Duality of Mechanism in the Tetramethylfluoroformamidinium Hexafluorophosphate-Mediated Synthesis of *N*-Benzyloxycarbonylamino Acid Fluorides

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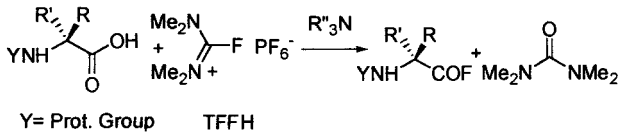
The use of protected amino acid fluorides as activated forms of the N-protected α-amino acids both for solution-phase[1] and for solid-phase synthesis[2] of peptides has recently acquired a remarkable expansion.[3] The main reasons for their success may be ascribed to their unique properties, namely, (i) their inherent stability after purification even in the presence of *tert*-butyl-based protecting groups, (ii) the scarce or even absent oxazolone formation in the presence of tertiary bases, (iii) their ability to afford efficient coupling even in the absence of base, and (iv) the ability to react in high yield and relatively short reaction time, also with sterically hindered amino acids.[1−3] Common procedures for the synthesis of the fluorides call for the use of cyanuryl fluoride in the presence of pyridine[4] or (diethylamino)sulfur trifluoride[5] in the absence of base. More recently, Carpino's group has introduced tetramethylfluoroformamidinium hexafluorophosphate (TFFH) as a fluoride source in the presence of stoichiometric amounts of a tertiary amine for the in situ formation of N-protected amino acid fluorides from the corresponding carboxylic acids (Scheme 1).[6] The procedure has the advantage of allowing the use of acyl fluorides directly in the coupling reaction without prior isolation. The reaction conditions are mild, and therefore, such a process has been considered a benign alternative to fluoride synthesis when non-shelf-stable

Scheme 1



acyl fluorides must be used (e.g., histidine or arginine derivatives). Furthermore, the in situ formed fluorides have been successfully employed for the coupling of some C^{α}-tetrasubstituted amino acids, like aminoisobutyric acid, although this coupling reaction appears to be sensitive to steric hindrance.[7]

Our interest in the use of short peptide frameworks for the construction of catalysts or molecular devices[8] has prompted us to investigate the scope of the fluorination reaction with TFFH. Particularly important was to establish the reactivity of C^{α}-tetrasubstituted amino acids. Because of their ability to induce helical conformation even in short sequences[9] (seven to eight amino acids, i.e., two helical turns), they are particularly appealing for the realization of simple and nevertheless highly organized structures. The easy synthetic access to such unnatural peptides is thus becoming a hot and, so far, still unsolved problem. In fact, despite considerable progress, both the synthesis of C^{α}-tetrasubstituted amino acid fluorides and their coupling reactions are very slow, particularly for the more hindered compounds.[10]

Preliminary work on key substrates suggested the occurrence of at least two concurrent pathways to the acyl fluoride (**2**): (i) the direct conversion of the activated intermediate into the product and (ii) the intramolecular cyclization to the corresponding oxazolone (**3**) followed by fluoride nucleophilic ring opening. The contribution of the second process appeared to depend strongly on the nature of the amino acid, the process being absent with the natural amino acids while becoming more and more relevant with the α-alkyl-α-methyl derivatives with the increase of the bulkiness of the substitutents at the α-carbon.

Results and Discussion

We have examined two classes of benzyloxycarbonyl-protected (Z) derivatives: those deriving from proteinogenic α-amino acids (*Z*-glycine, **1a**, and *Z*-valine, **1b**) and those deriving from unnatural α,α-disubstituted ones of increasing bulkiness of the C^{α}-substituents (*Z*-aminoisobutyric acid (**1c**), *Z*-α-methyl-valine (**1d**), and *Z*-α-methyl-*tert*-leucine (**1e**)).

All amino acids were available with the exception of α-methyl-*tert*-leucine, **6**, which was synthesized starting

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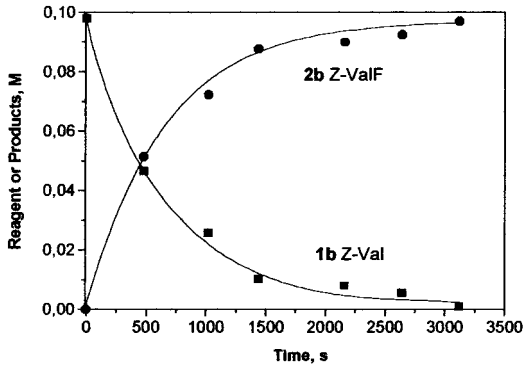
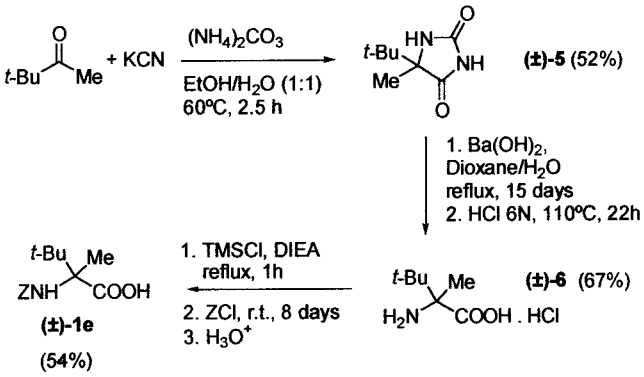


Figure 1. Time course of the TFFH-mediated fluorination of **1b** (*Z*-ValF) in the presence of pyridine in CD_2Cl_2. Conditions are as follows: $[\mathbf{1b}]_0 = 0.10$ M; $[\text{pyridine}]_0 = [\text{TFFH}]_0 = 0.15$ M; $T = 25$ °C.

