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9-(4-Bromophenyl)-9-fluorenyl as a Safety-Catch Nitrogen Protecting Group

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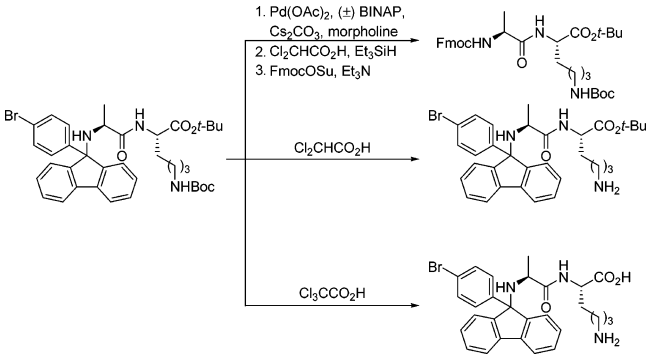

The 9-(4-bromophenyl)-9-fluorenyl (BrPhF) group has been developed as a novel safety-catch amine protection. This relatively acid-stable protecting group can be successfully activated by palladium-catalyzed cross-coupling reaction of the aryl bromide with morpholine and then cleaved effectively under mild conditions using dichloroacetic acid and triethylsilane. Complementary conditions are reported for selective removal of the BrPhF group in the presence of *tert*-butyl esters and carbamates as well as deprotection of *tert*-butyl esters and carbamates in the presence of BrPhF amines.

Protecting groups have been essential for controlling the reactivity of amines in organic synthesis, peptide science, and medicinal chemistry.[1,2] In the context of our research on the synthesis of peptide mimics,[3] the 9-phenyl-9-fluorenyl (PhF) group has been used to prevent the loss of enantiomeric purity during the employment of various amino carbonyl compounds.[4] The PhF group offers several advantages as amine protection. The steric bulk created by the PhF group acts as a barrier that prevents deprotonation of α-amino carbonyl compounds at the α-carbon. The PhF group is significantly more stable under acid conditions relative to the trityl group because of the antiaromatic character of the 9-phenyl-9-fluorenyl carbocation.[5] Furthermore, if deprotonation of the α-carbon occurs under severe conditions, the PhF anion can act as a leaving group and eliminate to furnish an imine intermediate prior to reprotonation and epimerization.[6] The PhF group is usually removed by hydrogenolysis[7] and by solvolysis with treatment under strongly acidic conditions.[8] Alternatively, the PhF group has been removed using sodium or lithium in liquid ammonia,[9] TMSOTf in the presence of triethylsilane,[10] and iodine in MeOH.[11]

Perceiving the advantages of having a chemical means for rendering the PhF group cleavable under mildly acidic conditions, we considered that *p*-aminophenylfluorenyl cations would be significantly more stable than the parent PhF cation. Strategies have been conceived for generating *p*-aminobenzylic intermediates from suitable para-substituted benzyl derivatives. For example, the *p*-nitrobenzyl ester has been used in the synthesis of carbapenems and removed by nitro group reduction and solvolysis.[12] More recently, *p*-halobenzyl ethers were reported to be as stable as normal benzyl ethers yet cleavable using a two-step process featuring catalytic amination of the aryl halide and solvolysis with acid.[13]

In our previous work, we used the 9-(4-bromophenyl)-9-fluorenyl (BrPhF) group in a linking-protecting group strategy for the synthesis of enantiopure norephedrines on solid support.[14] The BrPhF group proved tolerant to similar chemistry previously developed with PhF-protected amino acids before it reacted in a palladium-catalyzed cross-coupling with bis(pinacolato)-diboron ester to give a suitable boronate for attaching the PhF-protected substrate to aryl halide resins. Pursuing the development of this protecting group, we demonstrate now that the BrPhF group can be employed as a safety-catch[15] amine protecting group which can be released by catalytic amination followed by treatment with mild acid.

