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Base-labile *tert*-butoxycarbonyl (Boc) group on phenols ☆

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Abstract—Phenols are deprotected with weak bases from their *tert*-butoxycarbonyl (Boc) derivatives. Boc deprotection with bases can avoid side reactions during the deprotection with acids. We note the lability of the Boc to bases and are able to utilize it as a new cleavage condition for synthetic studies.

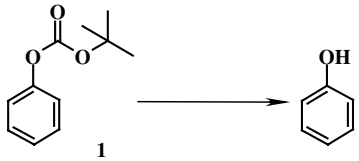
1. Introduction

A variety of natural polyphenols have become of interest to many scientists and synthetic research has been vigorously carried out in recent years.[1] The phenolic hydroxyl group(s) on them often play an important role in their biological activities.[2] Protection of the hydroxyl group(s) is necessary in order to maintain these activities and avoid expected side reactions. Variety kinds of protecting groups for phenols have been developed and utilized in synthetic studies.[3] Recent research has reported the usefulness of the *tert*-butoxycarbonyl (Boc) group for phenols.[4] The Boc group is extensively used for amino protection for chemically inertness to nucleophilic reagents including the base and deprotection using acid reagents.[5] Based on these properties, we could employ the Boc as a protecting group for phenols. We report herein our results that provide additional information about the already known properties of the Boc group on phenols.

2. Results and discussion

An electron donating *tert*-butyl group and resonance in the Boc deactivate the carbonyl carbon of the Boc group. Therefore, the Boc group can resist nucleophilic reagents. Actually, the Boc group on an amino group of D,L-phenylalanine was inert to treatment with 75% piperidine in CH_2Cl_2 or 1 N NaOH in THF.[6] However, the Boc group on phenol was labile to bases. Table 1 shows the cleavage conditions for the Boc group

Table 1



1

Base/solvent	Equiv[c]	Time (h)	Yield (%)
0.5%[a] MeONa/CH_2Cl_2	1.2	1	88
1 N NaOH/MeOH (2/1)	10	8	75
15 N NH_3 aq/MeOH (2/1)	150	5	94
25%[b] Piperidine/CH_2Cl_2	30	6	86
10%[b] DBU/CH_2Cl_2	20	3	83
10%[b] TEA/CH_2Cl_2	22	48	—[d]
20%[b] Pyridine/CH_2Cl_2	33	48	—[d]

[a] %, w/v.
[b] %, v/v.
[c] Equivalent of base.
[d] The Boc group was not cleaved under these basic conditions.

Keywords: Phenols; *tert*-Butoxycarbonyl (Boc) group; Deprotection; Base.

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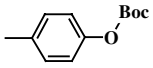
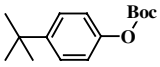
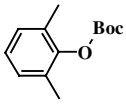
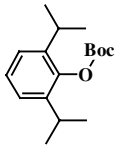
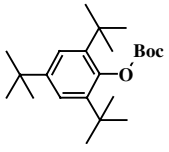
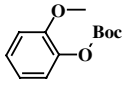
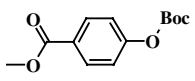
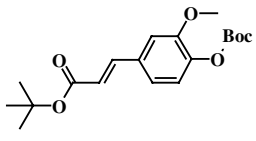
on a phenol with bases.[7,8] The Boc group was removed by treatment in dilute solutions of MeONa in CH_2Cl_2 for 1 h and the phenol was recovered in good yield. Only a catalytic amount of MeONa (1.2 equiv) was necessary to complete this deprotection. MeOH containing a catalytic amount of 1 N NaOH or excess amount of ammonia was the reagent used to remove the Boc group. Piperidine (25%) or 10% DBU in CH_2Cl_2 (both are reagents used to deprotect the base-labile Fmoc group[9] in the peptide synthesis) was enough to cleave the Boc group. However, the Boc group resisted 10% TEA or 20% pyridine in CH_2Cl_2. To examine the Boc deprotective conditions for several kinds of phenols with bases, **2**–**9** in Table 2 were synthesized using $(Boc)_2O$/DMAP.[4a,10,11] Though harder basic conditions than that for phenol were required, the Boc on **2** and **3** possessing an electron-releasing group were cleaved by treatment with piperidine or NaOH. As the electron-releasing effect by the substituted alkyl group(s) increased, more drastic basic conditions were required to cleave it. Steric hindrance is also one of the major factors making a phenolic Boc group stable for bases. The Boc where it locates between two methyl groups on **4** resisted 75% piperidine, though cleaved with 28% MeONa or 10 N NaOH, which are relatively harder basic conditions. Higher steric hindered Boc where it locates between two isopropyl groups on **5** was cleaved with 28% MeONa, but not with 10 N NaOH. It took longer to remove the Boc on **5** with 28% NaOMe completely than to remove it on **4**. The Boc on **6** possessing highest steric hindrance and electron-releasing properties among phenols in this paper was not cleaved under basic conditions showing in the table anymore. The Boc on **7** possessing a methoxy group, which had a relative electron-releasing property,