Scheme 2



from *tert*-butyl methyl ketone (Scheme 2).[11] Thus, reaction with potassium cyanide/ammonium carbonate afforded (±)-5-*tert*-butyl-5-methyl-hydantoin, **5** (52% yield), which was then hydrolyzed to the amino acid (±)-**6**. The hydantoin hydrolysis occurred only partially under basic conditions ($Ba(OH)_2$ in a 1:1 dioxane/water mixture for 15 days). Complete hydrolysis was achieved by further treatment under acidic conditions (6 N HCl in a sealed tube at 110 °C). Racemic α-methyl-*tert*-leucine hydrochoride, (±)-**6**, was obtained in 67% yield. The compound (±)-**1e** was synthesized via in situ silylation followed by reaction with benzyl chloroformate (Scheme 2).[12] Despite the hindrance of the C^{α}-substituents, carbamate (±)-**1e** was obtained in satisfactory yield (54%).

Fluorination Reactions. The study of the fluorination reaction was carried out in CD_2Cl_2 at 25 °C in the presence of a slight excess of pyridine as a base and 1,2-dichoroethane as an internal standard (Scheme 1) and monitored via ^{1}H NMR. The choice of pyridine was made on the basis of its absence of signals in the ^{1}H NMR spectrum in the region where selected signals of the reagents and products appear.

A. Proteinogenic Amino Acids. The reaction of TFFH with **1a** (see Supporting Information) and **1b** (the time course of the latter is shown in Figure 1) proceeds smoothly toward completion with formation of the acyl fluorides (**2a**,**b**) as the only detectable products. The rates of product formation and reagent disappearance are very

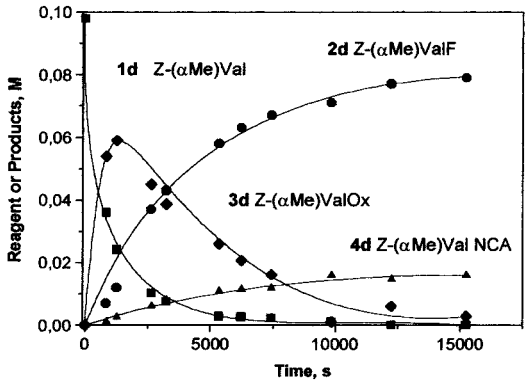
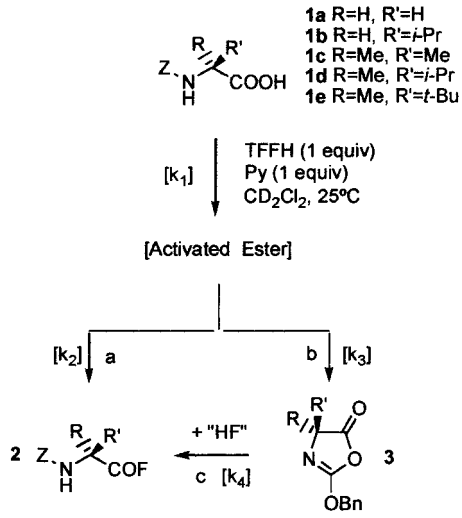


Figure 2. Time course of the TFFH-mediated fluorination of **1d** (*Z*-(αMe)Val) in the presence of pyridine in CD_2Cl_2. Conditions are as follows: $[\mathbf{1d}]_0 = 0.10$ M; $[\text{pyridine}]_0 = 0.13$ M; $[\text{TFFH}]_0 = 0.17$ M; $T = 25$ °C.

Scheme 3



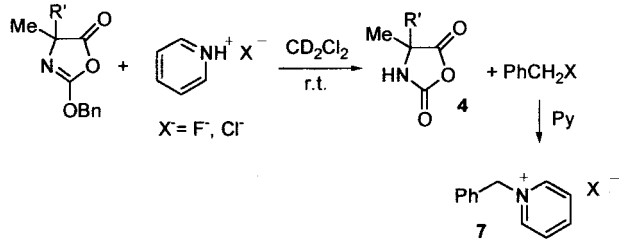
similar for both substrates indicating that there is little influence of the bulkiness of the substituents at C^{α} on the rate and that no intermediates accumulate during the reaction.

B. C^{α}-Tetrasubstituted Amino Acids. The picture of the fluorinations for the α-methyl-α-alkyl-substituted amino acids is more complicated. As it may be appreciated from the inspection of Figure 2, which shows the behavior of **1d**, the reaction becomes slower and, besides the acyl fluoride **2d**, two new α-methyl-valine derivatives are formed. The first one, intermediate **3d**, identified as the 2-benzyloxy-4-isopropyl-4-methyl-5(4*H*)-oxazolone, builds up at the early stages of the reaction, while the second one, corresponding to the 4-isopropyl-4-methyl-oxazolidine-2,5-dione **4d** ([α-methyl-valine *N*-carboxy-anhydride (NCA)], is detected at the last stages.

The kinetic profile provides insights into the course of the fluorination. It indicates that the activated intermediate formed upon reaction of the amino acid with TFFH may either be directly converted into the acyl fluoride or give an intramolecular cyclization to the oxazolone **3d** (see Scheme 3). Slow reaction of **3d** with F^- eventually leads to the formation of the acyl fluoride. A concurrent, acid-catalyzed, even slower reaction leads to the formation of the corresponding *N*-carboxyanhydride **4d**.[13,14]

(11) Obrecht, D.; Spiegler, C.; Schönholzer, P.; Müller, K.; Heimgartner, H.; Stierli, F. *Helv. Chim. Acta* **1992**, *75*, 1666.
(12) Bolin, D. R.; Sytwu, I.; Humiec, F.; Meienhofer, J. *Int. J. Pept. Protein Res.* **1989**, *33*, 353.

