Palladium-Catalyzed *tert*-Butoxycarbonylation of Trifluoroacetimidoyl Iodides

Hideki Amii, Yosuke Kishikawa, Katsuhiko Kageyama, and Kenji Uneyama*

Department of Applied Chemistry, Faculty of Engineering, Okayama University, Okayama 700-8530, Japan

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A modification and details of the palladium-catalyzed *tert*-butoxycarbonylation of 2,2,2-trifluoroacetimidoyl iodides **1**, which gave the iminocarboxylates **2**, one of the promising precursors to fluorinated α-amino acids, are described. The Pd-catalyzed carbonylation reaction was remarkably promoted by the use of DMF or DMI as an additive, enough to achieve the selective formation of *tert*-butyl iminoesters. Nucleophilic alkylation of the imine moiety of **2** and subsequent removal of *N*- and *O*-protecting groups gave a variety of 2-substituted 2-amino-3,3,3-trifluoropropanoic acid derivatives **3** in high yields.

Introduction

Fluorinated amino acids and peptides are an important class of unnatural molecules that have been successfully used in an expanded repertoire of biological applications, and they are receiving increasing attention in the medicinal, agricultural, and material sciences.[1,2] These compounds owe their unique biological properties to the profound electron-withdrawing effect caused by fluorine atom(s) that occurs without significant steric consequence. Some fluorine-containing amino acid derivatives exhibit enzyme inhibition activities.[3] So, the development of new synthetic methodology for preparing fluorine-containing α-amino acids is of particular interest.[4,5] Despite a growing interest, there are few synthetic methods available for the preparation of fluoro α-amino acids, and many of these methods utilize hazardous and expensive reagents or require harsh reaction conditions.[6] A more practical and general preparative method must be devised.[7]

The transition-metal-catalyzed carbonylation of organic halides is one of the most versatile and convenient processes for the introduction of a carbonyl group into the molecule.[8] The facile CO insertion into organometallic compounds, followed by the nucleophilic attack of various nucleophiles, affords ketones,[9] carboxylic acids,[10] esters,[11] and amides.[12] Carboalkoxylation of organic halides gives the homologated esters by the use of a catalytic amount of transition metal complexes. While much has been learned preparing the methyl, ethyl, and *n*-butyl esters as a carboalkoxylation product, to our knowledge very few studies have been performed on the synthesis of the *tert*-butyl esters,[13,14] which act as an easily removable *O*-protecting group. One serious drawback to the transition-metal-catalyzed carboalkoxylation of organic halide is the structural restriction, especially of the reactant alcohols. Actually, methanol, butanol, and benzyl alcohol can be used and gave the corresponding esters in good yield, whereas with tertiary alcohols, the carbonylation did not work well, probably as a result of steric hindrance of the alcohol nucleophiles.[13,15] For example, Tanaka[15a] and Watanabe[15b] reported that the reactions of organic

* Ph: 81-86-251-8075. Fax: 81-86-251-8075. E-mail: uneyamak@cc.okayama-u.ac.jp.

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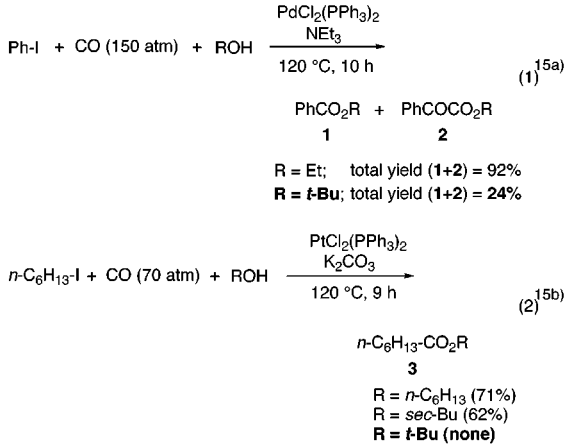
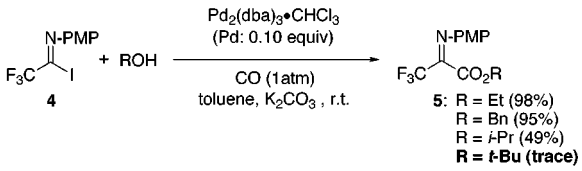
Scheme 1