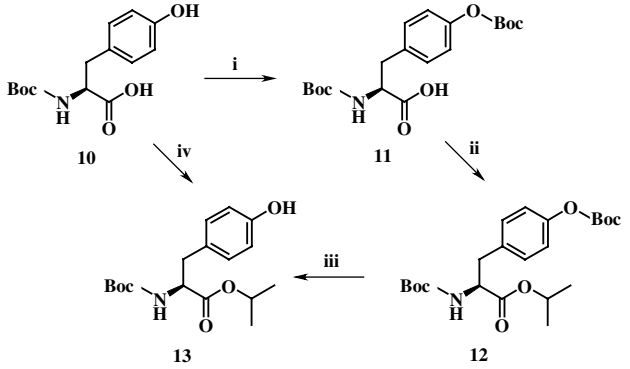
Table 2

	Boc–phenols	Base/solvent	Equiv[c]	Time (h)	Yield (%)
2		1 N NaOH/MeOH (2/1)	10	12	81
		25%[a] Piperidine/CH_2Cl_2	75	9	84
3		1 N NaOH/MeOH (2/1)	10	24	87
		50%[a] Piperidine/CH_2Cl_2	150	10	93
4		28%[b] MeONa/MeOH	12	3	98
		10 N NaOH/MeOH (3/20)	30	12	90
		75%[a] Piperidine/CH_2Cl_2	450	48	—[d]
5		28%[b] MeONa/MeOH	12	9	96
		10 N NaOH/MeOH (3/20)	30	48	—[d]
		75%[a] Piperidine/CH_2Cl_2	450	48	—[d]
6		28%[b] MeONa/MeOH	12	48	—[d]
		10 N NaOH/MeOH (3/20)	30	48	—[d]
		75%[a] Piperidine/CH_2Cl_2	450	48	—[d]
7		1 N NaOH/MeOH (2/1)	10	10	94
		25%[a] Piperidine/CH_2Cl_2	75	6	97
8		10%[a] DIPEA/CH_2Cl_2	17	48	—[d]
		1%[a] Piperidine/CH_2Cl_2	1.3	20	89
		10%[a] Piperidine/CH_2Cl_2	1.3	4	92
9		1 N NaOH/MeOH (2/1)	10	3	92
		1%[a] Piperidine/CH_2Cl_2	1.3	36	92
		10%[a] Piperidine/CH_2Cl_2	1.3	6	90
		20%[a] Pyridine/CH_2Cl_2	33	48	—[d]

[a] %, v/v.
[b] %, w/v.
[c] Equivalent of base.
[d] The Boc group was not cleaved under these basic conditions.

was cleaved under similar conditions as **2**. The electron-withdrawing group substituted on the benzene ring made the Boc much more sensitive to base. The Boc on methyl 4-*tert*-butoxycarbonyloxy-benzoate (**8**) and *tert*-butyl 4-*tert*-butoxycarbonyloxy-3-methoxy-cinnamate (**9**) were cleaved even with 1% piperidine in CH_2Cl_2. The methyl ester on **8** was completely safe during the deprotection using 10% or 1% piperidine, and methyl 4-hydroxylbenzoate was obtained in good yield as a deprotected product. Of course, the *tert*-butyl ester on **9** was stable under basic conditions and the selective cleavage of the Boc was achieved. These base-sensitive Boc, however, resisted DIPEA or pyridine.

