (Scheme 5). This procedure gave peptidic TFMK **32** as an approximately 1:1 mixture of diastereomers together with several, unidentifiable fluorine-containing species as minor byproducts by ^{19}F NMR analysis. Attempts to purify the crude product mixture by preparative thin-layer chromatography led to considerable loss of material, but analytically pure peptidic TFMKs were obtained in low yield (isolated: ca. 30%, crude recovery of the product: 50−60%). It is unclear whether the epimerization of the α-amino TFMK center occurred during the coupling procedure or at the stage of product purification. Formation of "free" α-amino TFMK hydrate **31** was regarded as a potentially complicating factor in this protocol. The presence of a highly acidic α-proton and the electrophilic carbonyl group of the ketone form could lead to reversible dimerization, and hence epimerization. Polymerization of the ketone form could likewise diminish the yield of the coupling step. Therefore, we investigated the use of amino acid fluorides as more powerful acylating reagents which would also allow in situ generation of free amine **31**.[34] Acylation of α-amino TFMK hydrochloride salt **15d** using *N*-CBZ protected phenylalanyl fluoride gave peptidic TFMK **32** (Scheme 5). Although the crude recovery was higher than in the case of the mixed-anhydride coupling (∼70%), the yields of isolated peptidic TFMK remained low (∼35%). Mass-spectrometric analysis of the crude reaction mixture indicated the presence of species with higher molecular masses, suggesting the formation of dimers or oligomers.

One isolated compound was tentatively assigned as **33** with a molecular weight of $M_r = 712$. Although a number of coupling reactions under different conditions (solvents, temperature) were attempted, the formation of dimers could not be suppressed. It is possible that alternative coupling procedures, e.g. employing silylated intermediates, might result in improved coupling efficiency.[34]



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Conclusion

We have shown that trifluoromethylation of amino acid derived oxazolidin-5-ones using TMS-CF_3 is an efficient process. The adducts can be converted into TFMKs via mild acid hydrolysis, giving access to a variety of *N*-acylated and *N*-CBZ protected TFMKs. Removal of the CBZ-protecting group by hydrogenolysis affords α-amino TFMK hydrochloride salts which can be coupled with amino acid fluorides to give peptidic TFMKs.

Experimental Section

Melting points are uncorrected. ^1H, ^{19}F, and ^{13}C NMR spectra were recorded at the indicated field strengths. ^{19}F NMR spectra were referenced externally to $CFCl_3$ at 0.00 ppm. Elemental analyses were performed at the Dyson Perrins Laboratory, University of Oxford. High-resolution mass spectra were obtained by the EPSRC mass spectrometry service, Swansea. All separations were effected under flash chromatography conditions using Acros C60 (0.035−0.07 mm) silica gel. Sonication was carried out in a Kerry Pulsatron. Amberlite IR 120 (Plus) ion-exchange resin was obtained from Aldrich and "activated" by refluxing in 2 M hydrochloric acid and washed several times with water before use. All reagents were obtained from commercial suppliers and used as received unless otherwise stated. THF was distilled from potassium/benzophenone ketyl under a nitrogen atmosphere. DCM was distilled from calcium hydride under a nitrogen atmosphere.

General Procedure A (Preparation of *N*-CBZ and *N*-BOC protected oxazolidin-5-ones 1−8). A mixture of *N*-CBZ or *N*-BOC-protected amino acid (10.0 mM), paraformaldehyde (400 mg), and *p*-toluenesulfonic acid (100 mg for *N*-CBZ protected amino acids, 30 mg for *N*-BOC protected amino acids) in benzene (150 mL) was refluxed for 1 h in a Dean−Stark apparatus. The benzene solution was allowed to cool to room temperature and washed with aqueous sodium bicarbonate solution (50 mL) and brine (50 mL). After being dried over magnesium sulfate and evaporation of solvents in vacuo, the crude product was purified by column chromatography or by crystallization from suitable solvents.

General Procedure B (Formation of Schiff base salts of amino acids 9−13). The amino acid (10.0 mM) was dissolved in a 1 M solution of sodium hydroxide (10.0 mL). Gentle warming or addition of ethanol was sometimes required to effect solution. The solution was then concentrated in vacuo until solid began to appear at which time 1 mol equiv of aldehyde was added. Concentration in vacuo was continued until the reaction mixture solidified. The solid was suspended in diethyl ether (150 mL), filtered, and washed thoroughly with same solvent and dried in vacuo. This procedure afforded the Schiff base salts in nearly quantitative yield.

General Procedure C (Preparation of *N*-CBZ protected, C-2 substituted oxazolidin-5-ones 14−16, 26). To a suspension of carefully ground Schiff base salt (10.0 mM) in DCM (150 mL) was added benzyl chloroformate (1.43 mL, 10.0 mM) slowly by syringe pump over a period of 6 h at −15 °C under an argon atmosphere. The resulting mixture was

(34) A number of methods have been developed to effect peptide coupling of sterically hindered, unreactive or unstable substrates; see for example: (a) Carpino, L. A.; Beyermann, M.; Wenschuh, H.; Bienert, M. *Acc. Chem. Res.* **1996**, *29*, 268−274. (b) Kricheldorf, H. R. *Liebigs Ann. Chem.* **1972**, *763*, 17−38.

stirred at −10 °C for 18 h and then allowing to warm to room temperature for 48−72 h after which time a turbid slurry had formed. Progress of the reaction was monitored by ^{1}H NMR analysis. The reaction mixture was reduced in vacuo, and ethyl acetate (100 mL) was added. The organic layer was washed with dilute aqueous hydrochloric acid (50 mL), saturated sodium bicarbonate solution (50 mL), and brine (50 mL). After re-extraction of the aqueous layer with ethyl acetate (50 mL), the combined organic layers were washed with brine (2 × 75 mL) and dried over magnesium sulfate. The solvents were removed in vacuo and the products purified by column chromatography or by crystallization from suitable solvents.

General Procedure D (Preparation of *N*-amide protected, C-2 substituted oxazolidin-5-ones 17−25). A mixture of carefully ground Schiff base salt (10 mM) and the required acid chloride (10 mM) in DCM (150 mL) was refluxed for 12 h under an argon atmosphere. The reaction mixture was concentrated in vacuo, and ethyl acetate (100 mL) was added. The organic layer was washed with aqueous hydrochloric acid (50 mL), saturated sodium bicarbonate solution (50 mL), and brine (50 mL). After re-extraction of the aqueous layer with ethyl acetate (50 mL) the combined organic layers were washed with brine (2 × 75 mL) and dried over magnesium sulfate. The solvents were removed in vacuo, and the products purified by column chromatography or by crystallization from suitable solvents.

General Procedure E (Trifluoromethylation using TMS-CF$_3$/CsF). To a solution of oxazolidin-5-one (1 mM) in dry THF (5 mL) were added cesium fluoride (catalytic amounts) and (trifluoromethyl)trimethylsilane (0.19 mL, 1.20 mM, 1.20 equiv) under an argon atmosphere. The flask was placed in a sonicator and the reaction followed by TLC analysis. After all starting material had been consumed (usually 20 to 60 min), the mixture was diluted with ethyl acetate (10 mL), washed with water (10 mL) and brine (10 mL), and dried over magnesium sulfate. The solvents were removed in vacuo and the products purified by flash column chromatography.

General Procedure F (Trifluoromethylation using TMS-CF$_3$/TBAF). To a solution of oxazolidin-5-one (1.00 mM) in dry THF (5 mL) under an argon atmosphere at room temperature were added (trifluoromethyl)trimethylsilane (0.19 mL, 1.20 mM, 1.20 equiv) and TBAF (25 μL of a 1.00 M solution in THF, 0.025 mM). The reaction was followed by TLC analysis. After all starting material had been consumed, the yellow mixture was taken up in ethyl acetate (10 mL), washed with water (2 × 10 mL) and brine (10 mL), and dried over magnesium sulfate. The solvents were removed in vacuo and the products purified by flash column chromatography.

General Procedure G (Desilylation). To a solution of *N*-CBZ or *N*-BOC protected 5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]oxazolidine (1.00 mM) in dry THF (5 mL) was added TBAF (1.20 mL of a 1.00 M solution in THF, 1.20 equiv). The reaction was followed by TLC analysis. After all starting material had been consumed, ethyl acetate (10 mL) and aqueous hydrochloric acid (10 mL) were added. The organic layer was separated and washed with saturated sodium bicarbonate solution (10 mL) and brine (10 mL). The combined organic phases were dried over magnesium sulfate and the solvents removed in vacuo.

General Procedure H (Hydrolysis). To a solution of 5-hydroxy-5-(trifluoromethyl)oxazolidine (1 mM) in acetonitrile (15 mL) was added strongly acidic cation-exchange resin Amberlite IR-120 (2.0 g) and stirred at 45 °C until all starting material had disappeared by TLC (usually 36−48 h) after which time a deeply red solution was obtained. The crude product was diluted with acetonitrile (25 mL) and filtered through Celite and the resin thoroughly washed with acetonitrile. After removal of the solvent in vacuo, the residue was taken up in ethyl acetate (25 mL) and washed with saturated sodium bicarbonate solution (15 mL) and brine (15 mL). After drying over magnesium sulfate, the solvent was removed in vacuo. Purification was achieved by crystallization from suitable solvents or column chromatography on silica gel.

General Procedure I (Hydrogenolysis). To a solution of *N*-CBZ α-amino trifluoromethyl ketone (1.00 mM) in ethanol (10 mL) was added palladium on carbon catalyst (150 mg) and hydrochloric acid (1 mL of a 1 M solution, 1.00 mM). The mixture was placed under a hydrogen balloon and stirred until TLC analysis indicated completion. After addition of ethanol (15 mL), the catalyst was filtered off through a plug of Celite. The solvents were removed in vacuo, and the solid residue was taken up in aqueous hydrochloric acid. The aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the water removed in vacuo. This procedure yielded the hydrochloride salts as off-white solids and in nearly quantitative yields.