Scheme 4



The capability of oxazolones to react with nucleophiles is well documented,[15,16] and they have also been used as activated intermediates in coupling reactions.[16] The time course of the reaction of **1d** is qualitatively similar to those observed for the fluorination of **1c** and **1e** (see Supporting Information). There are, however, important differences as to the time scale of the overall process and the relative amount of oxazolone and *N*-carboxyanhydride[17] observed. The half-times for the formation of the acylfluorides increase with the bulkiness of the substituents at C^{α} [**1e** (2900 s) > **1d** (1500 s) > **1c** (210 s)] as do the amounts of oxazolone **3** and *N*-carboxyanhydride **4** formed. For instance, the maximum amount of oxazolone **3** formed from **1c**, **1d**, and **1e** is, respectively, 20% (300 s), 52% (600 s), and 54% (1500 s).

Mechanism of the Reaction. The above experimental observations point to the mechanism outlined in Scheme 3, which shows the dual pathway toward the acyl fluoride: direct (a) and indirect (b, c). The indirect pathway is only operative with the C^{α}-tetrasubstituted derivatives. As already mentioned, the fluorination of the most hindered derivatives **1d** and **1e** yields also the corresponding *N*-carboxyanhydride at the last stages of the reaction. The latter may arise from acid-catalyzed debenzylation of **3d**,**e** with formation of benzyl fluoride which is eventually converted to the pyridinium salt (Scheme 4).

Such a reaction pathway could be independently demonstrated by following via ^{1}H NMR the reaction of **3d**,**e** in the presence of 1 equiv of pyridine hydrochloride in CD_2Cl_2.

Careful analysis of the concentration vs time profiles for the different amino acids allowed us to determine kinetic rate constants for the different steps of the fluorination process (see Scheme 3).[18] These values are reported in Table 1.

A closer look at this table shows that while the disappearance of the amino acid (k_1) is little influenced by the substituents at C^{α}, all other reactions are strongly dependent on the bulkiness of the groups present on that carbon. These, in fact, involve the attack at the C=O carbon with formation of a tetrahedral intermediate which is very sensitive to steric hindrance in the α-position as is well documented in the literature.[19] Thus, k_2 becomes more than 700 times slower for **1e** compared with **1a**. The intramolecular cyclization to the oxazolone **3** (k_3) is influenced not only by steric hindrance at C^{α} but also by the *gem*-dialkyl effect.[20] These two effects operate in opposite directions. The geminal alkyl substituents at the α-carbon favor the conformation that leads to ring closure. On the other hand, they make the intramolecular attack to the carbonyl slower because of steric hindrance. As a consequence, k_3 is unmeasurably slow with the derivatives of proteinogenic amino acids, becomes relatively fast with **1c**, and then decreases again with the more hindered C^{α}-tetrasubstituted derivatives. The k_2/k_3 ratio reflects the relative amount of oxazolone vs fluoride formation, and it clearly indicates that fluoride formation for the three C^{α}-tetrasubstituted amino acids is only favored in the case of **1c**, while for the other two amino acids the ring closure reaction is largely the most favored process.

Table 1. Rate Constants[a] Calculated for the TFFH-Mediated Fluorination of *Z*-Amino Acids 1a−e in the Presence of Pyridine in CH_2Cl_2 at 25 °C

substrate	k_1 (M^{-1} s^{-1})	k_2 (s^{-1})	k_3 (s^{-1})	k_2/k_3	k_4 (M^{-1} s^{-1})
1a	0.021	0.238	*b*		
1b	0.016	0.080	*b*		
1c	0.019	0.175	0.050	3.50	0.0074
1d	0.015	0.0057	0.016	0.35	0.0077
1e	0.012	0.000 31	0.0061	0.05	0.0072

[a] Rate constant values have been calculated by least-squares fitting (±20%) (ref 18). [b] No formation of oxazolone.

Maximization of Acyl Fluoride Production. From the mechanistic analysis we have described in the previous section, it is immediately clear that with C^{α}-tetrasubstituted amino acids the formation of the oxazolones is a problem that has to be dealt with. If one wants to improve the production of the acyl fluoride, because the oxazolone formation is an intrinsic property of the particular substrate, he can only operate on step c.

We thus examined more closely the oxazolone ring opening reaction. Oxazolone **3d** was prepared by treatment of **1d** with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (68% yield).[14] Subsequently, we followed via ^{1}H NMR the reaction of **3d** with TFFH in the presence of 1 equiv of pyridine. The kinetic picture is reported in Figure 3. The kinetic behavior shows the slow formation of acyl fluoride **2d** in low yield (16% after 42 000 s) together with a much larger amount of *N*-carboxyanhydride **4d** (39%). After approximately 12 000 s, no more acyl fluoride **2d** is produced and no more TFFH is consumed. However, upon addition of water (0.5 equiv at 60 000 s), the reaction starts again. Therefore, very likely the acyl fluoride **2d** formed initially derives from the reaction of the nucleophilic fluoride ion that is produced in small amounts at the beginning of the reaction as a consequence of TFFH hydrolysis by small quantities of water present in the reaction mixture. Further addition of water generates new fluoride, restoring the fluorination process. When the reaction is carried out starting directly from the N-protected amino acid, the production of the nucleophilic fluoride is the consequence of the attack of the carboxylate on TFFH with formation

(13) 2-*tert*-Butoxy-5(4*H*)-oxazolones can be converted into the corresponding *N*-carboxyanhydride on standing in *tert*-butyl alcohol, anhydrous acid, or in vacuo (see ref 14).

(14) Benoiton, L. N.; Chen, F. M. C. *Can. J. Chem.* **1981**, *59*, 384.