Scheme 2

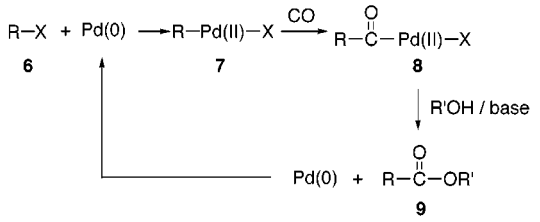


halides with *tert*-butyl alcohol under pressure of CO at high temperature gave the corresponding esters **1**−**3** in poor yields (Scheme 1).

In our previous communication, we reported an efficient route to prochiral fluoro α-amino acid derivatives **5** via the palladium-catalyzed carboalkoxylation of fluorinated imidoyl halides **4**.[16] The simple procedure, mild reaction conditions (rt, 1 atm of CO), and availability of the starting materials[17,18] render this method a valuable protocol for the preparation of fluoro amino acid derivatives[19,20] (Scheme 2).

In amino acid synthesis, the choice of the *N*- and *O*-protecting groups is of paramount importance. There remains a serious problem with deprotection in asymmetric amino acid syntheses, despite a wide number of amino acid derivatives having been made. For instance, hydrolysis of ethyl esters (removal of ethyl group) under basic conditions occasionally involves racemization of the stereogenic center(s) of the products, and in particular, dehydrofluorination is a serious side reaction in the alkaline hydrolysis of *β*-fluorinated amino esters. Thus, it is necessary to investigate the iminoesters **5** that have easily removable protecting groups under neutral or acidic conditions. From this viewpoint, benzyl ester **5** (R = Bn), which is a good precursor to the free amino acid as a result of the easy removal of the benzyl group (H_2, Pd/C) under neutral conditions, was obtained in high

Scheme 3



yield.[16,19] *tert*-Butyl ester **5** (R = *t*-Bu; **5a**) is an interesting alternate source of fluoro amino acids, because the *tert*-butyl group can be readily removed by treatment with an acid. However, the use of *tert*-butyl alcohol resulted in the production of a trace amount of *tert*-butyl ester **5a**.

In this paper, we describe details of the carboalkoxylation of the fluorinated imidoyl halides **4** under mild conditions and show a dramatic additive effect upon the reaction, which overcomes the limitations for the *tert*-butyl ester preparation, leading to a variety of fluorinated α-amino acids.

Results and Discussion

A Model Experiment: Stoichiometric Reactions of Organopalladium(II) Species with Alcohols. There remains a difficulty in introducing a *tert*-butoxycarbonyl group to an organic molecule by catalytic carboalkoxylation, probably due to steric hindrance of the alcohol nucleophiles. However, the carboalkoxylation with tertiary alcohols has received much less attention despite its great synthetic potential. To overcome this drawback, we have particularly investigated the nucleophilic substitution reaction of alkanoyl palladium(II) complexes with alcohols by direct observation of the reaction intermediates.

The Pd-catalyzed carboalkoxylation reactions are considered to proceed via an acylpalladium(II) intermediate **8** that is formed by oxidative addition of palladium(0) to halides **6**, followed by insertion of carbon monoxide into the palladium−carbon bond of **7**. The following nucleophilic attack of the alcoholic hydroxyl group at the acylpalladium intermediate **8** would terminate the catalytic cycle, affording the ester **9** as depicted in Scheme 3.

In this reaction, there seem to be two important steps: one is the carbonyl-insertion step to generate the acylpalladium complex **8**, and another is the nucleophilic attack of the alcohols to the acylpalladium **8**. The latter step is considered to be especially significant because the reaction rates of the carboalkoxylation decreased with increase of the bulkiness of the alcohol nucleophiles.