(4*S*)-4-Benzyl-*N*-(benzyloxycarbonyl)-1,3-oxazolidin-5-one (1) was prepared from *N*-(benzyloxycarbonyl)-(*S*)-phenylalanine (2.99 g, 10.0 mM) following general procedure A and obtained as fine white needles after crystallization from toluene (2.64 g, 85%): $[\alpha]^{20}_D$ +24.30 (*c* 0.5, $CHCl_3$); mp 81−83 °C; IR (KBr): 1800, 1720 cm^{-1}; ^{1}H NMR (500 MHz, $CD_3C_6D_5$, 90 °C): δ 6.95−7.15 (m, 10H), 4.93−4.98 (m, 2H), 4.73 (d, J = 4 Hz, 1H), 4.03 (dd, J = 3, 5 Hz, 1H), 4.01 (d, J = 4 Hz, 1H), 3.13 (dd, J = 5, 14 Hz, 1H), 2.91 (dd, J = 3, 14 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 171.1, 152.2, 135.7, 134.7, 129.6, 128.9, 128.5, 127.5, 77.3, 67.8, 56.3, 36.1; LRMS (NH_3): 329 (MNH_4^+). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.51; H, 5.84; N, 4.56.

(4*S*,5*S*)-4-Benzyl-*N*-(benzyloxycarbonyl)-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (1a)[35] was prepared from **1** (311 mg, 1.00 mM) following general procedure E using excess (trifluoromethyl)trimethylsilane (0.38 mL, 2.00 mM, 2.00 equiv) and obtained as colorless prisms after purification by flash column chromatography, using 25% chloroform/petroleum ether as eluant (430 mg, 95%, single diastereomer): $[\alpha]^{20}_D$ +1.1 (*c* 1, $CHCl_3$); mp 98−101 °C; IR (KBr): 1715, 1500 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.10−7.59 (m, 10H), 5.40−5.45 (m, 1H), 4.95−5.05 (m, 3H), 4.63−4.67 (m, 1H), 3.05 (dd, J = 6, 14 Hz, 1H), 2.69−2.76 (m, 1H), 0.26 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 154.7, 137.7, 136.1, 129.8, 129.2, 128.8, 128.7, 128.6, 127.6, 122.1 (q, J_{C-F} = 283 Hz), 102.7 (q, J_{C-F} = 32 Hz), 78.0, 68.0, 61.6, 35.0, 1.6; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.1; LRMS (NH_3): 471 (MNH_4^+). Anal. Calcd for $C_{22}H_{26}F_3NO_4Si$: C, 58.26; H, 5.78; N, 3.09. Found: C, 58.59; H, 5.77; N, 3.06.

(4*S*,5*S*)-4-Benzyl-*N*-(benzyloxycarbonyl)-5-hydroxy-5-(trifluoromethyl)-1,3-oxazolidine (1b) was prepared from **1a** (453 mg, 1.00 mM) following general procedure G and obtained as a colorless oil after purification by flash column chromatography, using 25% chloroform/petroleum ether as eluant (374 mg, 98%): $[\alpha]^{20}_D$ = +9.4 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 3570−3300, 1715 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21−7.39 (m, 10H), 5.44 (d, J = 4 Hz, 1H), 5.15 (s, 2H), 4.85 (d, J = 4 Hz, 1H), 4.65 (t, J = 7 Hz, 1H), 3.15 (dd, J = 7, 13 Hz, 1H), 3.02 (dd, J = 7, 13 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 153.6, 137.1, 135.6, 129.7, 129.4, 128.6, 128.2, 127.9, 126.6, 122.1 (q, J_{C-F} = 280 Hz), 100.8 (q, J_{C-F} = 33 Hz), 77.9, 67.8, 60.3, 34.5; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.6; LRMS (NH_3): 399 (MNH_4^+); HRMS: calcd for $C_{19}H_{22}F_3N_2O_4$ (MNH_4^+): 399.1532. Found: 399.1532.

(4*S*)-*N*-(Benzyloxycarbonyl)-4-methyl-1,3-oxazolidin-5-one (2) was prepared from *N*-(benzyloxycarbonyl)-(*S*)-alanine (2.23 g, 10.0 mM) following general procedure A and obtained as colorless prisms after crystallization from diethyl ether (2.16 g, 92%): $[\alpha]^{20}_D$ +53.1 (*c* 0.5, $CHCl_3$); IR (KBr): 1800, 1720 cm^{-1}; ^{1}H NMR (500 MHz, $CD_3C_6D_5$, 90 °C): δ 6.95−7.11 (m, 5H), 4.94 (d, J = 12 Hz, 1H), 4.88 (d, J = 12 Hz, 1H), 4.80 (d, J = 4 Hz, 1H), 4.64 (d, J = 4 Hz, 1H), 3.70 (q, J = 7 Hz, 1H), 1.18 (d, J = 7 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 172.8, 152.6, 135.7, 128.7, 128.5, 128.2, 77.3, 67.6, 50.6, 16.6; LRMS (NH_3): 253 (MNH_4^+). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.41; H, 5.58; N, 5.66.

(4*S*,5*S*)-*N*-(Benzyloxycarbonyl)-4-methyl-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (2a) was prepared from **2** (235 mg, 1.00 mM) following general procedure E and obtained as a colorless oil after purification by flash

(35) The assignment of the stereochemistry is based on a single-crystal X-ray analysis (see ref 21).

column chromatography, using 25% chloroform/petroleum ether as eluant (260 mg, 69%, single diastereomer): $[\alpha]^{20}_D$ +13.1 (*c* 1, $CHCl_3$); IR ($CHCl_3$): 1715, 1500 cm^{-1}; ^1H NMR (500 MHz, $CD_3C_6D_5$, 90 °C): δ 6.96−7.13 (m, 5H), 5.06 (d, J = 4 Hz, 1H), 4.99 (d, J = 12 Hz, 1H), 4.95 (d, J = 12 Hz, 1H), 4.71 (d, J = 4 Hz, 1H), 4.39 (q, J = 7 Hz, 1H), 1.15 (d, J = 7 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 152.9, 135.8, 128.6, 128.3, 127.9, 122.1 (q, J_{C-F} = 283 Hz), 102.7 (q, J_{C-F} = 32 Hz), 77.8, 67.5, 55.6, 14.2, 1.0; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.4; LRMS (NH_3): 395 (MNH_4^+), 378 (MH^+); HRMS: calcd for $C_{16}H_{23}F_3NO_4Si$ (MH^+): 378.1348. Found: 378.1348.

(4*S*)-*N*-(Benzyloxycarbonyl)-4-[(methoxycarbonyl)ethyl]-1,3-oxazolidin-5-one (3). To a solution of (4*S*)-3-(benzyloxycarbonyl)-4-(carboxyethyl)-1,3-oxazolidin-5-one[36] (1.0 g, 3.41 mM) in ethyl acetate (25 mL) was added a solution of diazomethane (10.0 mM) in diethyl ether (45 mL) over 25 min. Excess diazomethane was removed by addition of a few drops of acetic acid. The organic layer was then washed with aqueous sodium bicarbonate solution (3 × 50 mL) and brine (50 mL). After drying over magnesium sulfate and removal of solvents in vacuo, **3** was obtained as a colorless solid from diethyl ether (1.02 g, 97%): $[\alpha]^{20}_D$ +83.1 (*c* 2, $CHCl_3$); mp 96−97 °C; IR ($CHCl_3$): 1805, 1735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.38−7.49 (m, 5H), 5.54 (br, 1H), 5.23−5.47 (m, 3H), 4.45 (dd, J = 4 Hz, 1H), 3.61 (s, 3H), 2.01−2.46 (m, 4H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 172.5, 171.8, 153.0, 135.3, 128.7, 128.6, 128.3, 77.8, 68.1, 54.0, 51.8, 29.1, 25.9; LRMS (NH_3): 325 (MNH_4^+), 308 (MH^+); HRMS: calcd for $C_{15}H_{18}NO_6$ (MH^+): 308.1134. Found: 308.1134.

(4*S*,5*S*)-*N*-(Benzyloxycarbonyl)-4-[(methoxycarbonyl)ethyl]-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (3a) was prepared from **3** (307 mg, 1.00 mM) following general procedure E and obtained as a colorless oil after purification by flash column chromatography, using 25% chloroform/petroleum ether as eluant (330 mg, 73%): $[\alpha]^{20}_D$ +25.8 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): 3055, 1710, 1370 cm^{-1}; ^1H NMR (500 MHz, $CD_3C_6D_5$, 90 °C): δ 6.80−7.16 (m, 5H), 5.20 (d, J = 4.5 Hz, 1H), 4.96 (s, 2H), 4.58 (d, J = 4.5 Hz, 1H), 4.49 (dd, J = 6, 8 Hz, 1H), 3.34 (s, 3H), 1.80−2.17 (m, 4H), 0.15 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 173.2, 153.9, 135.7, 128.7, 128.3, 127.9, 122.0 (q, J_{C-F} = 288 Hz), 102.5 (q, J_{C-F} = 30 Hz), 77.8, 67.9, 59.0, 51.6, 30.2, 23.8, 1.2; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.5; LRMS (NH_3): 450 (MH^+); HRMS: calcd for $C_{19}H_{27}F_3NO_6Si$ (MH^+): 450.156. Found: 450.156.

(4*S*)-4-Benzyl-*N*-(*tert*-butyloxycarbonyl)-1,3-oxazolidin-5-one (4) was prepared from *N*-(*tert*-butyloxycarbonyl)-(*S*)-phenylalanine (2.65 g, 10.0 mM) following general procedure A and obtained as a white solid after crystallization from diethyl ether (1.49 g, 54%): $[\alpha]^{20}_D$ +23.5 (*c* 1.0, $CHCl_3$); mp 84−86 °C; IR (KBr): 1795, 1705 cm^{-1}; ^1H NMR (500 MHz, $CD_3C_6D_5$, 90 °C): δ 6.97−7.08 (m, 5H), 4.75 (d, J = 4 Hz, 1H), 4.03−4.05 (m, 2H), 3.17 (dd, J = 4, 14 Hz, 1H), 2.92 (dd, J = 3, 14 Hz, 1H), 1.31 (s, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 172.7, 153.2, 135.0, 129.8, 128.9, 127.6, 82.0, 78.0, 56.3, 34.3, 28.6; LRMS (NH_3): 295 (MNH_4^+). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.93; H, 6.73; N, 4.83.