During the deprotection of Boc on **9** in benzyl alcohol, *O*-Boc-benzyl alcohol was isolated in 76% yield besides the deprotected product, and the piperidine treatments of **8** and **9** quantitatively yielded *N*-Boc-piperidine. These products indicated that the main reactions for cleavage of the Boc with bases is the transesterification of the Boc to benzyl alcohol in the presence of bases and the transition of the Boc to an amino group on piperidine. It is suggested that the following particularity of phenol makes these reactions possible. More than a pair of electrons on the oxygen atom adjacent to the benzene ring can be shared with the ring and delocalized. This resonance could render the carbonyl carbon active enough to be attacked by a nucleophile including the amino or hydroxyl groups, even though the carbonyl carbon of the Boc is deactivated by an electron donating *tert*-butyl group and the effect of resonance in the Boc. However, hindered nucleophiles like tertiary amines or pyridine with a much weaker nucleophilicity could not attack the carbonyl carbon, even on **8** and **9**. The effects of the substituents on the benzene ring support this reaction mechanism. Electron-attracting substituents tend to induce the resonance described above and could make the Boc sensitive to base, whereas the electron-releasing substituents could make the Boc insensitive to base by maintaining the resonance.



Scheme 1. Reagents and conditions: (i) $(Boc)_2O$, DMAP (1 mol%), CH_2Cl_2, TEA, 3 h, rt, 89%; (ii) isopropanol, EDC·HCl, DMAP (10 mol%), CH_2Cl_2, 3 h, rt, 88%; (iii) 50% piperidine (150 equiv), CH_2Cl_2, 3 h, rt, 85%; (iv) $(Boc)_2O$, DMAP (1 mol%), CH_2Cl_2, TEA, 3 h; isopropanol, EDC·HCl, DMAP (20 mol%), 3 h; piperidine (75 equiv), 2 h, rt, 81%.

Scheme 1 shows a utilization of the Boc deprotection with base for a synthesis of tyrosine derivative **13**, which is one of available reactants of angiotensin-converting enzyme inhibitor.[12,13] **11** was prepared from commercially available Boc-Tyr-OH in ordinary method. Then the carbonyl group was esterified with isopropanol in good yield. Without Boc protection of phenol group, esterification among Tyr derivatives was imperative. The Boc on phenol worked as a protecting group in the esterification. In order to form **13**, the Boc on phenol ring was selectively removed from the Boc on amino group with piperidine. As a result of these successful reactions, **13** could be synthesized in one pot reaction in good yield (route iv in Scheme 1).

We confirmed that all Boc-phenols in this study could be cleaved with acids, such as 100% TFA and 4 N HCl/dioxane.[14] During the deprotection of the Boc group with acids, by-products substituted by the liberated *tert*-butyl cations on the aromatic ring were observed. During the deprotection of **3** with 30% TFA–CH_2Cl_2, 10% of a by-product was presented in the crude products.[15] Removal of the Boc with bases effectively avoids these side reactions. The data described in this paper display a unique property of the Boc on phenols. Thus, we should note the lability of the Boc to nucleophilic reagents including bases and be able to utilize it as a new cleavage condition for the Boc in synthetic studies.