(15) For example, upon reaction with hydrogen chloride, 2-*tert*-butoxy-5(4*H*)-oxazolones can afford the corresponding acyl chlorides (see: Chen, F. M. F.; Lee, Y. C.; Benoiton, L. N. *Int. J. Pept. Protein Res.* **1991**, *38*, 97 and ref 16).

(16) Benoiton, L. N. *Biopolymers* **1996**, *40*, 245 and references therein.

(17) *N*-carboxyanhydrides **4d** and **4e** were detected only in the fluorination of **1d** and **1e** (15% and 60% yields, respectively).

(18) Kinetic rate constants have been calculated by least-squares fittings. (*ScientistTM*; MicroMath Scientific Software: Salt Lake City, UT, 1995.)

(19) March, J. *Advanced Organic Chemistry, Reactions, Mechanisms and Structure*, 4th ed.; John Wiley & Sons: New York, 1992.

(20) Bruice, T. C.; Lightstone, F. C. *Acc. Chem. Res.* **1999**, *32*, 127. Sammes, P.; Weller, D. J. *Synthesis* **1995**, 1205 and references therein.

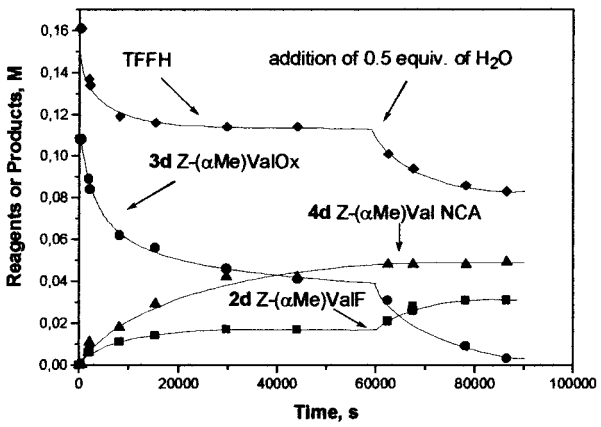


Figure 3. Time course of the TFFH-mediated fluorination of **3d** (*Z*-(αMe)ValOx) in the presence of pyridine in CD_2Cl_2. Conditions are as follows: $[\mathbf{3d}]_0 = 0.10$ M; $[\text{pyridine}]_0 = [\text{TFFH}]_0 = 0.15$ M; $T = 25$ °C.

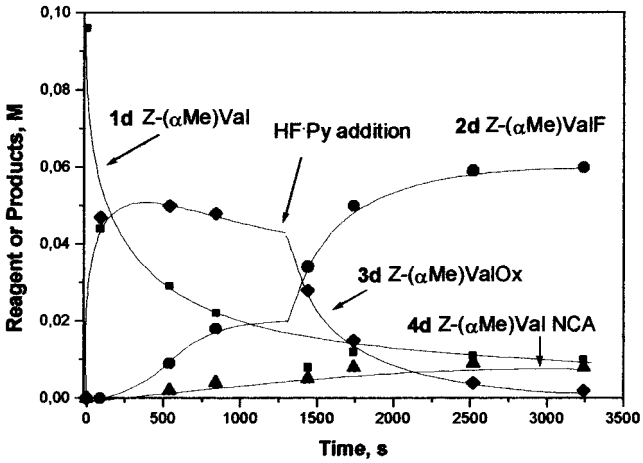


Figure 4. Time course of the TFFH-mediated fluorination of **1d** (*Z*-(αMe)Val) in the presence of pyridine in CD_2Cl_2. After 21 min, HF/Py (1.5 equiv) was added. Conditions are as follows: $[\mathbf{1d}]_0 = [\text{pyridine}]_0 = 0.10$ M; $[\text{TFFH}]_0 = 0.15$ M; $T = 25$ °C.

of the active intermediate. Thus, an extra source of nucleophilic fluoride is required in order to accelerate the fluorination process. For this purpose, the use of "naked" fluoride nucleophiles such as tetrabutylammonium fluoride (TBAF)[21] or potassium fluoride[22] was explored. Reaction with different TBAF sources ($TBAF{\cdot}3H_2O$ and $TBAF/SiO_2$) afforded an extended decomposition of oxazolone **3d** without any detectable acyl fluoride formation. On the other hand, reaction with dry KF in the presence of 18-crown-6 in benzene did not result in any formation of products, and the starting oxazolone **3d** was recovered unchanged. However, addition of a slight excess of a HF/pyridine 1:1 complex resulted in the fast conversion of the oxazolone **3d** into the acyl fluoride **2d** (40% after 16 000 s)[23] together with the formation of only 4% of *N*-carboxyanhydride **4d**.

To determine whether the formation of the acyl fluoride could be maximized also starting from the amino acid and TFFH, we ran the reaction directly on **1d**. Figure 4 shows the time course of the process monitored by ^{1}H NMR and the effect of the addition of HF/pyridine after ca. 1200 s. It is clearly apparent that HF/pyridine converts the formed oxazolone into the acyl fluoride at a much higher rate in this case, too. An analogous behavior was observed with **1e** (see Supporting Information). The failure of $Bu_4N^+F^-$ or KF/18-crown-6 to afford the fluoride **2d** indicates that, to occur, the F^- nucleophilic attack to the ozaxolone requires acid catalysis. It is noteworthy that the conversion of the intermediate oxazolone to the corresponding *N*-carboxyanhydride, which is also an acid-catalyzed process, is much less accelerated and, consequently, the overall amount of **4d** formed is much lower.