(4*S*,5*S*)-4-Benzyl-*N*-(*tert*-butyloxycarbonyl)-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (4a) was prepared from **4** (277 mg, 1.00 mM) following general procedure E and obtained as a white solid after flash column chromatography using 25% chloroform/petroleum ether as eluant (410 mg, 98%, single diastereomer): $[\alpha]^{20}_D$ +5.5 (*c* 1, $CHCl_3$); mp 53−55 °; IR (KBr): 1705, 1455 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.19−7.39 (m, 5H), 5.45−5.47 (m, 1H), 4.95 (d, J = 5 Hz, 1H), 4.49−4.53 (m, 1H), 3.03 (dd, J = 5, 14 Hz, 1H), 2.54−2.70 (m, 1H), 1.15 (s, 9H), 0.25 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 153.0, 137.7, 129.5, 128.2, 126.4, 122.5 (q, J_{C-F} = 292 Hz), 102.8 (q, J_{C-F} = 32 Hz), 80.6, 77.5, 61.5, 34.5, 27.6, 1.1; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.6; LRMS (NH_3): 437 (MNH_4^+). Anal. Calcd for $C_{19}H_{28}F_3NO_4Si$: C, 54.40; H, 6.73; N, 3.34. Found: C, 54.33; H, 6.76; N, 3.56.

(36) Scholtz, J. M.; Bartlett, P. A. *Synthesis* **1989**, 542−544.

(4*S*,5*S*)-4-Benzyl-*N*-(*tert*-butyloxycarbonyl)-5-hydroxy-5-(trifluoromethyl)-1,3-oxazolidine (4b) was prepared from **4a** following general procedure G and obtained as a colorless oil after purification by flash column chromatography, using 25% diethyl ether/petroleum ether as eluant (340 mg, 98%): $[\alpha]^{20}_D$ = +8.9 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): 3150−3350, 1705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.19−7.39 (m, 5H), 5.40 (d, br, J = 5 Hz, 1H), 4.85 (d, br, J = 5 Hz, 1H), 4.58 (dd, J = 5, 9 Hz, 1H), 3.10 (dd, J = 5, 15 Hz, 1H), 2.85 (dd, J = 9, 15 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 153.0, 137.4, 129.7, 128.3, 126.5, 122.3 (q, J_{C-F} = 285 Hz), 100.7 (q, J_{C-F} = 33 Hz), 81.4, 77.7, 60.5, 34.0, 27.8; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.6; LRMS (NH_3): 365 (MNH_4^+), 348 (MH^+); HRMS: calcd for $C_{16}H_{21}F_3NO_4$ (MH^+): 348.1423. Found: 348.1423.

(4*S*)-*N*-(*tert*-Butyloxycarbonyl)-4-methyl-1,3-oxazolidin-5-one (5) was prepared from *N*-(*tert*-butyloxycarbonyl)-(*S*)-alanine (1.89 g, 10.0 mM) following general procedure A and obtained as fine white needles after crystallization from chloroform (1.49 g, 74%): $[\alpha]^{20}_D$ +78.1 (*c* 1, $CHCl_3$); mp 64−67 °C; IR (KBr) 1795, 1705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.40 (d, J = 2 Hz, 1H), 5.20 (d, J = 2 Hz, 1H), 4.50 (q, J = 7 Hz, 1H), 1.55 (d, J = 7 Hz, 3H), 1.45 (s, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 173.5, 152.0, 81.4, 77.3, 50.3, 27.8, 16.3; LRMS (NH_3): 219 (MNH_4^+). Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.58; H, 7.71; N, 6.70.

(4*S*,5*S*)-*N*-(*tert*-Butyloxycarbonyl)-4-methyl-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (5a) was prepared from **5** (201 mg, 1.00 mM) following general procedure E and obtained as a colorless oil after flash column chromatography, using 25% chloroform/petroleum ether as eluant (292 mg, 85%, single diastereomer): $[\alpha]^{20}_D$ +58.4 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): 1700, 1475 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.17−5.20 (m, 1H), 4.89 (d, J = 4 Hz, 1H), 4.20−4.30 (m, 1H), 1.46 (s, 9H), 1.20 (d, J = 7 Hz, 3H), 0.20 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 152.0, 123.5 (q, J_{C-F} = 289 Hz), 102.2 (q, J_{C-F} = 32 Hz), 80.6, 77.6, 55.2, 27.0, 14.0, 0.6; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.6; LRMS (NH_3): 361 (MNH_4^+), 344 (MH^+); HRMS: calcd for $C_{13}H_{25}F_3NO_4Si$ (MH^+): 344.1505. Found: 344.1505.

(4*S*)-*N*-(*tert*-Butyloxycarbonyl)-4-isopropyl-1,3-oxazolidin-5-one (6) was prepared from *N*-(*tert*-butyloxycarbonyl)-(*S*)-valine (2.17 g, 10.0 mM) following general procedure A and obtained as a white solid after crystallization from chloroform (1.67 g, 73%): $[\alpha]^{20}_D$ +104.9 (*c* 1, $CHCl_3$); mp 43−45 °C; IR (KBr): 1795, 1705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.55 (br, 1H), 5.10 (d, J = 4 Hz, 1H), 4.15 (d, J = 4 Hz, 1H), 2.21−2.43 (m, 1H), 1.49 (s, 9H), 1.06 (d, J = 7 Hz, 3H), 1.02 (d, J = 7 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 171.8, 152.6, 81.6, 78.4, 59.9, 31.1, 27.9, 17.9, 17.5; LRMS (NH_3): 230 (MH^+). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.62; H, 8.54; N, 5.93.

(4*S*,5*S*)-*N*-(*tert*-Butyloxycarbonyl)-4-isopropyl-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (6a) was prepared from **6** (229 mg, 1.00 mM) following general procedure E and obtained as a colorless oil after purification by flash column chromatography, using 25% chloroform/petroleum ether as eluant (312 mg, 84%, single diastereomer): $[\alpha]^{20}_D$ +24.2 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): 1735, 1495 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.25−5.47 (m, 1H), 4.69 (br, 1H), 3.80−4.12 (m, 1H), 1.85−2.10 (m, 1H), 1.45 (s, 9H), 1.02 (d, J = 7 Hz, 3H), 0.96 (d, J = 7 Hz, 3H), 0.20 (s, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 153.9, 122.4 (q, J_{C-F} = 288 Hz), 102.1 (q, J_{C-F} = 31 Hz), 81.0, 78.0, 64.9, 27.9, 20.8, 18.6, 18.3, 0.9; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.7; LRMS (NH_3): 389 (MNH_4^+); HRMS: calcd for $C_{15}H_{29}F_3NO_4Si$ (MH^+): 372.1818. Found: 372.1818.

(4*S*)-*N*-(*tert*-Butyloxycarbonyl)-4-isobutyl-1,3-oxazolidin-5-one (7) was prepared from *N*-(*tert*-butyloxycarbonyl)-(*S*)-leucine (2.31 g, 10.0 mM) following general procedure A and obtained as a colorless, slowly solidifying oil after purification by flash column chromatography, using 30% chloroform/petroleum ether as eluant (1.91 g, 79%): $[\alpha]^{20}_D$ +88.5 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): 1790, 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.48 (d, J = 5 Hz, 1H), 5.09 (d, J = 5 Hz, 1H), 4.22

(t, $J = 6$ Hz, 1H), 1.43 (s, 9H), 1.23−1.16 (m, 3H), 0.92 (d, $J = 5$ Hz, 3H), 0.90 (d, $J = 5$ Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 172.9, 152.2, 81.5, 77.8, 53.2, 39.4, 27.9, 24.2, 22.4, 22.2; LRMS (NH_3): 244 (MH^+); HRMS: calcd for $C_{12}H_{22}NO_4$ (MH^+): 244.1549. Found: 244.1549.

(4*S*,5*S*)-*N*-(*tert*-Butyloxycarbonyl)-4-isobutyl-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (7a) was prepared from **7** (243 mg, 1.00 mM) following general procedure E and obtained as a colorless oil after purification by flash column chromatography, using 25% chloroform/petroleum ether as eluant (366 mg, 95%, single diastereomer): $[\alpha]^{20}_D$ +22.2 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): 1735, 1470 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.30−5.40 (m, 1H), 4.70−4.81 (m, 1H), 4.25−4.45 (m, 1H), 1.51−1.73 (m, 3H), 1.46 (s, 9H), 0.97 (d, $J = 6$ Hz, 3H), 0.95 (d, $J = 6$ Hz, 3H), 0.19 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 153.0, 122.0 (q, $J_{C-F} = 288$ Hz), 102.2 (q, $J_{C-F} = 32$ Hz), 81.2, 78.4, 57.9, 37.5, 28.1, 24.4, 22.7, 22.0, 1.0; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.6; LRMS (NH_3): 403 (MNH_4^+), 386 (MH^+); HRMS: calcd for $C_{16}H_{31}F_3NO_4Si$ (MH^+): 386.1974. Found: 386.1974.

(4*R*)-4-[(*S*-Benzylthio)methyl]-*N*-(*tert*-butyloxycarbonyl)-1,3-oxazolidin-5-one (8) was prepared from (S)-[(benzylthio)methyl]-*N*-(*tert*-butyloxycarbonyl)-(*R*)-cysteine (3.11 g, 10.0 mM) following general procedure A and obtained as fine white needles after crystallization from diethyl ether (1.68 g, 52%): $[\alpha]^{20}_D$ +140.0 (*c* 1.0, $CHCl_3$); mp 63−65 °C; IR (KBr): 1800, 1700 cm^{-1}; ^{1}H NMR (500 MHz, $CD_3C_6D_5$, 90 °C): δ 6.81−7.34 (m, 5H), 4.96 (br, d, $J = 4$ Hz, 1H), 4.93 (dd, $J = 1$, 4 Hz, 1H), 3.95 (dd, $J = 3$, 4 Hz, 1H), 3.52 (d, $J = 13$ Hz, 1H), 3.49 (d, $J = 13$ Hz, 1H), 3.03 (dd, $J = 4$, 14 Hz, 1H), 2.71 (dd, $J = 3$, 14 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 171.8, 152.4, 137.6, 129.0, 128.6, 127.3, 82.2, 78.9, 56.4, 37.4, 37.3, 28.3; LRMS (EI): 324 (MH^+). Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.55; N, 4.33. Found: C, 59.25; H, 6.40; N, 4.25.