We investigated details of the reaction of acylpalladium(II) species with alcohols by stoichiometric use of benzoylchlorobis(triphenylphosphine)palladium(II) complex (**10**)[21] as a model intermediate of the acylpalladium **8** (Scheme 4).

Several attempts to transform **10** to *tert*-butyl benzoate (**11**) have been made by the choice of temperature, solvents, ligands, and bases, but they were of limited success. Even use of *tert*-butyl alcohol as a solvent produced only 24% of *tert*-butyl ester **11**. Interestingly, the reaction was accelerated using DMF as an additive,

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Scheme 4

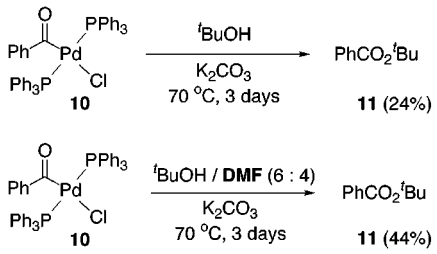
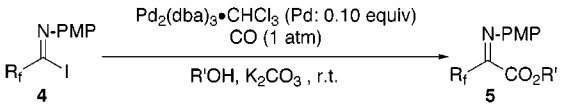


Table 1. Pd-Catalyzed Carbonylation with Bulky Alcohols



entry	R_f	R′	solvent/ additive[a]	time (days)	**5** (% yield)
1	CF_3 (**4a**)	*t*-Bu	*t*-BuOH	2	**5a** (25)
2	CF_3 (**4a**)	*t*-Bu	*t*-BuOH/DMF	4	**5a** (52)
3	CF_3 (**4a**)	*t*-Bu	*t*-BuOH/DMI	3	**5a** (62)
4	C_3F_7 (**4b**)	*t*-Bu	*t*-BuOH/DMI	4	**5b** (71)
5	C_7F_{15}(**4c**)	*t*-Bu	*t*-BuOH/DMI	4	**5c** (74)
6	CF_2Cl (**4d**)	*t*-Bu	*t*-BuOH/DMI	5	**5d** (41)
7[b]	CF_3 (**4a**)	*i*-Pr	toluene	1	**5e** (49)
8[b]	CF_3 (**4a**)	*i*-Pr	toluene/DMF	1	**5e** (72)
9	CF_3 (**4a**)	(*l*)-menthyl	toluene	2	**5f** (12)
10	CF_3 (**4a**)	(*l*)-menthyl	toluene/DMI	2	**5f** (51)

[a] *t*-BuOH/DMF (9:1 v/v), *t*-BuOH/DMI (9:1 v/v), toluene/DMF (9:1 v/v), and toluene/DMI (9:1 v/v). [b] $Pd_2(dba)_3$•$CHCl_3$ (Pd, 0.04 equiv) was used.

and the yields of the benzoate increased up to 44%. Addition of aprotic polar solvents induced a moderate acceleration of the reaction.

Pd-Catalyzed Carboalkoxylation of Trifluoroacetimidoyl Iodides: An Improved Procedure. Indeed, in our case we have found that the carboalkoxylation with secondary and tertiary alcohols afforded the iminoesters **5** (R = *i*-Pr, *t*-Bu) in poor yields (Scheme 2).

The Pd-catalyzed carboalkoxylation of 2,2,2-trifluoroacetimidoyl iodide **4** is also considered to proceed via insertion of CO into the Pd−C bond of the imidoyl palladium intermediate,[22] followed by nucleophilic attack of the alcohol. As mentioned above, formation of the *tert*-butyl esters from acylpalladium intermediates was accelerated using aprotic polar solvents as an additive. Encouraged by the promising effect of the additives, we next explored the catalytic version of the corresponding carboalkoxylation of fluorinated imidoyl iodides **4** according to this modified method.

A mixture of trifluoroacetimidoyl iodide **4a**, $Pd_2(dba)_3$•$CHCl_3$ (Pd atom; 0.10 equiv), K_2CO_3, 0.9 mL of *tert*-butyl alcohol, and 0.1 mL of DMI was sttirred at room temperature for 4 days under CO atmosphere (1 atm). The present modification dramatically increased the yield of the *tert*-butyl iminoester **5a** to 62%.