In conclusion, our study points out that in the TFFH-mediated *Z*-amino acid fluorination at least two concurrent pathways yielding the acyl fluoride can take place: the direct conversion of the activated intermediate into the product and the intramolecular cyclization to the corresponding oxazolone followed by fluoride nucleophilic ring opening. The contribution of the second process strongly depends on the nature of the amino acid, the process being absent in the natural amino acid derivatives while in the α-alkyl-α-methyl ones it parallels the steric bulkiness of the alkyl substituent (Me < *i*-Pr < *t*-Bu). The formation of the oxazolone with the subsequent slow ring opening seems to be one of the main causes of the decreased reactivity of the α,α-disubstituted amino acids. Furthermore, because of the longer reaction time, the formation of the corresponding *N*-carboxyanhydrides may become a significant side reaction. Addition of "HF" species to the reaction mixture appreciably accelerates the ring opening of the oxazolone and therefore the α,α-disubstituted acyl fluoride formation. Studies concerning the optimization of the reaction conditions for the synthesis of highly hindered α,α-disubstituted amino acid fluorides are currently being pursued in our laboratories.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 200 or 250 MHz, ^{13}C NMR at 62.9 MHz, and 2D-correlated spectra at 400 MHz, at 25 °C using Me_4Si as internal standard reference. C_q, CH, CH_2, and CH_3 were determined by distortionless enhancement by polarization transfer (DEPT) pulse sequence. Mass spectra were obtained by EI, matrix-assisted laser desorption ionization (MALDI) (matrix, α-cyano-hydroxycinnamic acid), or electrospray (ESI) (mobile phase, acetonitrile) ionizations. Radial chromatography has been performed using silica gel plates. Melting points are uncorrected.

Chemicals. Enantiopure L-α-methyl valine, **1d**, was prepared by DSM Research by enzymatic resolution of (±)-α-methyl valine amide.[24] TFFH has been synthesized following Carpino's procedure.[6] *Z*-Glycine fluoride (**2a**),[25] *Z*-L-valine fluoride (**2b**),[25] *Z*-aminobutyric fluoride (**2c**),[7] *Z*-L-α-methyl valine (**1d**),[10] *Z*−L-α-methyl valine fluoride (**2d**),[10] and 2-benzyloxy-4,4-dimethyl-5(4*H*)-oxazolone (**3c**)[26] have been prepared following previously reported procedures. Dichloromethane was distilled over CaH_2 and stored over molecular sieves. *Z*-Glycine (**1a**), *Z*−L-valine (**1b**), *Z*-aminoisobutyric acid (**1c**), dry pyridine, diisopropylethyl-

(21) Clark, J. H.; Smith, D. K. *Tetrahedron Lett.* **1985**, *26*, 2233.
(22) Liotta, C. L.; Harris, H. P. *J. Am. Chem. Soc.* **1974**, *96*, 2250. Smyth, T. P.; Carey, A.; Hodnett, B. K. *Tetrahedron* **1995**, *51*, 6363.
(23) The reaction of 2-(9-fluorenylmethoxy)-4-isopropyl-5(4*H*)-oxazolone with HCl has been reported to afford quantitatively the corresponding *N*-9-fluorenylmethoxycarbonyl valine chloride (ref 15).
(24) Kruizinga, W. Z.; Boster, J.; Kellogg, R. M.; Kamphuis, J.; Boesten, W. H. I.; Mejier, E. M.; Schoemaker, H. E. *J. Org. Chem.* **1988**, *53*, 1826. Kaptein, B.; Boesten, W. H. J.; Broxterman, Q. B.; Peters, P. J. H.; Schoemaker, H. E.; Kamphuis, J. *Tetrahedron: Asymmetry* **1993**, *4*, 1113.
(25) Carpino, L. A.; Mansour, E.-S. M. E.; Sadat-Aalaee, D. *J. Org. Chem.* **1991**, *56*, 2611.
(26) Formaggio, F.; Pantano, M.; Crisma, M.; Bonora, G. M.; Toniolo, C.; Kamphuis, J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1097.

amine (DIEA), trimethylsilyl chloride (TMSCl), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl), and cyanuryl fluoride are commercial products and have been used without further purification. Pyridine/hydrogen fluoride 1:1 complex has been obtained by addition of 1.1 mL of dry pyridine to 0.4 mL of pyridinium poly(hydrogen fluoride).

Synthesis of (±)-5-*tert*-Butyl-5-methyl-hydantoin, 5. *tert*-Butyl methyl ketone (50.0 mL, 0.4 mmol) was dissolved in 1.2 L of a 1:1 ethanol/water solution to which ammonium carbonate (160.6 g, 1.7 mmol) and potassium cyanide (55.4 g, 0.8 mmol) were added. The mixture was heated at 60 °C for 2.5 h until disappearance of the starting material (TLC, $CHCl_3$/EtOH 9:1). The solution was concentrated under vacuum, and the precipitate was filtered. Crystallization from EtOH/H_2O afforded hydantoin **5** (35.4 g, 52%) as a white solid, which readily sublimes; mp 224−226 °C (lit.[11] 218−219 °C). ^{1}H NMR (CD_3OD, δ, ppm): 1.54 (3H, s), 1.21 (9H, s). ^{13}C NMR (CD_3OD, δ, ppm): 180.69 (C), 159.69 (C), 69.53 (C), 37.86 (C), 25.40 (CH_3), 19.62 (CH_3). FT-IR (KBr, cm^{-1}): 3220, 1732. Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.55; H, 8.36; N, 16.54.