(4*R*,5*S*)-4-[(S-Benzylthio)methyl]-*N*-(*tert*-butyloxycarbonyl)-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (8a) was prepared from **8** (323 mg, 1.00 mM) following general procedure E and obtained as a colorless oil after purification by flash column chromatography, using 25% chloroform/petroleum ether as eluant (358 mg, 77%, single diastereomer): $[\alpha]^{20}_D$ +25.1 (*c* 1, $CHCl_3$); IR ($CHCl_3$): 1705, 1495 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.20−7.35 (m, 5H), 5.23−5.32 (m, 1H), 4.75−4.87 (m, 1H), 4.47−4.55 (m, 1H), 3.77 (s, 2H), 2.63 (dd, $J = 6$, 14 Hz, 1H), 2.49 (dd, $J = 7$, 14 Hz, 1H), 1.50 (s, 9H), 0.17 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 153.4, 138.0, 129.4, 128.9, 127.5, 122.3 (q, $J_{C-F} = 292$ Hz), 102.4 (q, $J_{C-F} = 32$ Hz), 82.0, 78.9, 59.4, 37.3, 30.5, 28.6, 1.5; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.6; LRMS (EI): 466 (MH^+); HRMS: calcd for $C_{20}H_{30}F_3NO_4SSi$ (MH^+): 466.1711. Found: 466.1695.

Sodium *N*-(*p*-methoxybenzylidene)-(*S*)-alaninate (9) was prepared from (*S*)-alanine (8.90 g, 100 mM) and anisaldehyde (12.0 mL, 100 mM) following general procedure B and obtained as a white solid (22.4 g, 98%): IR (KBr): 3600−3000 br, 1805, 1650 cm^{-1}; ^{1}H NMR (200 MHz, $(D_3C)_2SO$): δ 8.15 (s, 1H), 6.91−7.67 (m, 4H), 3.30−3.90 (m, 4H), 1.26 (d, $J = 7$ Hz, 3H); ^{13}C NMR (50.3 MHz, $(D_3C)_2SO$): δ 176.8, 160.9, 158.6, 130.2, 129.3, 124.4, 72.0, 55.6, 21.4.

Sodium *N*-(*p*-methoxybenzylidene)-(*S*)-phenylalaninate (10) was prepared from (*S*)-phenylalanine (16.5 g, 100 mM) and anisaldehyde (12.0 mL, 100 mM) following general procedure B and obtained as a white solid (30.2 g, 99%): IR (KBr): 3600−3000 br, 1805, 1650 cm^{-1}; ^{1}H NMR (200 MHz, $(D_3C)_2SO$): δ 7.85 (s, 1H), 6.88−7.66 (m, 9H), 3.50−3.79 (m, 4H), 3.24 (dd, $J = 3$, 12 Hz, 1H), 2.95 (dd, $J = 10$, 12 Hz, 1H); ^{13}C NMR (50.3 MHz, $(D_3C)_2SO$): δ 175.0, 160.8, 158.9, 140.7, 129.5, 129.4, 127.8, 125.4, 113.9, 78.6, 55.2, 40.4.

Sodium 2-[*N*-(*p*-methoxybenzylidene)amino]-2-methylpropionate (11) was prepared from (2-amino-2-methyl)-propionate (1.03 g, 10.0 mM) and anisaldehyde (1.20 mL, 10.0 mM) following general procedure B and obtained as a white solid (2.16 g, 89%); IR (KBr): 3500−3000 br, 1610, 1510 cm^{-1}; ^{1}H NMR (200 MHz, $(D_3C)_2SO$): δ 8.27 (s, 1H), 7.62 (d, $J = 7$ Hz, 2H), 6.93 (d, $J = 7$ Hz, 2H), 3.77 (s, 3H), 1.31 (s, 6H); ^{13}C NMR (50.3 MHz, $(D_3C)_2SO$): δ 177.6, 160.6, 155.6, 130.3, 129.1, 113.8, 66.4, 55.2, 28.0.

Sodium *N*-(*p*-methoxybenzylidene)-(*S*)-glycinate (12) was prepared from glycine (0.75 g, 10.0 mM) and anisaldehyde (1.20 mL, 10.0 mM) following general procedure B and obtained as a white solid (1.72 g, 80%); IR (KBr): 3500−3000br, 1600, 1595 cm^{-1}; ^{1}H NMR (200 MHz, $(D_3C)_2SO$): δ 8.07 (s, 1H), 7.65 (d, $J = 7$ Hz, 2H), 6.96 (d, $J = 7$ Hz, 2H), 3.78 (s, 2H), 3.38 (s, 3H); **12** was only poorly soluble in $(D_3C)_2SO$, and a ^{13}C NMR spectrum could not be obtained.

Sodium *N*-(*p*-methoxybenzylidene)-(*S*)-valinate (13) was prepared from (*S*)-valine (1.17 g, 10.0 mM) and anisaldehyde (1.20 mL, 10.0 mM) following general procedure B and obtained as a white solid (2.49 g, 97%); IR (KBr): 3500−3000 br, 1805, 1650, 1605 cm^{-1}; ^{1}H NMR (200 MHz, $(D_3C)_2SO$): δ 8.10 (s, 1H), 7.72 (d, $J = 8$ Hz, 2H), 6.96 (d, $J = 8$ Hz, 2H), 3.78 (s, 3H), 3.24−3.48 (m, 1H), 2.20−2.24 (m, 1H), 0.85 (d, $J = 6$ Hz, 3H), 0.78 (d, $J = 6$ Hz, 3H); ^{13}C NMR (50.3 MHz, $(D_3C)_2SO$): δ 176.8, 160.9, 158.6, 129.6, 129.4, 113.9, 84.6, 55.3, 31.2, 20.4, 19.2.

(2*S*,4*S*)-*N*-(Benzyloxycarbonyl)-2-(4′-methoxyphenyl)-4-methyl-1,3-oxazolidin-5-one (14) was prepared from **9** (2.29 g, 10.0 mM) and benzyl chloroformate (1.43 mL, 10.0 mM) following general procedure C and obtained as a white solid after purification by flash column chromatography, using 33% ethyl acetate/petroleum ether as eluant (1.75 g, 51%, single diastereomer): $[\alpha]^{20}_D$ +99.9 (*c* 1.0, $CHCl_3$); mp 97−99 °C; IR (KBr): 1790, 1695 cm^{-1}; ^{1}H NMR (500 MHz, $CD_3C_6D_5$, 90 °C): δ 6.56−7.06 (m, 9H), 6.11 (s, 1H), 4.82 (d, $J = 12$ Hz, 1H), 4.72 (d, $J = 12$ Hz, 1H), 4.13 (q, $J = 7$ Hz, 1H), 3.35 (s, 3H), 1.47 (d, $J = 7$ Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 172.3, 160.8, 152.0, 135.2, 128.4, 128.0, 127.7, 125.8, 121.3, 114.1, 89.2, 67.5, 55.3, 52.1, 16.5; LRMS (NH_3): 342 (MH^+). Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.80; H, 5.42; N, 4.15.

(2*S*,4*S*,5*S*)-*N*-(Benzyloxycarbonyl)-2-(4′-methoxyphenyl)-4-methyl-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (14a) was prepared from **14** (341 mg, 1.00 mM) following general procedure F and obtained as a colorless oil after purification by flash column chromatography, using 25% diethyl ether/petroleum ether as eluant (444 mg, 92%, mixture of diastereomers in a ratio of 10:1 by ^{19}F and ^{1}H NMR analysis): IR ($CHCl_3$): 1705, 1615, 1500 cm^{-1}; major diastereomer: ^{1}H NMR (500 MHz, $CD_3C_6D_5$, 90 °C): δ 6.61−7.20 (m, 9H), 6.22 (s, 1H), 4.88 (d, $J = 12$ Hz, 1H), 4.75 (d, $J = 12$ Hz, 1H), 4.47 (q, $J = 7$ Hz, 1H), 3.36 (s, 3H), 1.50 (d, $J = 7$ Hz, 3H), 0.19 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 160.1, 153.5, 135.9, 128.5, 128.2, 127.5, 123.5 (q, $J_{C-F} = 286$ Hz), 113.6, 101.6 (q, $J_{C-F} = 32$ Hz), 90.2, 67.1, 55.9, 55.2, 14.6, 1.1; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.1; LRMS (NH_3): 501 (MNH_4^+); HRMS: calcd for $C_{23}H_{29}F_3NO_5Si$ (MH^+): 484.1767. Found: 484.1767.

(2*S*,4*S*,5*RS*)-*N*-(Benzyloxycarbonyl)-5-hydroxy-2-(4′-methoxyphenyl)-4-methyl-5-(trifluoromethyl)-1,3-oxazolidine (14b) was obtained from **14a** (483 mg, 1.00 mM) and TBAF (1.1 mL of a 1M solution, 1.1 mM) following general procedure G as a yellow oil and directly used without purification for the preparation of **14c**.

(3*S*)-3-Amino-*N*-(benzyloxycarbonyl)-1,1,1-trifluorobutan-2-one (14c) was prepared following general procedure H and obtained as fine white needles after purification by preparative thin-layer chromatography, using 25% ethyl acetate/petroleum ether as eluant (116 mg, 42% from **14a**). **14c** was obtained as a mixture of ketone and hydrate in a ratio of 3:1 by ^{19}F NMR (235.19 MHz, $CDCl_3$): IR (KBr): 3500−3000, 1770, 1685 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.37−7.42 (m, 5H), 5.11−5.15 (m, 2 × 2H, ketone and hydrate), 4.86 (qui, $J = 7$ Hz, 1H, ketone), 3.99 (qui, $J = 7$ Hz, 1H, hydrate), 1.48 (d, $J = 7$ Hz, 3H, ketone), 1.37 (d, $J = 7$ Hz, 3H, hydrate); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 190.1 (q, $J_{C-F} = 35$ Hz), 158.5, 155.3, 135.7, 135.4, 128.6, 128.5, 128.4, 128.2, 123.1 (q, $J_{C-F} = 293$ Hz), 95.2 (m), 67.4, 67.9, 51.8, 51.6, 18.9, 16.5; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −76.4, −82.2; LRMS (Scan AP$^+$): 298 ($M^+ + Na$); HRMS: calcd for $C_{12}H_{13}F_3NO_3$ (MH^+): 276.085. Found: 276.085.