References and Notes

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6. After treatment of Boc-D,L-Phe-OH with 30 equiv of each base at room temperature for 24 h, it was recovered in over 90% yield.
7. Synthesis of 1-*tert*-butoxycarbonyloxybenzene (**1**): To a solution of 0.47 g (5.0 mmol) of phenol and 61 mg (0.5 mmol) of 4-dimethylaminopyridine (DMAP) in 5 mL CH_2Cl_2, 1.1 g (5.0 mmol) of di-*tert*-butyl dicarbonate ($(Boc)_2O$) was added at room temperature. After stirring for 1 h, the reaction mixture was evaporated under reduced pressure, then the residue was purified through a silica gel column (hexane/ethyl acetate = 1/0 to 10/1). The product was obtained as a colorless oil, 0.91 g (4.7 mmol), 94% yield; $R_f = 0.52$ (hexane/ethyl acetate = 5/1); IR (neat) 3045, 2982, 2936, 1759, 1497, 1371, 1275, 1259, 1217, 1150 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) δ 7.38–7.32 (2H, m, ArH), 7.23–7.18 (1H, tt, $J = 7.4$, 1.2 Hz, ArH), 7.17–7.14 (2H, m, ArH), 1.55 (9H, s, CH_3); 100 MHz ^{13}C NMR ($CDCl_3$) δ 151.9 (C), 151.1 (C), 129.3 (CH), 125.7 (CH), 121.2 (CH), 83.4 (C), 27.7 (CH_3).
8. Cleavage of the Boc on phenol with bases: Boc cleavage with MeONa on **1**: To a solution of 19 mg (100 μmol) of **1** in 1 mL CH_2Cl_2, 23 mg (120 μmol) of 28% sodium methoxide in methanol was added at room temperature. After stirring for 1 h, to the reaction mixture was added 30 mL of ethylacetate and 30 mL of 4% $KHSO_4$ aq solution. The organic layer was washed with 4% $KHSO_4$ aq solution (30 mL), water (30 mL), and saturated NaCl aq solution (30 mL), dried over $MgSO_4$, then evaporated under reduced pressure. The residue was purified by passage through a silica gel column (hexane/ethyl acetate = 1/0 to 10/1) to afford 8.3 mg (88 μmol, 88%) of a colorless solid. Analytical data for the product by mp, IR, ^1H, and ^{13}C NMR are identical with commercially available phenol.
   Boc cleavage with NaOH aq on **1**: To a solution of 19 mg (100 μmol) of **1** in 0.5 mL MeOH, 1 mL of 1 N NaOH aq was added at room temperature. After stirring for 8 h, to the reaction mixture was added 30 mL of ethylacetate and 30 mL of 4% $KHSO_4$ aq solution. The organic layer was washed with 4% $KHSO_4$ aq solution (30 mL), water (30 mL), and saturated NaCl aq solution (30 mL), dried over $MgSO_4$, then evaporated under reduced pressure. The residue was purified by passage through a silica gel column (hexane/ethyl acetate = 1/0 to 10/1) to afford 7.1 mg (75 μmol, 75%) of a colorless solid.
   Boc cleavage with NH_3 aq on **1**: To a solution of 19 mg (100 μmol) of **1** in 0.5 mL MeOH, 0.1 mL of 15 N NH_3 aq was added at room temperature. After stirring for 5 h, to the reaction mixture was added 30 mL of ethylacetate and 30 mL of 4% $KHSO_4$ aq solution. The organic layer was washed with 4% $KHSO_4$ aq solution (30 mL), water (30 mL), and saturated NaCl aq solution (30 mL), dried over $MgSO_4$, then evaporated under reduced pressure. The residue was purified by passage through a silica gel column (hexane/ethyl acetate = 1/0 to 10/1) to afford 8.8 mg (94 μmol, 94%) of a colorless solid.
   Boc cleavage with 25% piperidine on **1**: A 19 mg (100 μmol) sample of **1** was dissolved in 3 mL of 25% piperidine in CH_2Cl_2 at room temperature. After stirring for 3 h, to the reaction mixture was added 30 mL of ethylacetate and 30 mL of 4% $KHSO_4$ aq solution. The organic layer was washed with 4% $KHSO_4$ aq solution (30 mL), water (30 mL), and saturated NaCl aq solution (30 mL), dried over $MgSO_4$, then evaporated under reduced pressure. The residue was purified by passage through a silica gel column (hexane/ethyl acetate = 1/0 to 10/1) to afford 8.1 mg (86 μmol, 86%) of a colorless solid.