Other examples of the selective formation of the fluorinated *tert*-butyl iminoesters **5b**−**d** are given in Table 1. Generally, this optimized procedure was found to work well with various kinds of the fluorinated imidoyl iodides **4** (entries 5−7). As shown in Table 1, it is obvious that secondary alcohols such as isopropyl alcohol and (*l*)-menthol worked well in this modified protocol, while reactions in the absence of additives resulted in low conversion (entries 7 and 9).

The additives DMF and DMI might act as a polar solvent to enhance the nucleophilicity of *tert*-butyl alcohol and/or as a weak enough ligand to reduce aggregation[23] of the intermediate palladium species, which blocks Pd coordination sites, and to accelerate coordination of CO to palladium.

Synthesis of Fluorinated α-Amino Acids. Fluorinated iminoester **5a**, hardly accessible by means of other methods, possesses both an easily removable *N*-protecting group (PMP) and an *O*-protecting group (*t*-Bu) and can act as a precursor to fluorinated amino acids by reaction with a range of nucleophiles to the imino carbon of **5**.[7d,f,g,19] The iminoester **5a** has been converted to *tert*-butyl *N*-(*p*-methoxyphenyl)amino-3,3,3-trifluoropropanoate by nucleophilic alkylation of the imine moiety (Scheme 5). Oxidative removal of the *p*-methoxyphenyl group by treatment with CAN (cerium ammonium nitrate) gave the corresponding 2-amino-3,3,3-trifluoropropanoates.

The *tert*-butyl aminoesters **12**−**15**, which are an alternative precursor to fluoro amino acids, readily underwent deprotection of the *t*-Bu group under acidic conditions (HCl (aq)) to give the corresponding 2-amino-3,3,3-trifluoropropanoic acid derivatives **16**−**19** in high yields. It is noted that alkene and alkyne functionalities in **14** and **15**, which would be fragile under Pd-catalyzed hydrogenolytic conditions, were compatible under the present acidic conditions.

Conclusion

Now, fluorine-containing amino acids and their derivatives are receiving increasing attention in the medicinal, agricultural, and material sciences. So there still remains a great demand for more practical, versatile, and reliable methods for the synthesis of fluorinated amino acids. One of the potential advantages of our method is demonstrated by the ready availability of the starting materials and reagents. Furthermore, the success in introducing the easily removable *tert*-butyl group by fine-tuning of the palladium−catalyst system might well contribute to asymmetric amino acid synthesis. Enantioselective reduction or alkylation of the imine moiety of **5** is one of the subjects worthy of further investigation.[19]