(*RS*)-3-Amino-2,2-dihydroxy-1,1,1-trifluorobutane hydrochloride salt (14d) was prepared from **14c** (22 mg, 0.08 mM), palladium on carbon (8 mg), ethanol (5 mL), and hydrochloric acid (0.01 mL of a 1 M solution, 0.01 mM) following general procedure I and obtained as an off-white solid: IR (KBr): 3500−3000br, 1595m, 1495 cm^{-1}; ^1H NMR (500 MHz, D_2O): δ 3.66 (q, J = 7 Hz, 1H), 1.35 (d, J = 7 Hz, 3H); ^{13}C NMR (125.7 MHz, D_2O): δ 122.9 (q, J_{C-F} = 288 Hz), 92.2 (q, J_{C-F} = 32 Hz), 51.1, 12.6; ^{19}F NMR (235.19 MHz, D_2O): δ −82.2.

(2*S*,4*S*)-4-Benzyl-*N*-(benzyloxycarbonyl)-2-(4′-methoxyphenyl)-1,3-oxazolidin-5-one (15)[37] was prepared from **10** (3.05 g, 10.0 mM) and benzyl chloroformate (1.43 mL, 10.0 mM) following general procedure C and obtained as a white solid after crystallization from diethyl ether (2.87 g, 69%): $[\alpha]^{20}_D$ +50.1 (*c* 1.0, $CHCl_3$); mp 85 °C; IR (KBr): 1795, 1700 cm^{-1}; ^1H NMR (500 MHz, $CD_3C_6D_5$, 90 °C): δ 6.49−7.08 (m, 14H), 6.04 (s, 1H), 4.92 (d, J = 12 Hz, 1H), 4.83 (d, J = 12 Hz, 1H), 4.19 (dd, J = 4, 6 Hz, 1H), 3.39 (s, 3H), 3.25 (dd, J = 6, 14 Hz, 1H), 3.08 (dd, J = 4, 14 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 171.4, 160.3, 151.5, 135.3, 129.2, 128.8, 128.5, 128.2, 127.3, 113.4, 89.3, 67.8, 58.4, 55.3, 34.5; LRMS (EI): 418 (MH^+). Anal. Calcd for $C_{25}H_{23}NO_5$: C, 71.93; H, 5.55; N, 3.35. Found: C, 72.22; H, 5.36; N, 3.28.

(2*S*,4*S*,5*S*)-4-Benzyl-*N*-(benzyloxycarbonyl)-2-(4′-methoxyphenyl)-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (15a) was prepared from **15** (417 mg, 1.00 mM) following general procedure F and obtained as a colorless, waxy solid after purification by flash column chromatography, using 25% diethyl ether/petroleum ether as eluant (509 mg, 91%, single diastereomer): $[\alpha]^{20}_D$ −155.0 (*c* 2.0, $CHCl_3$); mp 41−42 °C; IR ($CHCl_3$): 1710, 1500 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.97−7.44 (m, 14H), 6.33 (s, 1H), 5.07 (d, J = 12 Hz, 1H), 4.91 (d, J = 12 Hz, 1H), 4.68−4.72 (m, 1H), 3.88 (s, 3H), 3.16 (dd, J = 7, 13 Hz, 1H), 2.80−2.85 (m, 1H), 0.21 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 160.1, 154.1, 137.4, 135.7, 130.7, 129.3, 128.3, 128.0, 127.7, 126.3, 122.1 (q, J_{C-F} = 290 Hz), 113.7, 102.0 (q, J_{C-F} = 33 Hz), 90.3, 67.5, 61.1, 55.2, 36.6, 1.2; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.1; LRMS (EI): 560 (MH^+). Anal. Calcd for $C_{29}H_{32}F_3NO_5Si$: C, 62.24; H, 5.76; N, 2.50. Found: C, 61.99; H, 5.68; N, 2.46.

(2*S*,4*S*,5*R* or 5*S*)-4-Benzyl-*N*-(benzyloxycarbonyl)-5-hydroxy-2-(4′-methoxyphenyl)-5-(trifluoromethyl)-1,3-oxazolidine (15b) was prepared from **15a** (2.50 g, 4.47 mM) and TBAF (4.50 mL of a 1 M solution, 4.50 mM) following general procedure G (2.11 g, ca. 97%, **15b** was unstable and contaminated with variable amounts of anisaldehyde): ^1H NMR (500 MHz, $CDCl_3$): δ 7.18−7.34 (m, 12H), 6.91−6.94 (m, 2H), 6.90 (s, 1H), 5.10 (s, 2H), 4.71 (t, J = 7 Hz, 1H), 4.20−4.24 (br, 1H), 3.84 (s, 3H), 3.17 (dd, J = 7 and 14 Hz, 1H), 2.86−2.91 (m, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 159.6, 154.0, 136.9, 135.5, 131.0, 129.6, 128.4, 128.1, 127.9, 127.8, 126.4, 122.5 (q, J_{C-F} = 288), 113.7, 101.0 (q, J_{C-F} = 33 Hz), 90.4, 67.8, 60.7, 55.3, 35.8; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.6 (CF_3); LRMS (NH3): 505 (MNH_4^+), 488 (MH^+); HRMS: calcd for $C_{26}H_{25}F_3NO_5$ (MH^+): 488.1685. Found: 488.1685.

(*S*)-3-Amino-2,2-dihydroxy-4-phenyl-1,1,1-trifluorobutane hydrochloride salt 15d was prepared from **15c**[38] (130 mg, 0.37 mM), Pd−C catalyst (30 mg), ethanol (5 mL), and hydrochloric acid (0.37 mL of a 1 M solution, 0.37 mM) following general procedure I and obtained as a pale yellow solid (90 mg, 90%): $[\alpha]^{20}_D$ = −37.0 (*c* 1.0, 1.0 M HCl); IR (KBr): 3500−3000br, 1595m, 1495s cm^{-1}; ^1H NMR (500 MHz, D_2O): δ 7.34−7.44 (m, 5H), 3.83 (dd, J = 3, 11 Hz, 1H), 3.39 (dd, J = 3, 14 Hz, 1H), 2.86 (dd, J = 11, 14 Hz, 1H); ^{13}C NMR (125.7 MHz, D_2O): δ 135.2, 130.0, 129.9, 128.4, 123.2 (q, J_{C-F} = 291 Hz), 92.4 (q, J_{C-F} = 32 Hz), 57.4, 33.3; ^{19}F NMR (235.19 MHz, D_2O): −81.7; LRMS (EI): 218 (free amine).

(2*S*,4*S*)-*N*-(Benzyloxycarbonyl)-4-isopropyl-2-(4′-methoxyphenyl)-1,3-oxazolidin-5-one (16) was prepared from **13** (2.57 g, 10.0 mmol) and benzyl chloroformate (1.42 mL, 10.0 mmol) following general procedure C and obtained as a colorless oil after purification by flash column chromatography, using 25% ethyl acetate/petroleum ether (30−40) as eluant (2.03 g, 55%, mixture of two diastereomers in a ratio of 10:1): IR ($CHCl_3$): 1795, 1715 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.92−7.41 (m, 9H), 6.87 (s, 1H), 5.24 (s, 2H), 4.26 (d, J = 6 Hz, 1H), 3.82 (s, 3H), 1.15−1.35 (m, 1H), 0.94 (d, J = 6 Hz, 3H), 0.98 (d, J = 6 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 171.2, 160.2, 155.1, 135.3, 128.7, 128.6, 128.0, 127.4, 113.8, 88.4, 68.3, 61.6, 55.3, 31.5, 19.1, 18.4; LRMS (NH_3): 370 (MH^+); HRMS: calcd for $C_{21}H_{24}NO_5$ (MH^+): 370.1654. Found: 370.1654.

(2*S*,4*S*,5*R*)- and (2*S*,4*S*,5*S*)-*N*-(Benzyloxycarbonyl)-4-isopropyl-2-(4′-methoxyphenyl)-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (16a) was prepared from **16** (369 mg, 1.00 mM) following general procedure F and obtained as a colorless oil after purification by flash column chromatography, using 25% diethyl ether/petroleum ether as eluant (439 mg, 86%, mixture of diastereomers in a ratio of 10:1): IR ($CHCl_3$): 1710, 1615 cm^{-1}; NMR data for major diastereomer: ^1H NMR (500 MHz, $CDCl_3$): δ 6.87−7.34 (m, 9H), 6.89 (s, 1H), 5.15−5.20 (m, 2H), 4.04 (d, J = 8 Hz, 1H), 3.83 (s, 3H), 1.91−1.98 (m, 1H), 1.05 (d, J = 6 Hz, 3H), 0.87−0.97 (m, 3H), 0.18 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 159.9, 155.1, 135.6, 130.7, 128.5, 128.1, 128.0, 127.7, 122.9 (q, J_{C-F} = 286 Hz), 113.5, 102.3 (q, J_{C-F} = 32 Hz), 90.2, 67.6, 64.2, 55.2, 28.8, 20.6, 19.5, 1.2; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.6; LRMS (Scan AP$^+$): 512 (MH^+); HRMS: calcd for $C_{25}H_{33}F_3NO_5Si$ (MH^+): 512.208. Found: 512.208.