The relative acid stability of the PhF group and an analogue bearing a *p*-aminophenyl substituent was studied by the synthesis of *N*-(9-(4-morpholinophenyl)-9-fluorenyl)alanine methyl ester **2** and comparison of its reactivity under acid conditions with *N*-(PhF)alanine methyl ester (Scheme 1, MPF = 9-(4-morpholinophenyl)-9-fluorenyl).

Both *N*-(PhF)- and *N*-(BrPhF)alanine methyl esters were synthesized as previously described.[14,16] Amination of BrPhF-Ala-OMe (**1**) with morpholine using 5 mol % of $Pd(OAc)_2$, (±)-BINAP, and excess Cs_2CO_3 provided *N*-(MPF)alanine methyl ester (**2**) in 81% yield. Competitive cleavage of *N*-(PhF)alanine

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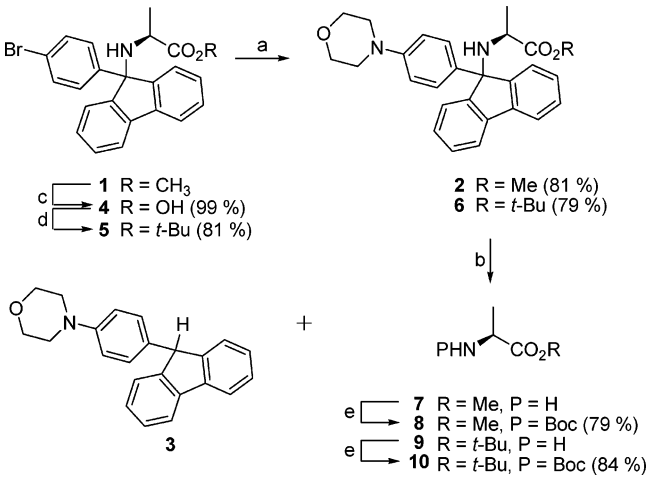
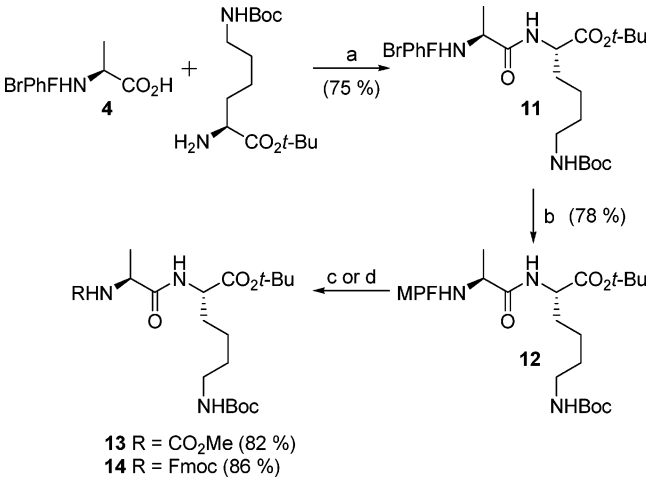
SCHEME 1. Synthesis and Solvolysis of *N*-(MPF)alanine Esters[a]



[a] Key: (a) $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, morpholine, $PhCH_3$, reflux; (b) $CHCl_2CO_2H$, Et_3SiH, CH_2Cl_2; (c) LiOH, H_2O/dioxane; (d) *O*-*tert*-butyl trichloroacetamidate, CH_2Cl_2; (e) Boc_2O, Et_3N, CH_2Cl_2.

SCHEME 2. Synthesis and Solvolysis of *N*-(MPF)-Protected Dipeptides[a]



[a] Key: (a) DCC, HOBt, DIEA, CH_2Cl_2; (b) $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, morpholine, $PhCH_3$, reflux; (c) (i) $CHCl_2CO_2H$, Et_3SiH, CH_2Cl_2, (ii) Et_3N, $ClCO_2Me$; (d) (i) $CHCl_2CO_2H$, Et_3SiH, CH_2Cl_2, (ii) Et_3N, FmocOSu.

methyl ester and *N*-(MPF)alanine methyl ester (**2**) was performed by treating an equimolar mixture of the protected amino acids in CH_2Cl_2 with trichloroacetic acid and triethylsilane. Under these conditions, the 9-(4-morpholinophenyl)-9-fluorenyl group was cleaved within 5 min as monitored by HPLC, which detected 9-(4-morpholinophenyl)-9-fluorene (**3**). The PhF-protected methyl ester remained stable and no trace corresponding to PhFH was observed by HPLC. Employing the milder dichloroacetic acid under the same conditions, complete solvolysis of *N*-(MPF)alanine methyl ester (**2**) occurred within 30 min.