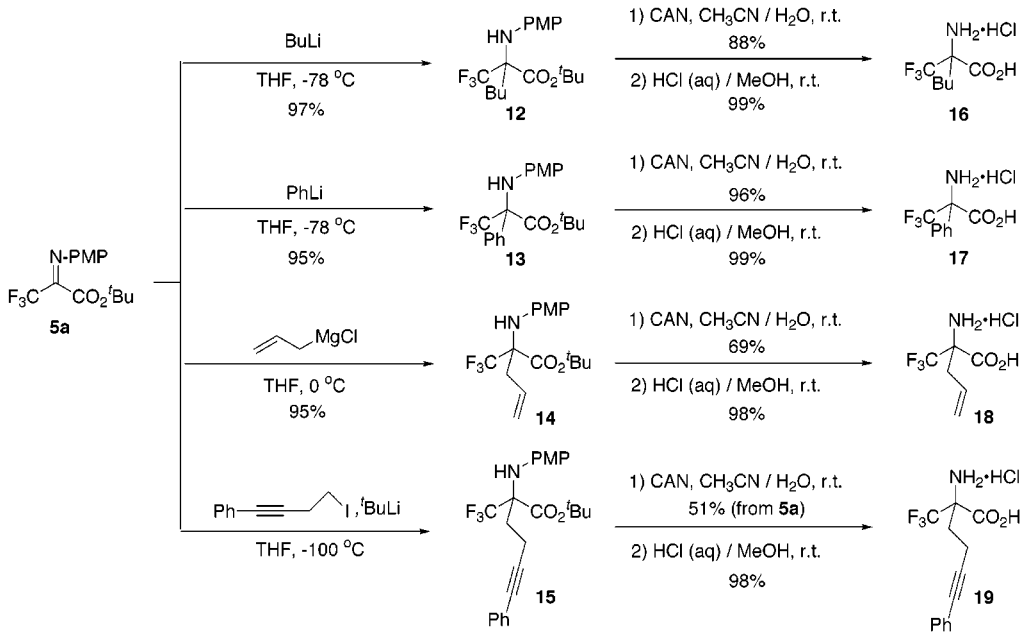
Experimental Section

^1H and ^{19}F NMR spectra were recorded at 200 and 188 MHz, respectively. The chemical shifts are reported in δ (ppm) values relative to TMS (δ 0 ppm for ^1H NMR), C_6F_6 (δ 0 ppm for ^{19}F NMR in $CDCl_3$), and CF_3CO_2H (δ 0 ppm for ^{19}F NMR in D_2O). Coupling constants are reported in hertz (Hz). All air- and/or water-sensitive reactions were carried out under argon atmosphere with dry, freshly distilled solvents using standard syringe-cannula/septa techniques. THF was distilled from sodium/benzophenone ketyl. Toluene, DMF, DMI, and *tert*-butyl alcohol were distilled from CaH_2. All other reagents and

(22) Imidoyl palladium complexes: (a) Tanaka, M.; Alper, H. *J. Organomet. Chem.* **1979**, *168*, 97. (b) Usón, R.; Forniés, J.; Espinet, P.; Lalinde, E.; Jones, P. G.; Sheldrich, G. M. *J. Chem. Soc., Dalton Trans.* **1982**, 2395. (c) Usón, R.; Forniés, J.; Espinet, P.; Garcia, A.; Tomas, M.; Foces-Foces, C.; Cano, F. H. *J. Organomet. Chem.* **1985**, *282*, C35.

(23) Recently, trifluoroacetimidoyl palladium(II) complex ([Pd(μ-I)-{μ-C(CF_3)═N(PMP)}]$_4$:**20**), which is considered to be a key intermediate of Pd-catalyzed carboalkoxylation of imidoyl iodides, has been synthesized by the reaction of **4** with $Pd_2(dba)_3$•$CHCl_3$ and has been confirmed a cyclic tetranuclear complex by X-ray crystal structure analysis. The details of the structure and reactions of the complex **20** will be discussed in a future paper.

Scheme 5



solvents were employed without further purification. E. Merck silica gel (Kieselgel 60, 230−400 mesh) was employed for the chromatography.

Trifluoroacetimidoyl iodide **4a** was prepared by replacement of the chlorine atom of the corresponding chloride **21** with sodium iodide in acetone quantitatively, which was prepared in 80−90% yields by refluxing a mixture of TFA (1 equiv), arylamines (1 equiv), triphenylphosphine (3 equiv), and triethylamine (1 equiv) in CCl_4. Other perfluoroalkaneimidoyl chlorides were also prepared by the same method using the corresponding perfluoroalkanoic acids as a starting material.

***tert*-Butyl 2-[*N*-(*p*-Methoxyphenyl)imino]-3,3,3-trifluoropropanoate (5a).** Typical procedure for the synthesis of *tert*-butyl ester. A two-necked flask with a CO (1 atm) balloon attached was charged with $Pd_2(dba)_3$•$CHCl_3$ (0.017 g, 0.016 mmol) and K_2CO_3 (0.088 g, 0.64 mmol). Then 0.100 g (0.30 mmol) of trifluoroacetimidoyl iodide (**4a**) in 0.9 mL of *tert*-butyl alcohol was added to the catalyst mixture. Subsequently, 0.1 mL of additive (DMI) was added. The reaction vessel was wrapped in aluminum foil to minimize exposure to light, and the mixture was stirred for 4 days at room temperature. The resulting suspension was filtered through a short Florisil column (CH_2Cl_2). After evaporation of the solvent, the residue was purified by silica gel column chromatography (hexane/ether, 15:1) to give a yellow oil (0.057 g, 0.19 mmol, 62%): IR (neat) 1740, 1606 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.01 (d, J = 9.1, 2 H), 6.89 (d, J = 9.1, 2 H), 3.82 (s, 3 H), 1.39 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ 92.1 (s, 3 F); MS m/z 303 (M^+, 16), 247 (100), 202 (91), 134 (20). Anal. Calcd for $C_{13}H_{16}F_3NO_3$: C, 55.45; H, 5.32; N, 4.62. Found: C, 55.54; H, 5.55; N, 4.66.