(*RS*)-3-Amino-2,2-dihydroxy-4-methyl-1,1,1-trifluoropentane hydrochloride salt 16d was prepared without isolation of the intermediates from **16a** (512 mg, 1.0 mM) with desilylation carried out following general procedure G using TBAF (1.1 mL of a 1 M solution, 1.1 mM). The crude product of this reaction was taken up in CH_3CN (50 mL), and hydrolysis was achieved according to general procedure H. After removal of solvents of in vacuo, the residue (ca. 475 mg) was taken up in ethanol (15 mL), and hydrogenolysis was carried out following general procedure I with palladium on carbon (150 mg) and hydrochloric acid (1.10 mL of a 1 M solution, 1.10 mM). Concentration of solvents in vacuo gave a brownish gumlike substance which was taken up in water and extracted with ethyl acetate (25 mL). The aqueous layer was concentrated in vacuo and **16d** obtained as a pale yellow solid after trituration with diethyl ether/chloroform (90 mg, 40% from **16a**): IR (KBr): 3500−2800br, 1595, 1495; ^1H NMR (500 MHz, D_2O): δ 3.40−3.41 (d, J = 3.5 Hz, 1H), 2.34−2.40 (m, 1H), 1.09 (d, J = 7 Hz, 3H), 1.04 (d, J = 7 Hz, 3H); ^{13}C NMR (125.7 MHz, D_2O): δ 122.4 (q, J_{C-F} = 288 Hz), 92.4 (q, J_{C-F} = 32 Hz), 59.6, 25.6, 20.3, 15.8; ^{19}F NMR (235.19 MHz, D_2O): δ −82.5.

(2*S*,4*S*)-*N*-Benzoyl-4-benzyl-2-(4′-methoxyphenyl)-1,3-oxazolidin-5-one (17) was prepared from **10** (3.05 g, 10.0 mM) and benzoyl chloride (1.16 mL, 10.0 mM) following general procedure D and obtained as a white solid after crystallization from diethyl ether (1.62 g, 42%, single diastereomer): $[\alpha]^{20}_D$ +300.1 (*c* 1.0, $CHCl_3$); mp 130−132 °C; IR (KBr): 1800, 1650, 1615 cm^{-1}; ^1H NMR (500 MHz, $CD_3C_6D_5$, 90 °C): δ 6.37−7.24 (m, 14H), 5.58 (s, 1H), 4.91 (dd, J = 2, 6 Hz, 1H), 3.55 (s, 3H), 3.30−3.55 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 173.5, 171.4, 160.4, 135.4, 129.9, 128.9, 128.5, 128.1, 127.7, 126.6, 113.9, 91.2, 57.5, 55.2, 34.5; LRMS (NH_3): 388 (MH^+); HRMS: calcd for $C_{24}H_{22}NO_4$ (MH^+): 388.1549. Found: 388.1549.

(2*S*,4*S*)-*N*-Benzoyl-2-(4′-methoxyphenyl)-4-methyl-1,3-oxazolidin-5-one (18) was prepared from **9** (2.29 g, 10.0 mM) and benzoyl chloride (1.16 mL, 10.0 mM) following general procedure D and obtained as a white solid after purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant (2.15 g, 69%, mixture of two diastereomers in a ratio of 3:1 by ^1H NMR). After crystallization from diethyl ether **18** was obtained as very fine white needles and as a single diastereomer by ^1H NMR: $[\alpha]^{20}_D$ +78.2 (*c* 1.0, $CHCl_3$); mp 145−147 °C; IR (KBr): 1795, 1735, 1650 cm^{-1}; ^1H NMR (500 MHz, $CD_3C_6D_5$, 90 °C): δ 6.80−7.21 (m,

(37) The assignment of the stereochemistry is based on a single-crystal X-ray analysis the details of which will be published elsewhere.

5H), 6.51−6.53 (m, 4H), 6.43 (s, 1H), 4.44 (q, J = 7 Hz, 1H), 3.29 (s, 3H), 1.25 (d, J = 7 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 172.5, 170.5, 160.6, 135.2, 130.9, 128.0, 127.6, 126.9, 126.8, 114.0, 90.3, 55.3, 52.7, 18.4; LRMS (NH_3): 312 (MH^+). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.45; H: 5.50; N, 4.50. Found: C, 69.18; H, 5.55; N, 4.38.

(2*S*,4*S*,5*S*)- and (2*S*,4*S*,5*R*)-*N*-Benzoyl-2-(4′-methoxyphenyl)-4-methyl-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (18a) were prepared from **18** (311 mg, 1.00 mM) following general procedure F and obtained as a colorless oil after purification by flash column chromatography, using 25% diethyl ether/petroleum ether as eluant (425 mg, 94%, mixture of two diastereomers in a ratio of 1.5:1 by ^{1}H and ^{19}F NMR analysis): IR ($CHCl_3$): 1650, 1495 cm^{-1}; ^{1}H NMR (500 MHz, $CD_3C_6D_5$, 90 °C): δ 6.41−7.23 (m, 10H), 4.81 (q, J = 6 Hz, 1H, minor diastereomer), 4.66 (q, J = 7 Hz, 1H, major diastereomer), 3.36 (s, 3H, major diastereomer), 3.28 (s, 3H, minor diastereomer), 1.34 (d, J = 6 Hz, 3H, minor diastereomer), 1.27 (d, J = 7 Hz, 3H, major diastereomer), 0.24 (s, 9H, minor diastereomer), 0.07 (s, 9H, major diastereomer); ^{13}C NMR (125.7 MHz, $CDCl_3$, all signals were very broad): δ 170.5, 159.9, 135.6, 130.1, 128.7, 128.5, 127.9, 127.1, 126.3, 122.8 (q, J_{C-F} = 290 Hz), 102.2 (q, J_{C-F} = 33 Hz), 90.2, 55.3, 16.2, 1.1; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.0, −86.0; LRMS (EI): 454 (MH^+); HRMS calcd for $C_{22}H_{27}F_3NO_4Si$: 454.1661. Found: 454.1661.

(2*S*,4*S*,5*RS*)-*N*-Benzoyl-5-hydroxy-2-(4′-methoxyphenyl)-4-methyl-5-(trifluoromethyl)-1,3-oxazolidine (18b) was prepared from **18a** (300 mg, 0.66 mM) and TBAF (0.66 mL of a 1 M solution, 0.66 mM) following general procedure G and directly used without purification for the preparation of **18c**.

(3*S*)-3-Amino-*N*-benzoyl-1,1,1-trifluorobutan-2-one (18c) was prepared from **18b** following general procedure H and obtained as colorless crystals after purification by preparative thin-layer chromatography, using 50% petrol/diethyl ether as eluant (100 mg, ca. 62% from **18a**) as a mixture of ketone and hydrate in a ratio of 2:1 by ^{19}F NMR (235.19 MHz, $CDCl_3$). The assignment of NMR signals to ketone or hydrate is based on this ratio and the integrals in the ^{1}H NMR spectrum: mp 115 °C; IR: 3400−3000, 1625 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2CO$): δ 7.69−7.80 (m, 2H), 7.37−7.54 (m, 3H), 6.95 (d, br, J = 7 Hz, 1H, hydrate), 6.85 (d, br, J = 7 Hz, 1H, ketone), 5.18 (qui, J = 7 Hz, 1H, hydrate), 4.22 (qui, J = 7 Hz, 1H, ketone), 1.56 (d, J = 7 Hz, 3H, ketone), 1.47 (d, J = 7 Hz, 3H, hydrate); ^{13}C NMR (125.7 MHz, $(CD_3)_2CO$): δ 192.0 (m), 170.4, 167.1, 132.3, 132.1, 128.6, 127.6, 127.3, 127.1, 123.3, 122.6 (q, J_{C-F} = 291 Hz), 122.4, 116.8 (q, J_{C-F} = 292 Hz), 94.8 (q, J_{C-F} = 32 Hz), 51.5, 50.4, 16.4, 14.8; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −76.4, −82.2; LRMS (EI): 246 (MH^+); HRMS calcd for $C_{11}H_{11}F_3NO_2$: 246.0742. Found: 246.0742.

(*RS*)-*N*-Benzoyl-2-(4′-methoxyphenyl)-1,3-oxazolidin-5-one (19) was prepared from **12** (2.15 g, 10.0 mM) and benzoyl chloride (1.16 mL, 10.0 mM) following general procedure D and obtained as a white solid after purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant (2.08 g, 70%): mp 130−132 °C; IR (KBr): 1795, 1635 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.84−7.55 (m, 10H), 4.35 (br, 2H), 3.78 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 169.4, 169.3, 160.6, 133.6, 131.6, 128.6, 128.3, 127.7, 127.5, 114.3, 89.9, 55.4, 46.7; LRMS (EI): 298 (MH^+). Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.62; H, 5.01; N, 4.57.

(*RS*)-*N*-Benzoyl-2-(4′-methoxyphenyl)-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (19a) was prepared from **19** (297 mg, 1.00 mM) following general procedure F. Analysis of the crude reaction mixture indicated that partial desilylation and hydrolysis had already occurred. A further 1 eq of TBAF-sol. in THF was added to complete desilylation and the product **19b** was immediately taken over to the next step.

3-Amino-*N*-benzoyl-1,1,1-trifluoropropan-2-one hydrate (19c) was prepared following general procedure H and obtained as a white solid after purification by preparative thin-layer chromatography, using 25% ethyl acetate/petroleum ether (105 mg, 42% from **19a**): mp 115−116 °C (from diethyl ether/petrol); IR: 3500−3000, 1625 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2CO$): δ 8.44 (br, 1H), 7.48−7.98 (m, 5H), 3.79 (d, J = 6 Hz, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 171.5, 134.0, 132.9, 129.4, 128.4, 124.6 (q, J_{C-F} = 294 Hz), 94.4 (q, J_{C-F} = 288 Hz), 46.0; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.6; LRMS (EI): 232 (MH^+ for ketone); HRMS calcd for $C_{10}H_9F_3NO_2$ (MH^+ for ketone): 232.0585. Found: 232.0585.

(*RS*)-*N*-Benzoyl-4,4-dimethyl-2-(4′-methoxyphenyl)-1,3-oxazolidin-5-one (20) was prepared from **11** (2.43 g, 10.0 mM) and benzoyl chloride (1.16 mL, 10.0 mM) following general procedure D and obtained as a white solid after purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant (1.71 g, 52%): mp 82−83 °C; IR (KBr): 1800, 1650 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.10−7.29 (m, 6H), 6.63−6.71 (m, 4H), 3.69 (s, 3H), 1.88 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 172.5, 169.5, 160.5, 136.4, 130.0, 128.4, 128.2, 128.1, 126.2, 113.9, 89.2, 59.7, 55.2, 25.2, 23.8; LRMS (EI): 326 (MH^+). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.88; N, 4.30. Found: C, 69.94; H, 6.08; N, 4.64.