The selective removal of the BrPhF group from an amino *tert*-butyl ester was next studied to establish cleaving conditions tolerant to a more acid-labile group. *N*-(BrPhF)Alanine **4** was synthesized as previously described by hydrolysis of methyl ester **1** using LiOH.[14] *N*-(BrPhF)alanine *tert*-butyl ester (**5**) was then prepared in 81% yield by treating the amino acid with *O*-*tert*-butyl trichloroacetimidate[17] in dichloromethane followed by chromatography. The conversion of *N*-(BrPhF)alanine *tert*-butyl ester (**5**) to *N*-(MPF)alanine *tert*-butyl ester (**6**) was achieved in 79% yield using the palladium-catalyzed reaction conditions mentioned above. Exposure of a 1:1 mixture of *N*-(PhF)alanine *tert*-butyl ester[18] and *N*-(MPF)alanine *tert*-butyl ester (**6**) to dichloroacetic acid and triethylsilane in CH_2Cl_2 caused selective deprotection in 30 min as monitored by HPLC which indicated the appearance of morpholine **3** and no traces of 9-phenylfluorene nor any corresponding acids after 30 min. Treatment of *N*-(MPF)alanine *tert*-butyl ester (**6**) with 20 equiv of dichloroacetic acid and 2 equiv of triethylsilane in CH_2Cl_2 for 30 min followed by addition of 22 equiv of triethylamine and Boc_2O provided *N*-(Boc)alanine *tert*-butyl ester in 84% yield. Alternatively, alanine *tert*-butyl ester could be isolated as its hydrochloride salt in 89% yield after MPF deprotection, extraction with dilute aqueous HCl, and lyophilization.

To explore more deeply the strengths and limitations of this protection group *N*-(BrPhF)alaninyl(ω-Boc)lysine *tert*-butyl ester (**11**) was synthesized by coupling acid **4** with (ω-Boc)-lysine *tert*-butyl ester using DCC and HOBt in 75% yield (Scheme 2).

Conversion to the *N*-(MPF) dipeptide **12** was effected as previously described in 78% yield. The MPF-protected amine was selectively deblocked using $CHCl_2CO_2H$ and Et_3SiH and the free amine was subsequently converted in situ to a methyl carbamate using methylchloroformate and Et_3N in 82% yield. The ^1H NMR spectrum of the crude mixture showed a one-to-three ratio of singlets corresponding to the methyl and *tert*-butyl protons for the carbamates indicating that no deprotection of the Boc-protected amine had occurred. The LC−MS analysis of the crude mixture also confirmed that Boc-deprotection did not occur during the sequence. Using a similar protocol, *N*-(Fmoc)alaninyl(ω-Boc)lysine *tert*-butyl ester (**14**) was synthesized by deprotecting the MPF-amine and reprotecting using FmocOSu and Et_3N in 86% yield.

Selective removal of *tert*-butyl esters in the presence of PhF amines has been recently reported to be effectively accomplished using $ZnBr_2$ in CH_2Cl_2.[18] When BrPhF-Ala-O*t*Bu (**5**) was submitted to these conditions, *N*-(BrPhF)alanine was obtained in 82% yield (Scheme 3). The acid stability of the BrPhF group was demonstrated by the selective removal of the Boc group using Cl_2CHCO_2H which afforded dipeptide **15** in 72% yield, as well as by removal of both the *tert*-butyl ester and carbamate groups using the stronger acid Cl_3CCO_2H to give dipeptide **16** in 73% yield. These results demonstrated that the orthogonal nature of the BrPhF/*tert*-Bu combination of protecting groups can be utilized in both directions.