   Boc cleavage with DBU on **1**: A 19 mg (100 μmol) sample of **1** was dissolved in 3 mL of 10% 1,8-diazabicyclo[5.4.0]-7-undecene in CH_2Cl_2 at room temperature. After stirring for 3 h, to the reaction mixture was added 30 mL of ethylacetate and 30 mL of 4% $KHSO_4$ aq solution. The organic layer was washed with 4% $KHSO_4$ aq solution (30 mL), water (30 mL), and saturated NaCl aq solution (30 mL), dried over $MgSO_4$, then evaporated under reduced pressure. The residue was purified by passage through a silica gel column (hexane/ethyl acetate = 1/0 to 10/1) to afford 7.8 mg (83 μmol, 83%) of a colorless solid.
9. Fmoc is 9-fluorenylmethoxycarbonyl group for α-*N*-protection on amino acid. Fmoc is employed as another major strategy for automatic peptide synthesis as well as Boc.
10. Synthesis of Boc-phenols: **2**–**9** were synthesized in a similar fashion as **1**. Analytical data for **2**–**9** are as follows.
    1-*tert*-Butoxycarbonyloxy-4-methylbenzene (**2**): 90% yield; $R_f = 0.44$ (hexane/ethyl acetate = 5/1); IR (neat) 3045, 3007, 2976, 2932, 1749, 1510, 1277, 1221, 1151 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) δ 7.16–7.13 (2H, m, ArH), 7.05–7.02 (2H, m, ArH), 2.32 (3H, s, CH_3), 1.54 (9H, s, CH_3); 100 MHz ^{13}C NMR ($CDCl_3$) δ 152.1 (C), 148.8 (C), 135.3 (C), 129.8 (CH), 120.9 (CH), 83.2 (C), 27.6 (CH_3), 20.8 (CH_3).
    1-*tert*-Butoxycarbonyloxy-4-*tert*-butylbenzene (**3**): 88% yield; $R_f = 0.43$ (hexane/ethyl acetate = 5/1); IR (neat) 3045, 2966, 1755, 1512, 1369, 1275, 1258, 1223, 1151, 1111 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) δ 7.39–7.34 (2H, m, ArH), 7.10–7.05 (2H, m, ArH), 1.55 (9H, s, CH_3), 1.30 (9H, s, CH_3); 100 MHz ^{13}C NMR ($CDCl_3$) δ 152.2 (C), 148.8 (C), 148.5 (C), 126.2 (CH), 120.6 (CH), 83.2 (C), 34.4 (C), 31.4 (CH_3), 27.7 (CH_3).
    1-*tert*-Butoxycarbonyloxy-2,6-dimethylbenzene (**4**): 99% yield; $R_f = 0.44$ (hexane/ethyl acetate = 9/1); 500 MHz ^1H NMR ($CDCl_3$) δ 7.04–7.02 (3H, m, ArH), 2.20 (6H, s, CH_3), 1.55 (9H, s, CH_3); 125 MHz ^{13}C NMR ($CDCl_3$) δ 151.3 (C), 148.4 (C), 130.3 (C), 128.6 (CH), 125.8 (CH), 83.1 (C), 27.7 (CH_3), 16.1 (CH_3).
    1-*tert*-Butoxycarbonyloxy-2,6-diisopropylbenzene (**5**): 99% yield; $R_f = 0.50$ (hexane/ethyl acetate = 9/1); 500 MHz ^1H NMR ($CDCl_3$) δ 7.26–7.13 (3H, m, ArH), 3.08–3.02 (2H, sep, $J = 6.9$ Hz, CH), 1.55 (9H, s, CH_3), 1.21 (12H, d, $J = 6.9$ Hz, CH_3); 125 MHz ^{13}C NMR ($CDCl_3$) δ 152.2 (C), 145.7 (C), 140.6 (C), 126.5 (CH), 124.0 (CH), 83.0 (C), 27.7 (CH), 27.3 (CH_3), 23.3 (CH_3).
    1-*tert*-Butoxycarbonyloxy-2,4,6-tri-*tert*-butylbenzene (**6**): 94% yield; $R_f = 0.41$ (hexane/ethyl acetate = 25/1); IR (KBr) 3088, 2984, 2872, 1759, 1269, 1258, 1157, 1111 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) δ 7.29 (2H, s, ArH), 1.52 (9H, s, CH_3), 1.36 (18H, s, CH_3), 1.29 (9H, s, CH_3); 100 MHz ^{13}C NMR ($CDCl_3$) δ 153.1 (C), 147.2 (C), 145.9 (C), 141.5 (C), 123.3 (CH), 82.8 (C), 35.6 (C), 34.8 (C), 31.5 (CH_3), 31.5 (CH_3), 27.8 (CH_3).
    1-*tert*-Butoxycarbonyloxy-2-methoxybenzene (**7**): 94% yield; $R_f = 0.16$ (hexane/ethyl acetate = 5/1); IR (KBr) 3108, 2984, 1755, 1614, 1487, 1308, 1263, 1150, 1117 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) δ 7.09 (1H, t, $J = 8.4$ Hz, ArH), 6.58 (2H, d, $J = 8.4$ Hz, ArH), 3.81 (6H, s, CH_3), 1.53 (9H, s, CH_3); 100 MHz ^{13}C NMR ($CDCl_3$) δ 152.4 (C), 151.3 (C), 129.2 (C), 126.0 (CH), 104.8 (CH), 83.1 (C), 56.1 (CH_3), 27.5 (CH_3).
    Methyl 4-*tert*-Butoxycarbonyloxybenzoate (**8**): 91% yield; IR (KBr) 3007, 2987, 1750, 1749, 1719, 1605, 1279, 1151 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) δ 8.06–8.02 (2H, m, ArH), 7.25–7.20 (2H, m, ArH), 3.89 (3H, s, CH_3), 1.54 (9H, s, CH_3); 100 MHz ^{13}C NMR ($CDCl_3$) δ 166.3 (C), 154.6 (C), 151.1 (C), 131.1 (CH), 127.5 (C), 121.1 (CH), 84.1 (C), 52.2 (CH_3), 27.6 (CH_3).
    tert-Butyl 4-*tert*-butoxycarbonyloxy-3-methoxycinnamate (**9**): 95% yield; $R_f = 0.41$ (hexane/ethyl acetate = 2/1); IR (neat) 3062, 2980, 1763, 1709, 1638, 1510, 1256, 1144,