***N*-Benzoyl-4,4-dimethyl-2-(4′-methoxyphenyl)-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (20a)** was prepared from **20** (325 mg, 1.00 mM) following general procedure F and obtained as a colorless oil after purification by flash column chromatography, using 15% ethyl acetate/petroleum ether as eluant (336 mg, 72%, single diastereomer): mp 120−123 °C; IR (KBr): 1650, 1495 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.65−7.85 (m, 9H), 6.19 (s, 1H), 3.79 (s, 3H), 1.62 (s, 6H), 0.18 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 169.6, 160.0, 137.5, 132.0, 129.7, 128.1, 126.4, 122.1 (q, J_{C-F} = 293 Hz), 113.5, 103.8 (q, J_{C-F} = 31 Hz), 90.5, 65.1, 55.2, 23.1, 20.3, 1.2; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −77.7; LRMS (NH_3): 468 (MH^+); HRMS: calcd for $C_{23}H_{29}F_3NO_4Si$ (MH^+): 468.1818. Found: 468.1818.

***N*-Benzoyl-4,4-dimethyl-5-hydroxy-2-(4′-methoxyphenyl)-5-(trifluoromethyl)-1,3-oxazolidine (20b)** was prepared from **20a** (467 mg, 1.00 mM) following general procedure G and directly taken over to the next step.

3-Amino-*N*-benzoyl-3-methyl-1,1,1-trifluorobutan-2-one (20c) was prepared from **20b** following general procedure H and obtained as colorless prisms after crystallization from diethyl ether/petroleum (176 mg, 68% from **20a**) as a mixture of ketone and hydrate in a ratio of 10:1 by ^{19}F NMR (235.19 MHz, $CDCl_3$): mp 178−180 °C: IR (KBr): 3300−3100, 1730, 1630 cm^{-1}; NMR data for ketone: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45−7.78 (m, 5H), 6.49 (s, 1H), 1.66 (s, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 189.9 (q, J_{C-F} = 32 Hz), 167.6, 136.3, 128.5, 116.2 (q, J_{C-F} = 294 Hz), 113.9, 58.9, 24.1, 23.7; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −73.0; LRMS (EI): 260 (MH^+). Anal. Calcd for $C_{12}H_{12}F_3NO_2$: C, 55.60; H, 4.66; N, 5.40. Found: C, 55.46; H, 4.72; N, 5.41.

(*RS*)-4,4-Dimethyl-2-(4′-methoxyphenyl)-*N*-(phenoxyacetyl)-1,3-oxazolidin-5-one (23) was prepared from **11** (2.43 g, 10.0 mM) and phenoxyacetyl chloride (1.37 mL, 10.0 mM) following general procedure D and obtained as a white solid after purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant (2.10 g, 59%): mp 78−82 °C; IR (KBr): 1795, 1680 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.21−7.40 (m, 5H), 6.77−7.03 (m, 4H), 6.71 (s, 1H), 4.10−4.15 (m, 2H), 3.83 (s, 3H), 1.92 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 174.6, 166.4, 161.4, 157.0, 129.7, 128.6, 127.3, 122.0, 114.6, 114.3, 88.5, 68.2, 60.4, 55.4, 24.3, 22.6; LRMS (EI): 356 (MH^+). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.45; H, 5.91; N, 3.94.

4,4-Dimethyl-2-(4′-methoxyphenyl)-*N*-(phenoxyacetyl)-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (23a) was prepared from **23** (355 mg, 1.00 mM) following general procedure F and obtained as a white solid after purification by flash column chromatography, using 25% ethyl acetate/petroleum ether as eluant (372 mg, 75%, single diastereomer): mp 89−92 °C; IR (KBr): 1650, 1515, 1495 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.39−7.48 (m, 9H), 6.29 (s, 1H), 3.90−4.14 (m, 2H), 3.84 (s, 3H), 1.67 (s, 3H), 1.66 (s, 3H), 0.15 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 166.7, 160.8, 157.3, 129.5, 129.1, 128.9, 122.8 (q, J_{C-F} = 290 Hz), 121.6, 114.2,

103.4 (q, J_{C-F} = 30 Hz), 89.1, 68.4, 66.1, 55.3, 22.9, 19.9, 1.2; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −77.7; LRMS (NH_3): 498 (MH^+). Anal. Calcd for $C_{24}H_{30}F_3NO_5Si$: C, 57.93; H, 6.08; N, 2.82. Found: C, 58.07; H, 5.91; N, 2.91.

4,4-Dimethyl-5-hydroxy-2-(4′-methoxyphenyl)-*N*-(phenoxyacetyl)-5-(trifluoromethyl)-1,3-oxazolidine (23b) was prepared from **23a** (497 mg, 1.00 mM) following general procedure G and directly taken over to the next step.

3-Amino-3-methyl-*N*-(phenoxyacetyl)-1,1,1-trifluorobutan-2-one (23c) was prepared from **23b** following general procedure H and obtained as colorless prisms after crystallization from diethyl ether/petroleum (101 mg, 35% from **23a**), mixture of ketone and hydrate in a ratio of 11:1 by ^{19}F NMR (235.19 MHz, $CDCl_3$): mp 116−118 °C; IR ($CHCl_3$): 3200−3000br, 1750, 1650, 1600; NMR data for ketone: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92−7.36 (m, 6H), 4.50 (s, 2H), 1.60 (s, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 189.9 (q, J_{C-F} = 33 Hz), 168.4, 156.7, 129.9, 116.1 (q, J_{C-F} = 293 Hz), 114.7, 66.9, 58.5, 24.0; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −72.9; LRMS (EI): 290 (MH^+); HRMS: calcd for $C_{13}H_{15}F_3NO_3$ (MH^+): 290.1004. Found: 290.1004.

(2*S*,4*S*)-*N*-Acetyl-4-benzyl-2-(4′-methoxyphenyl)-1,3-oxazolidin-5-one (24) was prepared from **10** (3.05 g, 10.0 mM) and acetyl chloride (0.71 mL, 10.0 mM) following general procedure D and obtained as a slowly crystallizing oil after purification, using 50% ethyl acetate/petroleum ether (30−40) as eluant (1.60 g, 49%, mixture of two diastereomers in a ratio of 3:1). Data for major diastereomer only: $[\alpha]^{20}_D$ = +200.5 (*c* 1.0, $CHCl_3$); mp 83 °C; IR (KBr): 3030, 1805, 1650 cm^{-1}; ^{1}H NMR (500 MHz, $C_6D_5CD_3$): δ 6.48−7.26 (m, 9H), 5.24 (s, 1H), 4.73−4.75 (m, 1H), 3.91 (dd, *J* = 6.5 and 13.5 Hz, 1H), 3.18 (s, 3H), 3.20 (dd, *J* = 1.5 and 13.5 Hz, 1H), 1.29 (s, br, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 171.1, 168.5, 161.3, 135.0, 129.2, 128.4, 127.5, 114.6, 90.5, 58.6, 55.4, 34.1, 23.5; LRMS (EI): 326 (MH^+). Anal. Calcd for $C_{19}H_{19}NO_4$: C: 70.14, H: 5.89, N: 4.30%. Found: C: 70.14, H: 5.63, N: 4.04%.

(2*S*,4*S*)-*N*-Acetyl-2-(4′-methoxyphenyl)-4-methyl-1,3-oxazolidin-5-one (25) was prepared from **9** (2.29 g, 10.0 mM) and acetyl chloride (0.71 mL, 10.0 mM) following general procedure D and obtained as colorless crystals after purification by flash column chromatography, using 20% ethyl acetate/petroleum ether (30−40) as eluant (1.15 g, 46%, mixture of two inseparable diastereomers in a ratio of 5:1 by ^{1}H NMR); mp 136−138 °C; IR (KBr): 1785, 1660, 1515 cm^{-1}; NMR spectroscopic data for major diastereomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.94−7.28 (m, 4H), 6.51 (s, 1H), 4.71 (q, *J* = 7 Hz, 1H), 3.83 (s, 3H), 1.71 (br, 2 × 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 172.2, 168.1, 161.2, 131.9, 129.7, 114.2, 89.8, 55.3, 52.5, 23.2, 16.4; LRMS (NH_3): 250 (MH^+). Anal. Calcd for $C_{13}H_{15}NO_4$: C: 62.64, H: 6.07, N: 5.62%. Found: C: 62.84, H: 6.08, N: 5.55%.

(2*S*,4*S*)-4-Benzyl-*N*-(benzyloxycarbonyl)-2-*tert*-butyl-1,3-oxazolidin-5-one (26) was prepared from sodium *N*-(*tert*-butylidene)-(*S*)-phenylalaninate[29] (2.55 g, 10.0 mM) and benzyl chloroformate (1.43 mL, 10.0 mM) following general procedure C and obtained as a colorless oil, after purification by flash column chromatography, using 25% diethyl ether/petroleum ether as eluant (2.08 g, 57%, single diastereomer): $[\alpha]^{20}_D$ −3.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 1795, 1725 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26−7.43 (m, 10H), 5.59 (s, 1H), 5.17 (d, *J* = 12 Hz, 1H), 4.95 (d, *J* = 12 Hz, 1H), 4.51 (dd, *J* = 6, 7 Hz, 1H), 3.25 (dd, *J* = 7, 12 Hz, 1H), 3.15 (dd, *J* = 6, 12 Hz, 1H), 1.04 (s, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 171.9, 155.8, 136.7, 135.1, 129.4, 128.9, 126.9, 128.5, 128.4, 96.1, 68.2, 58.8, 39.2, 36.9, 24.8; LRMS (NH_3): 385 (MNH_4^+), 368 (MH^+); HRMS: calcd for $C_{22}H_{26}NO_4$ (MH^+): 368.1862. Found: 368.1862.