In sum, we have demonstrated the utility of the 9-(4-bromophenyl)-9-fluorenyl group as safety-catch amine protection. Similar to the PhF group, the BrPhF group may be used to ensure the configurational stability of amino carbonyl compounds. This relatively acid stable group can then be rendered susceptible to mild acid solvolysis by palladium-catalyzed amination. The potential of this strategy has been illustrated by the palladium-mediated selective cleavage of the BrPhF-amine in the presence of the acid labile *tert*-butyl ester and carbamate groups and complementary removal of either Boc

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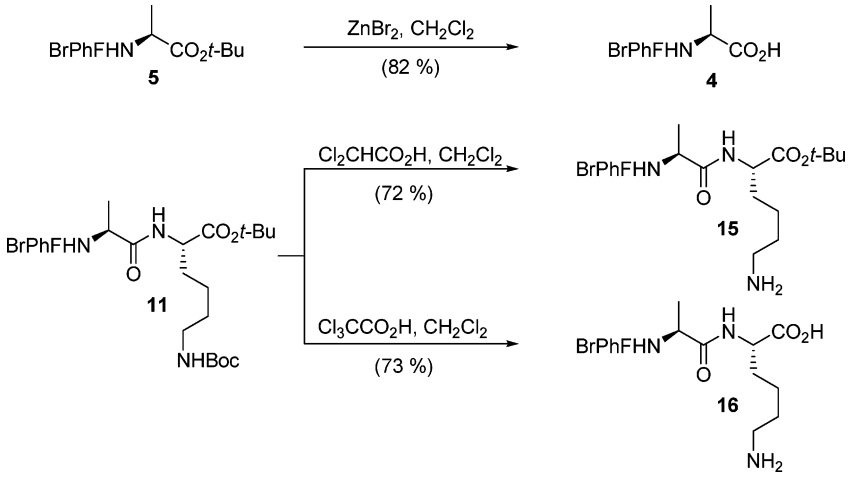
SCHEME 3. Selective *tert*-Butyl Ester and Carbamate Cleavage



group or both Boc and *tert*-butyl ester groups in the presence of the BrPhF-amine. Considering the need for selective methods for removing acid labile protecting groups, the BrPhF group should find general utility in the synthesis of amines.

Experimental Section

(2*S*)-*N*-(BrPhF)alanine *tert*-Butyl Ester (5). To a stirred suspension of (2*S*)-*N*-(BrPhF)alanine (540 mg, 1.32 mmol, prepared according to ref 14) in CH_2Cl_2 (4 mL) was added *O*-*tert*-butyl trichloroacetimidate (578 mg, 2.64 mmol). The mixture was stirred for 1 day, filtered, evaporated, and resubmitted to the same conditions as above for 2 days. Filtration and evaporation, followed by chromatography (5% EtOAc in hexanes) gave ester **5** (495 mg, 81%) as a clear oil: $[\alpha]^{20}_D$ −51.3 (*c* 1.5, CH_3OH); ^{1}H NMR δ 7.72 (d, J = 7.8 Hz, 2H) 7.40−7.26 (m, 10H), 3.09 (s, 1H), 2.69 (q, J = 7.1 Hz, 1H), 1.23 (s, 9H), 1.13 (d, J = 7.1 Hz, 3H); ^{13}C NMR δ 175.4, 148.9, 148.6, 143.7, 140.3, 139.7, 130.9, 127.99, 127.96, 127.7, 127.6, 127.5, 125.4, 124.8, 120.7, 119.7, 119.5, 80.1, 72.3, 51.6, 27.5, 21.8; HRMS calcd for $C_{26}H_{27}BrNO_2$ $[M + H]^+$ 464,1227, found 464.1219.

General Procedure for *N*-(MPF)amine Synthesis. The BrPhF-protected amine (2.5 mmol) was dissolved in 5 mL of dry and degassed toluene and treated with $Pd(OAc)_2$ (28 mg, 0.13 mmol), BINAP (79 mg, 0.13 mmol), and dry Cs_2CO_3 (4.07 g, 12.5 mmol), followed by morpholine (257 μL, 3.0 mmol). The mixture was heated at reflux and stirred for 24 h, filtered on Celite, washed with CH_2Cl_2, and the combined filtrate and washings were evaporated. The residue was chromatographed to afford the MPF-protected amine.