Synthesis of (±)-α-Methyl-*tert*-leucine, 6. Hydantoin (±)-**5** (2.16 g, 13 mmol) was dissolved in 30 mL of water containing $Ba(OH)_2 \cdot 8H_2O$ (32.31 g, 86 mmol). The mixture was refluxed for 15 days. The reaction was followed by TLC ($CHCl_3$/EtOH 9:1 for reagent; *t*-BuOH/H_2O/AcOH 3:1:1 for product). Then, the mixture was cooled to room temperature, filtered, concentrated under vacuum, and treated twice with solid CO_2 to precipitate barium as $BaCO_3$. After the solvent was removed under vacuum, the crude of the reaction, containing a mixture of reagent, ureic acids, and hydantoin, was treated with 50 mL of HCl (6 N) in a sealed vial at 110 °C for 22 h. The solvent was removed under vacuum, and the solid was treated with water three times, and the solvent was evaporated again to dryness. Washing with EtOAc and lyophilization of the aqueous phase afforded (±)-**6** hydrochloride[11] (1.54 g, 67%) as a white solid; mp 310−313 °C (lit.[27] 309−312 °C). ^{1}H NMR (CD_3OD, δ, ppm): 1.56 (3H, s), 1.06 (9H, s). ^{13}C NMR (CD_3OD, δ, ppm): 173.40 (C), 67.30 (C), 36.70 (C), 25.99 (CH_3), 18.83 (CH_3). FT-IR (KBr, cm^{-1}): 3424, 2976, 1735.

Synthesis of (±) *Z*-α-Methyl-*tert*-leucine, 1e. Hydrochloride **6** (1.41 g, 7.8 mmol) was dissolved in 50 mL of dry CH_2Cl_2. DIEA (7.0 mL, 40.9 mmol) and TMSCl (3.00 mL, 23.6 mmol) were slowly added, and the mixture was refluxed for 1 h. After the mixture was cooled to 0 °C, benzyl chloroformate (*Z*-Cl, 1.10 mL, 7.7 mmol) was added. The reaction was stirred at 0 °C for 1 h and then warmed to room temperature. The course of the reaction was monitored by TLC ($CHCl_3$/EtOAc/AcOH 9:0.8:0.2), and the pH was maintained in the 8−9 interval by addition of DIEA. After 3 days, additional *Z*-Cl (0.8 mL, 5.6 mmol) was added. After 8 days, the mixture was treated with 100 mL of $KHSO_4$ and vigorously stirred for 2 h. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The aqueous phases were then acidified with 5% HCl to pH 1−2 and extracted with CH_2Cl_2. The organic phases were extracted with 0.5 M NaOH, washed with brine and water, and dried over $MgSO_4$, and the solvent was removed under vacuum. Carbamate **1e** was obtained as a white foam (1.19 g, 55%); mp 105−108 °C. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.33 (5H, m), 5.38 (1H, br s), 5.10 (2H, s), 1.64 (3H, s), 1.05 (9H, s). ^{13}C NMR (CD_3OD, δ, ppm): 177.99 (C), 155.77 (C), 136.21 (C), 128.50 (CH), 128.16 (CH), 66.88 (CH_2), 65.09 (C), 36.71 (C), 25.65 (CH_3), 18.09 (CH_3). FT-IR (neat, cm^{-1}): 3336, 1706, 1657. MALDI-TOF MS *m*/*z*: 279.9 $[MH]^+$; calcd 280.3. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.71; H, 7.62; N, 4.89.

Synthesis of Oxazolones 3d and 3e (via EDC·HCl).[14] The *Z*-amino acid (**1d** or **1e**, 2.0 mmol) was dissolved in dry CH_2Cl_2 (20 mL). After the solution was cooled to 0 °C, EDC·HCl (460 mg, 3.0 mmol) was added, and the reaction mixture was allowed to slowly warm to room temperature. After the mixture was stirred for 2−3 h, a cold 0.1 M $KHSO_4$ solution was added. The organic phase was separated and washed with cold water, with cold 5% $NaHCO_3$ aqueous solution, and with cold water a second time. After the organic phase was dried over $MgSO_4$, the solvent was removed, and the resulting product was purified by radial chromatography (EtOAc/petroleum ether 4:96).

2-Benzyloxy-4-isopropyl-4-methyl-5(4*H*)-oxazolone, 3d. Oxazolone **3d** was obtained in 84% yield as a colorless oil. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.40 (5H, m), 5.34 (2H, m), 1.98 (1H, m), 1.42 (3H, s), 0.98 (3H, d, J = 6.7 Hz), 0.84 (3H, d, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$, δ, ppm,): 178.56 (C), 156.91 (C), 134.25 (C), 128.83 (CH), 128.58 (CH), 128.46 (CH), 73.35 (C), 71.44 (CH_2), 35.16 (CH), 22.09 (CH_3), 17.06 (CH_3), 16.39 (CH_3). $[\alpha]^{25}_D$ −30.1 (*c* 1.1, $CHCl_3$). FT-IR (neat, cm^{-1}): 3446, 1830, 1686. EI-MS *m*/*z* (relative intensity): 347 (M^+, 3), 205 (7), 91 (100). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.12; H, 6.99; N, 5.61.

2-Benzyloxy-4-*tert*-butyl-4-methyl-5(4*H*)-oxazolone, 3e. Oxazolone **3e** was obtained in 98% yield as a colorless oil. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.39 (5H, m), 5.34 (2H, m), 1.40 (3H, s), 0.97 (9H, s). ^{13}C NMR ($CDCl_3$, δ, ppm): 177.97 (C), 156.60 (C), 134.39 (C), 128.83 (CH), 128.56 (CH), 75.35 (C), 71.35 (CH_2), 36.75 (C), 24.62 (CH_3), 19.66 (CH_3). FT-IR (neat, cm^{-1}): 3446, 1828, 1684. EI-MS *m*/*z* (relative intensity): 261 (M^+, 4), 205 (9), 91 (100). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.07; H, 7.41; N, 5.27.