1124 cm^{-1}; 400 MHz ^1H NMR ($CDCl_3$) δ 7.50 (1H, d, $J = 16.0$ Hz, ArCH=), 7.11–7.04 (3H, m, ArH), 6.28 (1H, d, $J = 15.6$ Hz, =CH–), 3.85 (3H, s, OCH_3), 1.53 (9H, s, CH_3), 1.51 (9H, s, CH_3); 100 MHz ^{13}C NMR ($CDCl_3$) δ 166.1 (C),151.5 (C), 151.2 (C), 142.8 (CH), 141.6 (C), 133.5 (C), 122.8 (CH), 121.1 (CH), 120.4 (CH), 111.2 (CH), 83.6 (C), 80.6 (C), 55.9 (CH_3), 28.2 (CH_3), 27.6 (CH_3).

11. Cleavage of the Boc on phenol with bases: Boc on **2**–**9** were cleaved with bases in a similar fashion as **1**.
12. (a) Fink, Cynthia A.; Carlson, J. Eric; McTaggart, Patricia A.; Qiao, Ying; Webb, Randy; Chatelain, Ricardo; Jeng, Arco Y.; Trapani, Angelo J. *J. Med. Chem.* **1996**, *39*(16), 3158–3168; (b) Kayahara, H.; Kawakami, A.; Tanji, Y.; Tadasa, K. In *Chemistry of Novel Foods*; Spanier, Arthur M., Ed.; Allured Publishing Corp.: Illinois, 1997; pp 355–366.
13. Synthesis of Tyr derivatives: BocTyr(OBoc)OH (**11**): To a solution of 1.4 g (5.0 mmol) of BocTyrOH (**10**), 6.1 mg (0.05 mmol) of DMAP and 0.69 mL (5.0 mmol) of triethylamine (TEA) in 5 mL CH_2Cl_2, 1.4 g (6.5 mmol) of $(Boc)_2O$ was added at room temperature. After stirring for 3 h, to the reaction mixture was added 80 mL of ethylacetate and 80 mL of 4% $KHSO_4$ aq solution. The organic layer was washed with 4% $KHSO_4$ aq solution (80 mL), water (80 mL), and saturated NaCl aq solution (80 mL), dried over Na_2SO_4, then evaporated under reduced pressure. The residue was purified through a silica gel column (hexane/ethyl acetate = 3/1 to 1/1). The product was obtained as a colorless solid: 1.7 g (4.4 mmol), 89% yield; $R_f = 0.58$ (chloroform/methanol = 5/1); 500 MHz ^1H NMR ($CDCl_3$) δ 7.20–7.09 (4H, m, ArH), 5.00–4.94 (1H, m, NH), 4.63–4.57 (1H, m, α-CH), 3.23–3.04 (2H, m, CH_2), 1.55 (9H, s, CH_3), 1.42 (9H, s, CH_3); 125 MHz ^{13}C NMR ($CDCl_3$) δ 175.2 (C), 151.9 (C), 150.2 (C), 133.5 (C), 130.4 (CH), 125.9 (C), 121.4 (CH), 83.6 (C), 80.6 (C), 54.2 (CH), 37.1 (CH_2), 28.3 (CH_3), 27.7 (CH_3).