(2*S*)-*N*-(MPF)alanine Methyl Ester (2). Chromatography of the product from **1** (1.00 g, 2.4 mmol) using 20% EtOAc in hexanes as eluant gave **2** (820 mg, 81% yield) as a yellowish solid: mp 62−64 °C; $[\alpha]^{20}_D$ −121.1 (*c* 2.2, CH_3OH); ^{1}H NMR δ 7.68 (dd, J = 7.5 Hz, 2.5 Hz, 2H), 7.33 (m, 5H), 7.23 (m, 3H), 6.77 (d, J = 8.9 Hz, 2H), 3.82 (t, J = 4.8 Hz, 4H), 3.30 (s, 3H), 3.10 (t, J = 4.8 Hz, 4H), 2.77 (q, J = 7.0 Hz, 1H), 1.12 (d, J = 7.0 Hz, 3H); ^{13}C NMR δ 177.1, 150.1, 149.4, 148.8, 140.6, 139.9, 135.6, 128.0, 127.6, 127.2, 126.9, 125.8, 124.8, 119.8, 119.7, 115.1, 72.4, 66.7, 51.4, 51.2, 49.0, 21.4; HRMS calcd for $C_{27}H_{28}N_2O_3Na$ $[M + Na]^+$ 451.1989, found 451.1992.

General Procedure for MPF-Solvolysis. The MPF-protected amine (0.4 mmol) was dissolved in 4 mL of CH_2Cl_2, treated with dichloroacetic acid (660 μL, 8 mmol) and triethylsilane (128 μL, 0.8 mmol), stirred at rt for 30 min, and evaporated on a rotary evaporator. The residue was dissolved in 10 mL of Et_2O and treated with 10 mL of 0.5 M HCl solution. The aqueous phase was separated, washed twice with 5 mL of Et_2O, and lyophilized to give the unprotected amine as a hydrochloride salt. Alternatively, after complete solvolysis of MPF-amine was observed by TLC, the reaction mixture was treated with 22 equiv of Et_3N followed by 200 mol % of either Boc_2O, methyl chloroformate or FmocOSu, stirred overnight, diluted with CH_2Cl_2, washed with H_2O, 0.5 N HCl, and brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by flash chromatography[20] to give, respectively, the Boc-, methyl carbamoyl- or Fmoc-protected amino ester.

(2*S*)-Alanine *tert*-Butyl Ester Hydrochloride (9). Lyophilization of aqueous layer after solvolysis of **6** (190 mg, 0.4 mmol) gave **9** (65 mg, 89% yield) as a white solid: mp 170 °C dec (lit.[19] mp 168 °C dec); $[\alpha]^{20}_D$ 6.1 (*c* = 1.0, EtOH) [lit.[19] $[\alpha]^{20}_D$ 3.0 (*c* = 2.0, EtOH)]; HRMS calcd for $C_7H_{15}NO_2Na$ $[M + Na]^+$ 168.0995, found 168.0987.

***N*-(Fmoc)alaninyl-ω-(Boc)lysine *tert*-Butyl Ester (14).** Chromatography of the product from **12** (30 mg, 0.11 mmol) using 30% EtOAc/hexanes as eluant gave **14** as a white powder (22.0 mg, 86% yield): mp 67−69 °C; $[\alpha]^{20}_D$ −16.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.76 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 7.4 Hz, 2H), 7.39 (t, J = 7.2 Hz, 2H), 7.31 (tt, J = 7.5, 1.2 Hz, 2H), 6.59 (d, J = 6.7 Hz, 1H), 5.59 (s, 1H), 4.69 (s, 1H), 4.45 (m, 1H), 4.38 (d, J = 7.0 Hz, 2H), 4.29 (m, 1H), 4.22 (t, J = 7.0 Hz, 1H), 3.06 (d, J = 5.5 Hz, 1H), 1.84 (m, 2H), 1.65 (m, 1H), 1.52−1.27 (m, 6H), 1.46 (s, 9H), 1.42 (s, 9H); ^{13}C NMR δ 171.8, 171.0, 156.0, 155.8, 143.6, 141.1, 127.6, 126.9, 125.0, 119.8, 82.1, 79.0, 67.0, 52.4, 50.3, 47.0, 39.9, 33.5, 29.2, 28.3, 27.8, 21.9, 18.6; HRMS calcd for $C_{33}H_{45}N_3O_7$ $[M + Na]^+$ 618.31389, found 618.31389.