***tert*-Butyl 2-[*N*-(*p*-Methoxyphenyl)imino]-3,3,4,4,5,5,5-heptafluoropentanoate (5b).** Yellow oil; IR (neat) 1738, 1606 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.02 (d, J = 8.7, 2 H), 6.88 (d, J = 8.7, 2 H), 3.82 (s, 3 H), 1.38 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ 81.5 (t, J = 8.8, 3 F), 48.0 (q, J = 8.8, 2 F), 36.3−36.1 (m, 2 F); MS m/z 403 (M^+, 10), 347 (70), 302 (100), 178 (10), 134 (54). Anal. Calcd for $C_{16}H_{16}F_7NO_3$: C, 47.65; H, 4.00; N, 3.47. Found: C, 47.51; H, 4.04; N, 3.52.

***tert*-Butyl 2-[*N*-(*p*-Methoxyphenyl)imino]-3,3,4,4,5,5,-6,6,7,7,8,8,9,9,9-pentadecafluorononanoate (5c).** Yellow oil; IR (neat) 1738, 1604 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.03 (d, J = 9.0, 2 H), 6.88 (d, J = 9.0, 2 H), 3.82 (s, 3 H), 1.37 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ 81.0 (t, J = 9.4, 3 F), 49.0 (t, J = 12.6, 2 F), 41.0−40.1 (m, 4 F), 40.0−39.4 (m, 2 F), 39.4−38.5 (m, 2 F), 35.9−35.4 (m, 2 F); MS m/z 603 (M^+, 5), 547 (55), 502 (100), 134 (87). Anal. Calcd for $C_{20}H_{16}F_{15}NO_3$: C, 39.82; H, 2.67; N, 2.32. Found: C, 40.06; H, 2.65; N, 2.53.

***tert*-Butyl 2-[*N*-(*p*-Methoxyphenyl)imino]-3-chloro-3,3-difluoropropanoate (5d).** Yellow oil; IR (neat) 1738, 1604 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.01 (d, J = 9.0, 2 H), 6.88 (d, J = 9.0, 2 H), 3.82 (s, 3 H), 1.38 (s, 9 H); ^{19}F NMR ($CDCl_3$) δ 104.4 (s, 2 F); MS m/z 319 (M^+, 15), 263 (89), 218 (78), 178 (17), 134 (100). Anal. Calcd for $C_{14}H_{16}ClF_2NO_3$: C, 52.59; H, 5.04; N, 4.38. Found: C, 52.46; H, 5.27; N, 4.68.

***tert*-Butyl 2-[*N*-(*p*-Methoxyphenyl)amino]-2-trifluoromethylhexanoate (12).** To a THF (3.0 mL) solution of *tert*-butyl iminoester **5a** (0.201 g, 0.66 mmol) stirring under an argon atmosphere at −78 °C was added *n*-butyllithium (1.57 M, 0.46 mL, 0.72 mmol) dropwise. The reaction mixture was stirred for 10 min and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ether (5 mL × 3), and the combined organic phase was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ether, 15:1) to give a slightly yellow oil (0.2314 g, 0.64 mmol, 97%): IR (neat) 3388, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.84 (d, J = 9.2, 2 H), 6.75 (d, J = 9.2, 2 H), 3.76 (s, 3 H), 2.23−2.00 (m, 2 H), 1.51 (s, 9 H), 1.30−1.00 (m, 4 H), 0.76 (t, J = 6.6, 3 H), NH not observable; ^{19}F NMR ($CDCl_3$) δ 88.5 (s, 3 F); MS m/z 361 (M^+, 10), 305 (59), 260 (100), 236 (11), 217 (8), 202 (13). Anal. Calcd for $C_{18}H_{26}F_3NO_3$: C, 59.82; H, 7.25; N, 3.88. Found: C, 59.86; H, 7.49; N, 4.19.