Synthesis of (±)-*Z*-α-Methyl-*tert*-leucine Fluoride, 2e. *Z*-α-Methyl-*tert*-leucine, **1e** (96 mg, 0.4 mmol), was dissolved in dry CH_2Cl_2 (10 mL). After the mixture was cooled to 0 °C, pyridine (60 μL, 0.7 mmol) and cyanuryl fluoride (80 μL, 0.9 mmol) were added. The solution was slowly warmed to room temperature. After 3 h, crushed ice was added to the reaction mixture along with additional CH_2Cl_2. The organic phase was washed with ice-cold water and dried over $MgSO_4$, and the solvent was removed under vacuum. (±)-*Z*-α-Methyl-*tert*-leucine fluoride **3e** (78 mg, 84%) was recovered as a colorless oil. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.34 (5H, m), 5.11 (2H, s), 1.50 (3H, d, J_{H-F} = 1.5 Hz), 1.06 (9H, s). ^{13}C NMR ($CDCl_3$, δ, ppm): 163.18 (C, d, J = 380.0 Hz), 155.56 (C), 135.80 (C), 128.75 (CH), 128.57 (CH), 67.23 (CH_2), 36.85 (C, J = 47.1 Hz), 24.93 (CH_3, J = 56.9 Hz), 18.57 (CH_3, J = 37.7 Hz). FT-IR (neat, cm^{-1}): 3446, 1837, 1684. MALDI-TOF MS *m*/*z*: 282.0, calcd 282.1.

Synthesis of 4-Alkyl-4-methyl-oxazolidine-2,5-diones 4d and 4e from the Corresponding Oxazolones 3d and 3e. In a screw-capped 5 mm NMR tube, 0.01 mmol of oxazolones **3d** or **3e** was dissolved in 0.50 mL of CD_2Cl_2. Pyridine hydrochoride (11.5 mg, 0.01 mmol) was added, and the reactions were monitored via ^{1}H NMR. The immediate disappearance of the starting materials was observed together with the product formation, which was complete after 24 h. The *N*-carboxyanhydrides **4d** and **4e** and benzyl pyridinium chloride **7**[29] are stable in CD_2Cl_2 for more than 1 month (see Supporting Information). Filtration over silica gel of both reaction mixtures allowed the recovery in 25% and 28% yields, respectively, of *N*-carboxyanhydrides **4d** and **4e** for which the spectroscopic data are consistent with those of the products obtained via the procedure described later.[29]

Heteronuclear multiple-bond correlation (HMBC) and nuclear Overhauser effect spectroscopy (NOESY) experiments were useful in the identification of products **4d** and **7** in the reaction mixture deriving from **1d** and for the assignment of their ^{1}H and ^{13}C NMR signals (Figure 5, see also Supporting Information). The spectral data reported below are those of the reaction mixtures.

4-Isopropyl-4-methyl-oxazolidine-2,5-dione, 4d. ^{1}H NMR (CD_2Cl_2, δ, ppm): 9.23 (1H, br s), 2.03 (1H, sept, J = 6.8 Hz), 1.47 (3H, s), 1.02 (3H, d, J = 6.8 Hz), 0.91 (3H, d, J = 6.8 Hz). ^{13}C NMR (CD_2Cl_2, δ, ppm,): 174.00 (C), 151.86 (C), 66.85 (C), 35.20 (CH), 21.67 (CH_3), 16.97 (CH_3), 16.31 (CH_3).

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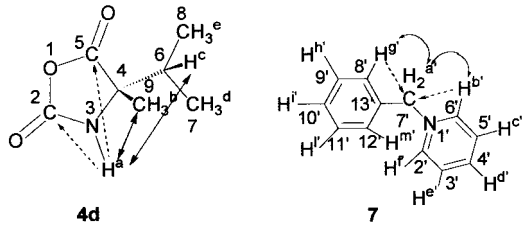
(29) ^{1}H NMR resonances of authentic **4d** and **4e** in CD_2Cl_2 and $CHCl_3$ have significant shifts with respect to the in situ formed products obtained from oxazolones **3d** or **3e** in the presence of pyridine hydrochoride. The identity of the two compounds was ascertained by adding authentic **4d** and **4e** to the reaction mixtures obtained from **3d** and **3e**, respectively. The remarkable differences of the ^{1}H and ^{13}C NMR resonances are very likely due to specific interactions with benzyl pyridinium chloride, **7**.



4d **7**

Figure 5. HMBC correlations (- - -) and NOESY (−) observed for **4d** and **7**.

4-*tert*-Butyl-4-methyl-oxazolidine-2,5-dione, 4e. ^{1}H NMR (CD_2Cl_2, δ, ppm): 9.21 (1H, br s), 1.48 (3H, s), 1.04 (9H, s). ^{13}C NMR (CD_2Cl_2, δ, ppm,): 173.23 (C), 151.90 (C), 69.05 (C), 37.25 (C), 22.58 (CH_3), 18.99 (CH_3).

Benzyl Pyridinium Chloride, 7.[28] ^{1}H NMR (CD_2Cl_2, δ, ppm): 9.51 (2H, d, J = 5.5 Hz), 8.42 (1H, t, J = 8.0 Hz), 8.05 (2H, m), 7.57−7.70 (2H, m), 7.31−7.43 (3H, m), 6.20 (2H, s). ^{13}C NMR (CD_2Cl_2, δ, ppm,): 145.30 (CH), 145.15 (CH), 133.29 (C), 129.87 (CH), 129.52 (CH), 129.48 (CH), 128.43 (CH), 64.31 (CH_2). ESI-TOF MS m/z: 170.107 (100%), 171.1092 (12%); calcd 170.096 (100%), 171.100 (12%).