4-[4-(9*H*-Fluoren-9-yl)phenyl]morpholine (3). The *N*-arylamine **3** was isolated by flash chromatography as the second eluting compound of the crude residue in the solvolysis of the MPF-protected amine **5**: ^{1}H NMR δ 7.82 (d, J = 7.5 Hz, 2H), 7.42−7.26 (m, 6H), 7.03 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.3 Hz, 2H), 5.02 (s, 1H), 3.87 (t, J = 4.8 Hz, 4H), 3.15 (t, J = 4.8 Hz, 4H); ^{13}C NMR δ 149.7, 147.9, 140.5, 128.7, 126.9, 126.8, 124.9, 119.4, 115.5, 66.6, 53.3, 49.0; MS (ESI, *m*/*z*) 328.3 $(MH)^+$.

(2*S*)-*N*-(BrPhF)alanine (4). A stirred solution of *N*-(BrPhF)-alanine *tert*-butyl ester (**6**) (45 mg, 0.1 mmol) in 0.5 mL of dichloromethane was treated with $ZnBr_2$ (110 mg, 0.5 mmol) at rt,

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stirred for 24 h, treated with water (2 mL), stirred for 2 h, and treated with CH_2Cl_2 (5 mL). The organic phase was separated. The aqueous layer was extracted twice with CH_2Cl_2 (2 mL). The organic portions were combined, dried, filtered, and evaporated. The residue was chromatographed (50% EtOAc:hexanes containing 1% AcOH) to afford 32.5 mg (82% yield) of *N*-(BrPhF)alanine as a white solid: mp 116−118 °C; $[\alpha]^{20}_D$ −16.5 (*c* 1.1, CH_3OH). The spectroscopic data were identical to those reported.[14]

***N*-(BrPhF)alaninyl-ω-(Boc)lysine *tert*-Butyl Ester (11).** *N*-(BrPhF)alanine (**4**), (514 mg, 1.26 mmol), DCC (311 mg, 1.51 mmol), and HOBt (204 mg, 1.51 mmol) were dissolved in 13 mL of CH_2Cl_2, treated with ω-(Boc)lysine *tert*-butyl ester (380 mg, 1.26 mmol), stirred for 24 h, filtered, washed with a 10% HCl solution, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated to a residue that was purified by chromatography (50% EtOAc/hexanes) to afford 651 mg (75% yield) of **11** as a white powder: mp 83−85 °C; $[\alpha]^{20}_D$ −20.8 (*c* 1.0, CH_3OH); ^{1}H NMR δ 7.96 (d, J = 7.6 Hz, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.44−7.25 (m, 9H), 7.05 (t, J = 7.5 Hz, 1H), 4.68 (m, 1H), 4.27 (q, J = 7.2 Hz, 1H), 3.10 (m, 2H), 2.47 (q, J = 7.1 Hz, 1H), 2.25−1.80 (bs, 1H), 1.75 (m, 1H), 1.62 (m, 1H), 1.54 (s, 9H), 1.43 (s, 9H), 1.54−1.43 (m, 2H), 1.29 (m, 2H), 1.09 (d, J = 7.1 Hz, 3H); ^{13}C NMR δ 175.1, 171.8, 156.1, 148.9, 147.3, 143.5, 141.4 140.0, 131.6, 128.9, 128.8, 128.2, 128.1, 127.7, 126.1, 124.3, 121.4, 120.4, 120.2, 82.2, 79.1, 73.0, 52.8, 51.9, 40.4, 33.0, 29.5, 28.5, 28.1, 22.2, 21.8; HRMS calcd for $C_{37}H_{46}BrN_3O_5Na$ $[M + Na]^+$ 714.25131, found 714.25002.