    BocTyr(OBoc)O*i*Pr (**12**): To a solution of 0.38 g (1.0 mmol) of **11** and 12 mg (0.1 mmol) of DMAP in 1 mL CH_2Cl_2, 0.1 mL (1.3 mmol) of isopropanol and 0.25 g (1.3 mmol) of 1-ethyl-3-(3-dimethyl aminopropyl)-carbodiimide hydrochloride (EDC·HCl) were added at room temperature. After stirring for 3 h, to the reaction mixture was added 50 mL of ethylacetate and 50 mL of 4% $KHSO_4$ aq solution. The organic layer was washed with 4% $KHSO_4$ aq solution (50 mL), water (50 mL), and saturated NaCl aq solution (50 mL), dried over Na_2SO_4, then evaporated under reduced pressure. The residue was purified through a silica gel column (hexane/ethyl acetate = 3/1). The product was obtained as a colorless solid: 0.37 g (0.88 mmol), 88% yield; $R_f = 0.51$ (hexane/ethyl acetate = 3/1); 500 MHz ^1H NMR ($CDCl_3$) δ 7.16–7.08 (4H, m, ArH), 5.01–4.97 (2H, m, NH, CH), 4.52–4.49 (1H, m, α-CH), 3.08–3.05 (2H, m, CH_2), 1.55 (9H, s, CH_3), 1.42 (9H, s, CH_3), 1.20 (6H, dd, $J = 13$, 6.3 Hz, CH_3); 125 MHz ^{13}C NMR ($CDCl_3$) δ 171.2 (C), 151.8 (C), 150.1 (C), 133.7 (C), 130.4 (CH), 125.9 (C), 121.2 (CH), 83.5 (C), 79.9 (C), 69.2 (CH), 54.5 (CH), 37.7 (CH_2), 28.3 (CH_3), 27.7 (CH_3), 21.8 (CH_3).

    BocTyrO*i*Pr (**13**): A 42 mg (100 μmol) sample of **12** was dissolved in 3 mL of 50% piperidine in CH_2Cl_2 at room temperature. After stirring for 3 h, to the reaction mixture was added 30 mL of ethylacetate and 30 mL of 4% $KHSO_4$ aq solution. The organic layer was washed with 4% $KHSO_4$ aq solution (30 mL), water (30 mL), and saturated NaCl aq solution (30 mL), dried over Na_2SO_4, then evaporated under reduced pressure. The residue was purified through a silica gel column (hexane/ethyl acetate = 3/1). The product was obtained as a white solid: 28 mg (85 μmol), 85% yield; $R_f = 0.21$ (hexane/ethyl acetate = 3/1); 500 MHz ^1H NMR ($CDCl_3$) δ 7.01–6.72 (4H, m, ArH), 5.04–4.96 (2H, m, NH, CH), 4.50–4.44 (1H, m, α-CH), 3.06–2.96 (2H, m, CH_2), 1.42 (9H, s, CH_3), 1.20 (6H, dd, $J = 10$, 6.3 Hz, CH_3); 125 MHz ^{13}C NMR ($CDCl_3$) δ 171.5 (C), 154.7 (C), 130.6 (CH), 128.2 (C), 125.9 (C), 115.4 (CH), 79.8 (C), 69.1 (CH), 54.7 (CH), 37.6 (CH_2), 28.3 (CH_3), 21.8 (CH_3).

    One pot synthesis of **13**: To a solution of 0.28 g (1.0 mmol) of **10**, 1.2 mg (0.01 mmol) of DMAP and 0.14 mL (1.0 mmol) of TEA in 1 mL CH_2Cl_2, 0.28 g (1.3 mmol) of $(Boc)_2O$ was added at room temperature. After stirring for 3 h, to the reaction mixture was added 1 mL (13 mmol) of isopropanol, 24 mg (0.2 mmol) of DMAP, and 0.25 g (1.3 mmol) of EDC·HCl. Then, after stirring for 3 h, the reaction mixture was added 7.5 mL (75 mmol) of piperidine. After stirring for 2 h, to the reaction mixture was added 50 mL of ethylacetate and 50 mL of 4% $KHSO_4$ aq solution. The organic layer was washed with 4% $KHSO_4$ aq solution (50 mL), water (50 mL), and saturated NaCl aq solution (50 mL), dried over Na_2SO_4, then evaporated under reduced pressure. The residue was purified through a silica gel column (hexane/ethyl acetate = 3/1). The product was obtained as a white solid; 0.26 g (0.81 mmol), 81% yield.
14. Acids (50 equiv) were used for Boc cleavage and reactions completed in 6 h at room temperature.
15. By-product content was estimated from ^1H NMR spectrum ratio of *tert*-butyl group in crude product.