Synthesis of *N*-Oxazolidine-2,5-diones 4d and 4e from *Z*-α-Methyl Amino Acids 1d and 1e. In a 1 mL screw-capped vial, *Z*-α-methyl amino acids **1** (1.06 mml) were added to $SOCl_2$ (0.500 mL) under magnetic stirring. The mixture was warmed to 60 °C, and then, after 30 min, the reaction was cooled to room temperature, and the solvent was removed under vacuum. The products were purified by crystallization.

4-Isopropyl-4-methyl-oxazolidine-2,5-dione, 4d. Yield 57%, mp 54−56 °C (crystallized from ethyl acetate/pentane), $[\alpha]^{25}_D$ −33.5 (*c* 1.0, chloroform). ^{1}H NMR ($CDCl_3$, δ, ppm): 6.60 (1H, br s), 2.08 (1H, sept, J = 6.5 Hz), 1.53 (3H, s), 1.02 (3H, d, J = 6.5 Hz), 0.99 (3H, d, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$, δ, ppm,): 170.66 (C), 151.86 (C), 66.79 (C), 34.99 (CH), 21.99 (CH_3), 17.07 (CH_3), 16.14 (CH_3). IR (neat, cm^{-1}): 3300, 1853, 1780. Anal. Calcd for $C_7H_{11}NO_3$: C, 53.50; H, 7.05; N, 8.91. Found: C, 53.62; H, 7.11; N, 8.83.

4-*tert*-Butyl-4-methyl-oxazolidine-2,5-dione, 4e. Yield 75%, mp 138−140 °C (sublimes, crystallized from dichloromethane/pentane). ^{1}H NMR ($CDCl_3$, δ, ppm): 6.62 (1H, br s), 1.54 (3H, s), 1.08 (9H, s). ^{13}C NMR ($CDCl_3$, δ, ppm): 171.63 (C), 152.69 (C), 69.04 (C), 37.26 (C), 24.46 (CH_3), 19.51 (CH_3). IR (neat, cm^{-1}): 3250, 1836, 1783. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.22; H, 7.60; N, 8.11.

Procedure for the Kinetic Study of TFFH-Mediated Fluorination Reaction of *Z*-Amino Acids 1a−e. In a screw-capped 5 mm NMR tube, 0.05 mmol of *Z*-amino acid **1** was dissolved in 0.500 mL of CD_2Cl_2, together with 2 μL of 1,2-dichoroethane as an internal standard. TFFH (19.88 mg, 0.075 mmol) and, after 5 min, dry pyridine (5 μL, 0.049 mmol) were added. The reactions were monitored via ^{1}H NMR at 25 °C by integration of the signals at the selected chemical shifts listed in Table S-1 (see Supporting Information) at the reaction times reported in Figures 1 and 2 and Figures S-1, S-2, and S-3 (see Supporting Information).

Procedure for the Kinetic Study of TFFH-Mediated Fluorination Reaction of 2-Benzyloxy-4-isopropyl-4-methyl-5(4*H*)-oxazolone, 3d. In a screw-capped 5 mm NMR tube, **3d** (13.43 mg, 0.054 mmol) was dissolved in 0.50 mL of CD_2Cl_2 together with 2 μL of 1,2-dichoroethane as an internal standard. TFFH (20.45 mg, 0.077 mmol) and, after 5 min, dry pyridine (4 μL, 0.039 mmol) were added. After 64 200 s, 0.5 equiv of water (0.5 μL) was added. The reaction was monitored via ^{1}H NMR at 25 °C by integration of the signals at the selected chemical shifts listed in Table S-1 at the reaction times reported in Figure 3.

Procedure for the Kinetic Study of HF/Pyridine 1:1 Complex-Mediated Fluorination Reaction of 2-Benzyloxy-4-isopropyl-4-methyl-5(4*H*)-oxazolone, 3d. In a screw-capped 5 mm NMR tube, oxazolone **3d** (13.43 mg, 0.054 mmol) was dissolved in 0.500 mL of CD_2Cl_2, together with 2 μL of 1,2-dichoroethane as an internal standard. A total of 7.3 μL (1.4 equiv) of a 1:1 HF/pyridine solution was added. The reaction was monitored via ^{1}H NMR at 25 °C by integration of the signals at the selected chemical shifts listed in Table S-1 at the reaction times reported in Figure S-4 (see Supporting Information).

Procedure for the Kinetic Study of (TFFH + HF/Py)-Mediated Fluorination Reaction of *Z*-Amino Acids 1d and 1e. In a screw-capped 5 mm NMR tube, 0.05 mmol of *Z*-amino acid **1d** or **1e** was dissolved in 0.500 mL of CD_2Cl_2 together with 2 μL of 1,2-dichoroethane (DCE) as an internal standard. TFFH (19.88 mg, 0.075 mmol) and, after 5 min, dry pyridine (5 μL, 0.049 mmol) were added. After 21 min, 0.075 mmol of HF/pyridine 1:1 complex was added. The reactions were monitored via ^{1}H NMR at 25 °C by integration of the signals at the selected chemical shifts listed in Table S-1 (see Supporting Information) at the reaction times stated in Figures 4 and S-5 (see Supporting Information).

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Supporting Information Available: Kinetic profiles (Figures S-1−S-5), selected ^{1}H and ^{13}C NMR spectra (Figures S-6 and S-7), NOESY spectrum (Figure S-8), and HMBC correlations (Figure S-9) of in situ formed derivatives **4d** and **7** in CD_2Cl_2 and selected ^{1}H NMR chemical shifts (Table S-1). This material is available free of charge via the Internet at http://pubs.acs.org.

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