(2*S*,4*S*,5*S*)-4-Benzyl-*N*-(benzyloxycarbonyl)-2-*tert*-butyl-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (26a) was prepared from **26** (367 mg, 1.00 mM) following general procedure E and obtained as a colorless oil after purification by flash column chromatography, using 25% diethyl ether/petroleum ether as eluant (407 mg, 80%, single diastereomer): $[\alpha]^{20}_D$ −5.1 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): 1715 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19−7.37 (m, 10H), 5.19 (s, 1H), 5.07−5.09 (m, 1H), 5.06 (d, *J* = 12 Hz, 1H), 4.57 (dd, *J* = 6, 7 Hz, 1H), 3.15 (dd, *J* = 7, 14 Hz, 1H), 2.84 (dd, *J* = 6, 14 Hz, 1H), 1.05 (s, 9H), 0.26 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 156.1, 138.3, 135.7, 129.2, 128.4, 128.1, 128.0, 126.2, 122.9 (q, J_{C-F} = 290 Hz), 101.1 (q, J_{C-F} = 32 Hz), 97.9, 67.7, 62.7, 36.8, 36.5, 25.9, 1.35; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.4; LRMS (NH_3): 510 (MH^+); HRMS: calcd for $C_{26}H_{35}F_3NO_4Si$ (MH^+): 510.229. Found: 510.229.

(2*S*,4*S*,5*S*)-*N*-Benzoyl-4-benzyl-2-*tert*-butyl-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (27a) was prepared from (2S,4*S*)-*N*-benzoyl-4-benzyl-2-*tert*-butyl-1,3-oxazolidin-5-one **27**[29] (337 mg, 1.00 mM) following general procedure E and obtained as a colorless oil after purification by flash column chromatography, using 25% diethyl ether/petroleum ether as eluant (340 mg, 71%, single diastereomer): $[\alpha]^{20}_D$ −33.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 1665, 1600 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09−7.51 (m, 8H), 6.70−6.81 (m, 2H), 5.69 (s, 1H), 4.24 (dd, *J* = 2, 6 Hz, 1H), 3.35 (dd, *J* = 6, 7 Hz, 1H), 2.93 (dd, *J* = 2, 7 Hz, 1H), 1.12 (s, 9H), 0.21 (s, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 174.8, 137.0, 130.4, 129.1, 128.7, 128.4, 126.8, 126.6, 126.5, 121.5 (q, J_{C-F} = 292 Hz), 100.7 (q, J_{C-F} = 32 Hz), 96.6, 63.3, 37.9, 26.0, 14.0, 1.2; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −85.7; LRMS (NH_3): 480 (MH^+). Anal. Calcd for $C_{25}H_{32}F_3NO_3Si$: C: 62.61, H: 6.72, N: 2.92%. Found: C: 62.52, H: 6.44, N: 2.92%.

(3*S*)-3-Amino-*N*-benzoyl-4-phenyl-1,1,1-trifluorobutan-2-one (27c) was prepared without isolation of **27b** from **27a** (480 mg, 1.0 mM) with desilylation carried out following general procedure G using TBAF (1.1 mL of a 1 M solution, 1.1 mM). The crude product of this reaction (ca. 408 mg) was taken up in CH_3CN (50 mL) and hydrolyzed according to general procedure H. **28c** was obtained as fine white needles after crystallization from ethyl acetate/hexane (244 mg, 76% from **27a**, mixture of hydrate and ketone in a ratio of 10:1 by ^{19}F NMR (235.19 MHz, $(CD_3)_2CO$)): $[\alpha]^{20}_D$ = −154.0 (*c* 0.5, acetone); mp 158−160 °C; IR ($CHCl_3$): 3400−2800, 1770, 1705, 1680 cm^{-1}; NMR spectroscopic data for hydrate form: ^{1}H NMR (500 MHz, $(CD_3)_2CO$): δ 8.06 (d, *J* = 8 Hz, 1H), 7.16−7.51 (m, 10H), 6.80 (s, 1H), 4.34 (ddd, *J* = 3, 8, 12 Hz, 1H), 3.38 (dd, *J* = 3, 14 Hz, 1H), 3.27 (dd, *J* = 12, 14 Hz, 1H); ^{13}C NMR (125.7 MHz, $(CD_3)_2CO$): δ 170.8, 139.6, 134.6, 130.6, 130.1, 129.1, 128.2, 127.2, 124.9 (q, J_{C-F} = 289 Hz), 95.4 (q, J_{C-F} = 30 Hz), 58.9, 33.5; ^{19}F NMR (235.19 MHz, $(CD_3)_2CO$): δ −82.7; LRMS (EI): 322 (MH^+); HRMS calcd for $C_{17}H_{15}F_3NO_2$ (MH^+): 322.1055. Found: 322.1055.

(2*S*,4*S*,5*S*)-4-Benzyl-*N*-(benzyloxycarbonyl)-2-phenyl-5-(trifluoromethyl)-5-[(trimethylsilyl)oxy]-1,3-oxazolidine (28a) was prepared from (2*S*,4*S*)-4-Benzyl-*N*-(benzyloxycarbonyl)-2-phenyl-1,3-oxazolidin-5-one **28**[39] (387 mg, 1.00 mM) following general procedure E and obtained as a colorless oil after purification by flash column chromatography, using 50% diethyl ether/petroleum ether as eluant (280 mg, 53%, single diastereomer): $[\alpha]^{20}_D$ −19.1, (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): 1720, 1605 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10−7.63 (m, 15H), 6.40 (s, 1H), 5.03−5.09 (m, 2H), 4.72−4.74 (m, 1H), 3.14 (dd, *J* = 7, 14 Hz, 1H), 2.75−2.85 (m, 1H), 0.17 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 154.2, 138.5, 137.3, 129.6, 129.3, 129.0, 128.8, 128.3, 128.1, 127.8, 127.7, 126.5, 126.3, 122.6 (q, J_{C-F} = 290 Hz), 102.1 (q, J_{C-F} = 33 Hz), 90.3, 67.6, 61.1, 36.4, 1.2; ^{19}F NMR (235.19 MHz, $CDCl_3$): δ −86.2; LRMS (NH_3): 547 (MNH_4^+), 530 (MH^+); HRMS: calcd for $C_{28}H_{31}F_3NO_4Si$ (MH^+): 530.1974. Found: 530.1970.

(Benzyloxycarbonyl)-(*S*)-phenylalanyl-*N*-[(3*RS*)-(4-phenyl-1,1,1-trifluorobutan-2-one)] Amide (32). Preparation Using the Mixed Anhydride Procedure. To a cooled solution (−15 °C) of (*S*)-*N*-(benzyloxycarbonyl)phenylalanine (87 mg, 0.29 mM) and triethylamine (41 μL, 0.29 mM) in THF was added ethyl chloroformate (27 μL, 0.28 mM) followed by the formation of a white precipitate. After 10 min a precooled solution (−15 °C) of **15d** (65 mg, 0.24 mM) and

(38) The experimental details for **15c** have been published elsewhere (see ref 12b).

(39) Karady, S.; Amato, J. S.; Weinstock, L. M. *Tetrahedron Lett.* **1984**, *25*, 4337−4340.

triethylamine (35 μL, 0.26 mM) was added and stirring continued at −10 °C for 30 min and then for another 30 min allowing to warm slowly to room temperature. After addition of ethyl acetate (15 mL), the organic layer was washed with aqueous hydrochloric acid (10 mL) and saturated sodium bicarbonate solution (15 mL) and dried over magnesium sulfate. After evaporation of solvents in vacuo, the product was obtained as a white solid after purification by preparative thin-layer chromatography using 50% petroleum ether (30−40)/diethyl ether as eluant (39 mg, ca.30%, two diastereomers each in a ratio of 1:1 as a 1:4 mixture of ketone and hydrate). **Preparation Using the Acid Fluoride Procedure.** To a cooled (−15 °C) solution of *N*-(benzyloxycarbonyl)phenylalanyl fluoride[40] (60 mg, 0.2 mM) in dry DCM (5 mL) were added α-amino trifluoromethyl ketone hydrochloride salt (51 mg, 0.2 mM) and pyridine (16 μL, 0.2 mM). The resulting suspension was stirred at the same temperature for 30 min. After addition of DCM (15 mL), the organic layer was washed with aqueous hydrochloric acid (15 mL), concentrated sodium bicarbonate solution (15 mL), and brine (15 mL). After evaporation of solvents in vacuo, the product was obtained as a white solid after purification by preparative thin-layer chromatography using 50% petroleum ether (30−40)/diethyl ether as eluant (35 mg, ca. 35%, two diastereomers each in a ratio of 1:1 as a 1:4 mixture of ketone and hydrate): IR (KBr): 3500−3000br, 1765w, 1695s, 1665s, 1535m, 1455s cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2CO$, relative intensities only): δ 7.66 (d, br, J = 8.5 Hz, 1H), 7.75 (d, br, J = 8.5 Hz, 1H), 7.09−7.39 (m, 4 × 15H), 6.41 (d, br, J = 8 Hz, 1H), 6.36 (d, br, J = 8 Hz, 1H), 4.94−5.06 (m, 10H), 4.25−4.52 (m, 4 × 1H), 2.60−3.01 (m, 4 × 4H); ^{13}C NMR (125.7 MHz, $(CD_3)_2CO$, only the signals for the hydrated form were observed): δ 174.6, 174.4, 156.8, 139.3, 138.6, 138.4, 138.3, 138.1, 137.8, 130.2, 130.1, 130.0, 129.4, 129.2, 129.1, 129.0, 128.6, 128.5, 128.4, 127.3, 127.2, 127.1, 124.9 (q, J_{C-F} = 289 Hz), 124.8 (q, J_{C-F} = 289 Hz), 94.1−95.7 (m), 66.7, 66.6, 57.3, 57.2, 57.1 38.4, 38.5; ^{19}F NMR (235.19 MHz, $(CD_3)_2CO$): δ −82.3, −82.5; LRMS (NH_3): 499 (MH^+); HRMS: calcd for $C_{27}H_{26}F_3N_2O_4$: 499.1844. Found: 499.1845.

(40) Phenylalanyl fluoride was obtained according to a literature procedure: Carpino, L. A.; Mansour, E. M. E.; Sadat-Aalaee, D. *J. Org. Chem.* **1991**, *56*, 2611−2614.

Acknowledgment. This work was supported by the European Community via a Human Capital and Mobility Network (M.W.W.)

Supporting Information Available: Authentic NMR spectra of compounds which were not characterized by microanalysis (38 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Note Added in Proof: Very recently the reaction of methyl esters with $TMSCF_3$/cat. TBAF/THF has been reported. See Wiedemann, J.; Heiner, T.; Mloston, G.; Surga Prakash, G. K.; Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 820−821.

JO980443+