***tert*-Butyl 2-Phenyl-2-[*N*-(*p*-methoxyphenyl)]-3,3,3-trifluoropropanoate (13).** To a THF (0.5 mL) solution of *tert*-butyl iminoester **5a** (0.050 g, 0.167 mmol) stirring under an argon atmosphere at −78 °C was added phenyllithium (0.88 M, 0.21 mL, 0.183 mmol) dropwise. The reaction mixture was stirred for 5 min and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ether (2 mL × 3), and the combined organic phase was washed with brine and dried over $MgSO_4$. After rotary evaporation of the solvent, the residue was purified by silica gel column chromatography (hexane/ether, 15:1) to give a slightly yellow oil (0.0606 g, 0.159 mmol, 95%): IR (neat) 3416, 1742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60−7.50 (m, 2 H), 7.40−7.30 (m, 3 H), 6.59 (d, J = 9.0, 2 H), 6.45 (d, J = 9.0, 2 H), 3.67 (s, 3 H), 1.34 (s, 9 H), NH not observable; ^{19}F NMR ($CDCl_3$) δ 92.7 (s, 3 F); MS m/z 381 (M^+, 5), 325 (24), 280 (100), 256 (5), 210 (45), 202 (10). Anal. Calcd for $C_{20}H_{22}F_3NO_3$: C, 62.98; H, 5.81; N, 3.67. Found: C, 62.61; H, 6.01; N, 3.83.

***tert*-Butyl 2-[*N*-(*p*-Methoxyphenyl)]-2-trifluoromethyl-4-pentenoate (14).** To a THF (1.0 mL) solution of *tert*-butyl iminoester **5a** (0.300 g, 0.989 mmol) stirring under an argon

atmosphere at 0 °C was added allylmagnesium chloride (0.158 M, 8.1 mL, 1.28 mmol) dropwise. The reaction mixture was stirred for 10 min and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ether (5 mL × 3), and the combined organic phase was washed with brine and dried over $MgSO_4$. Rotary evaporation and chromatography (hexane/ether, 15:1) gave the product **14** as a slightly yellow oil (0.324 g, 0.938 mmol, 95%): IR (neat) 3388, 1738, cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.85 (d, J = 9.1, 2 H), 6.75 (d, J = 9.1, 2 H), 5.70−5.35 (m, 1 H), 5.20−5.00 (m, 2 H), 3.76 (s, 3 H), 3.02 (dd, J = 14.6, 5.8, 1 H), 2.77 (dd, J = 14.6, 8.1, 1 H), 1.48 (s, 9 H), NH not observable; ^{19}F NMR ($CDCl_3$) δ 89.0 (s, 3 F); MS m/z 345 (M^+, 9), 289 (54), 244 (55), 202 (100), 174 (13). Anal. Calcd for $C_{17}H_{22}F_3NO_3$: C, 59.12; H, 6.42; N, 4.06. Found: C, 59.37; H, 6.68; N, 4.19.

***tert*-Butyl 6-Phenyl-2-[*N*-(*p*-methoxyphenyl)]-2-trifluoromethyl-5-hexynoate (15).** To a THF (2.0 mL) solution of *tert*-butyl iminoester **5a** (0.201 g, 0.664 mmol) and 4-iodo-1-phenyl-2-butyne (0.204 g, 0.795 mmol) stirring under an argon atmosphere at −100 °C was added *tert*-butyllithium (1.64 M, 0.96 mL, 1.57 mmol) dropwise. The reaction mixture was stirred for 5 min and quenched by adding saturated aqueous NH_4Cl. The aqueous layer was extracted with ether (5 mL × 3), and the combined organic phase was washed with brine and dried over $MgSO_4$. After filtration and evaporation of the solvent, the residue was used in the next deprotection steps without further purification: ^{19}F NMR ($CDCl_3$) δ 88.8 (s, 3 F).