***N*-(BrPhF)alaninyllysine *tert*-Butyl Ester (15).** *N*-(BrPhF)-alaninyl(ω-Boc)lysine *tert*-butyl ester **11** (50 mg, 0.072 mmol) was dissolved in 150 μL of CH_2Cl_2, treated with 150 μL of Cl_2CHCO_2H, and stirred for 21 h. The mixture was diluted with 5 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ (2 × 3 mL), dried over $MgSO_4$, concentrated, and purified by chromatography (5% MeOH/$CHCl_3$ + 1% Et_3N) to give amine **15 (**30.7 mg, 72% yield) as a brownish oil: $[\alpha]^{20}_D$ 39.7 (*c* 2.6, $CHCl_3$); ^{1}H NMR (CD_3OD) δ7.80 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.46−7.26 (m, 9H), 7.08 (dt, J = 1.0, 7.6 Hz, 1H), 4.06 (m, 1H), 2.90 (m, 2H), 2.44 (q, J = 7.1 Hz, 1H), 1.73 (m, 1H), 1.64 (m, 3H), 1.53 (s, 9H), 1.29 (m, 2H), 1.08 (d, J = 7.1 Hz, 3H); ^{13}C NMR (CD_3OD) δ 178.6, 172.5, 150.5, 149.3, 145.3, 142.4, 141.6, 132.3, 129.9, 129.7, 129.3, 128.4, 127.2, 125.8, 122.0, 121.1, 83.5, 74.2, 53.8, 53.3, 40.5, 33.1, 28.3, 28.0, 23.5, 21.5; HRMS calcd for $C_{32}H_{39}BrN_3O_3Na$ $[M + H]^+$ 592.21693, found 592.21666.

***N*-(BrPhF)alaninyllysine (16).** The BrPhF-protected dipeptide **11** (40 mg, 0.058 mmol) was dissolved in 300 μL of CH_2Cl_2, treated with Cl_3CCO_2H (236 mg, 1.44 mmol), and stirred for 72 h. The mixture was diluted with 5 mL of CH_2Cl_2, washed with 0.1 N HCl (2 × 3 mL), lyophilized, triturated with Et_2O, and purified on reversed-phase preparative HPLC to afford **16** (22.6 mg, 73% yield) as a white gum: $[\alpha]^{20}_D$ −3.1 (*c* 1.1, CH_3OH); ^{1}H NMR (D_2O) δ 7.78 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 7.4 Hz, 1H), 7.47 (t, J = 7.2 Hz, 1H), 7.32 (m, 3H) 7.21 (d, J = 8.5 Hz, 2H), 7.12 (m, 2H), 6.98 (d, J = 8.6 Hz, 2H), 3.47 (t, J = 6.6 Hz, 1H), 3.12 (q, J = 6.6 Hz, 1H), 2.87 (m, 2H), 1.51 (m, 2H), 1.33 (m, 2H), 1.19 (d, J = 7.1 Hz, 3H), 1.01 (m, 2H);^{13}C NMR (D_2O) δ 175.5, 170.1, 140.8, 140.3, 140.1, 131.6, 130.8, 130.6, 129.0, 127.9, 126.9, 126.8, 124.9, 122.0, 120.9, 120.4, 73.3, 53.2, 52.7, 38.6, 29.5, 26.0, 21.6, 16.9; HRMS calcd for $C_{28}H_{31}BrN_3O_3$ $[M + H]^+$ 536.15433, found 536.15304.

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Supporting Information Available: General Experimental Section, ^{1}H and ^{13}C NMR data for compounds **6**, **8**, **10**, **12**, and **13**, copies of ^{1}H and ^{13}C NMR spectra of compounds **2**, **3**, **5**, **6**, and **11**−**16**, and HPLC traces of competitive cleavage experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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