2-Amino-2-trifluoromethylhexanoic Acid Hydrochloride (16). Typical procedure for oxidative deprotection of *p*-methoxyphenyl group and subsequent hydrolytic removal of *tert*-butyl group. A water (1.7 mL) solution of CAN (cerium(IV) ammonium nitrate) (0.341 g, 0.622 mmol) was added dropwise to **12** (0.075 g, 0.208 mmol) in acetonitrile (5 mL). The mixture was stirred at room temperature for 1.5 h, poured into water (2 mL), and succesively extracted with ether (5 mL × 3). The combined organic phase was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel column chromatography to afford *tert*-butyl 2-amino-3,3,3-trifluoromethylhexanoate (0.0357 g, 0.14 mmol). Concentrated hydrochloric acid (1.0 mL) was added dropwise to the *tert*-butyl ester (0.0357 g, 0.14 mmol) in MeOH (0.5 mL). The mixture was stirred at room temperature for 12 h. Evaporation of the solvent gave a colorless solid (0.033 g, 0.138 mmol, 99%): mp > 143 °C (decomp); IR (KBr) 3400−2300 (br), 1754, 1532 cm^{-1}; ^1H NMR (D_2O) δ 2.20−1.92 (m, 1 H), 1.90−1.70 (m, 1 H), 1.30−0.98 (m, 4 H), 0.72 (t, J = 6.8, 3 H); ^{19}F NMR (D_2O) δ 1.3 (s, 3 F). Anal. Calcd for $C_7H_{13}ClF_3NO_2$: C, 35.68; H, 5.56; N, 5.94. Found: C, 35.67; H, 5.65; N, 6.07.

2-Amino-2-phenyl-3,3,3-trifluoropropanoic Acid Hydrochloride (17). Pale yellow solid; mp > 158 °C (decomp); IR (KBr) 3400−2300 (br), 1726, 1504 cm^{-1}; ^1H NMR (D_2O) δ 7.49−7.37 (m, 5 H); ^{19}F NMR (D_2O) δ 5.6 (s, 3 F). Anal. Calcd for $C_9H_9ClF_3NO_2$: C, 42.29; H, 3.55; N, 5.48. Found: C, 42.01; H, 3.36; N, 5.62.

2-Amino-2-trifluoromethyl-4-pentenoic Acid Hydrochloride (18). Colorless solid; mp > 139 °C (decomp); IR (KBr) 3400−2300 (br), 1728, 1512 cm^{-1}; ^1H NMR (D_2O) δ 5.70−5.40 (m, 1 H), 5.35−5.15 (m, 2 H), 2.86 (dd, J = 14.6, 6.0, 1 H), 2.58 (dd, J = 14.6, 8.0, 1 H); ^{19}F NMR (D_2O) δ 1.9 (s, 3 F). Anal. Calcd for $C_6H_9ClF_3NO_2$: C, 32.82; H, 4.13; N, 6.38. Found: C, 32.75; H, 3.88; N, 6.31.

2-Amino-6-phenyl-2-trifluoromethyl-5-hexynoic Acid Hydrochloride (19). Colorless solid; mp > 146 °C (decomp); IR (KBr) 3300−2300 (br), 1760, 1516 cm^{-1}; ^1H NMR (D_2O) δ 7.30−7.13 (m, 5 H), 2.50−2.27 (m, 3 H), 2.25−2.00 (m, 1 H); ^{19}F NMR (D_2O) δ 1.7 (s, 3 F). Anal. Calcd for $C_{13}H_{13}ClF_3NO_2$: C, 50.75; H, 4.26; N, 4.55. Found: C, 51.02; H, 4.50; N, 4.38.

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