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A novel *tert*-butoxycarbonylation reagent: 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI)

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Abstract—The use of 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI) as a *tert*-butoxycarbonylation reagent for acidic proton-containing substrates such as phenols, aromatic and aliphatic amines hydrochlorides, and aromatic carboxylic acids in the absence of a base is described. The reactions proceed chemoselectively in high yield under mild conditions.

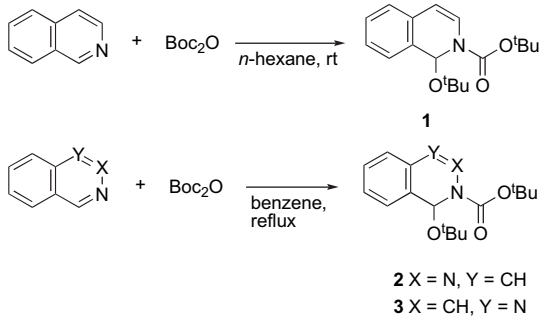
1. Introduction

The development of mild and selective methods for the protection and deprotection of functional groups continues to be an important tool in the synthetic chemistry of functional molecules.[1] Among the various protection groups available, the *tert*-butoxycarbonyl (Boc) group is resistant to nucleophilic reagents, because of the electron donating and sterically bulky *tert*-butyl group.[1] It is noteworthy that the Boc group for protecting amino functionalities is most frequently used in organic synthesis due to its chemical stability to nucleophiles and strong basic conditions and its ease of removal under specific conditions.[2] In addition, the Boc group can also act as a useful protecting group for alcohols and phenols, since it is more stable than the corresponding ester under basic conditions.[3] Various reagents and methods for introducing this group using Boc_2O have been developed. Most reactions are carried out in the presence of a base such as DMAP[4] or organic/inorganic bases.[3a,5] In addition, the *tert*-butoxycarbonylation of acidic substrates such as phenol and thiophenol also require a base.[6] On the other hand, the use of a Lewis acid catalyst to perform this protection has not been extensively studied.[7] In these contexts, we discovered that the Reissert like reaction of Boc_2O with isoquinoline afforded 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI) **1**, which appears to be a promising *tert*-butoxycarbonylating agent.[8] Our efforts toward the use of BBDI **1** as a de novo *tert*-butoxycarbonylation reagent for acidic proton-containing substrates such as amine hydrochlorides, phenols, and carboxylic acids have been described in detail.[9]

2. Results and discussion

2.1. The reaction of Boc_2O with nitrogen-containing aromatic compounds

We, first, found that the exposure of isoquinoline to Boc_2O in *n*-hexane at room temperature resulted in the loss of carbon dioxide to give **1** in 86% yield, which is stable and can be stored at room temperature for periods of over 1 year without any decomposition. Similarly, when a solution of phthalazine and quinazoline is refluxed with Boc_2O in benzene, the adducts **2** and **3** are produced, in 86% and 68% yields, respectively (Scheme 1). Surprisingly, the addition of Boc_2O to pyridine, pyrimidine, quinoline, and quinoxaline gave no adducts, resulting in the recovery of starting materials. Only heterocycles bearing a nitrogen at the β-position in the naphthalene ring such as isoquinoline, phthalazine, and quinazoline were amenable to reaction with Boc_2O to give the corresponding adducts **1**–**3**, although the reasons for this remain unclear.



Scheme 1. Synthesis of **1**–**3**.

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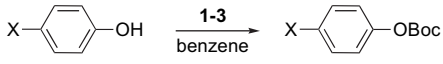
2.2. *tert*-Butoxycarbonylation of phenols with BBDI

A variety of natural polyphenols that have attracted the interest of scientists and synthetic research into this class of compounds has been vigorously carried out in recent years.[10] The phenolic hydroxyl group(s) on those compounds often play an important role in their biological activities.[11] The protection of the hydroxyl group(s) is necessary in order to maintain these activities and to avoid expected side reactions. A variety of protecting groups for phenols have been developed and have been utilized in synthetic studies.[1] Recent studies have highlighted the utility of the *tert*-butoxycarbonyl (Boc) group for phenols.[4] Based on these properties, we embarked on an investigation of the *tert*-butoxycarbonylation of phenol (**4a**) using **1**. A solution of **4a** and **1** in benzene was heated under reflux for 1 h to give phenyl *tert*-butyl carbonate (**5a**) in quantitative yield. The *tert*-butoxycarbonylation of **4a** using **2** and **3**, however, resulted in low yields (Table 1, entries 2 and 3). The reaction of *p*-methoxy- and *p*-nitorophenol (**4b** and **4c**), respectively, with **1** afforded the corresponding carbonates **5b** and **5c** in high yields, respectively (Table 1, entries 4 and 5). In the case of **4c**, however, the reaction proceeded easily at room temperature. Unfortunately, the exposure of **2** and **3** to **4c** also resulted in low yields (Table 1, entries 6 and 7). It is noteworthy that the *tert*-butoxycarbonylation of *p*-hydroxymethylphenol (**4d**) took place chemoselectively to give **5d** without any substitution of the hydroxymethyl group. Surprisingly, although the *tert*-butoxycarbonylation of phenols in alkaline media has been reported,[4,6] this is the first example of such a reaction in the absence of base.

2.3. *tert*-Butoxycarbonylation of amine hydrochlorides with BBDI

The Boc group is extensively used for amino protection because of its chemical inertness to nucleophilic reagents including base and deprotection using acid reagents.[12] The *tert*-butoxycarbonylation of aniline with **1** was examined first. However, no reaction occurred and **1** was recovered. As described above, it was found that the *tert*-butoxycarbonylation at **4c** (pK_a=10.8)[13] proceeds under more mild conditions compared with those of **4a** (pK_a=18.0).[13] With these results in hand, we concluded that reactivity is proportional to the acidity of the substrates. Because the conjugate acid **6a** (pK_a=3.6)[13] of aniline (pK_a=30.6)[13] is stronger acid than **4a**, we tried the *tert*-butoxycarbonylation of aniline hydrochloride (**6a**). Treatment of **6a** with **1** in benzene at room temperature afforded *N*-Boc aniline **7a**, as expected, in 81% yield (Table 2, entry 1). The use of dimethoxyethane (DME) instead of benzene as solvent dramatically increased the yield of **7a** (entry 2). A similar treatment of *p*-methoxyaniline hydrochloride (**6b**) with **1** afforded *N*-Boc aniline **7b** in high yield (entry 3). On the other hand, the reaction of *p*-nitroaniline hydrochloride (**6c**) with **1** resulted in low yields. Although this reason remains unclear, a decomposition of **1** may occur due to a stronger acidity of **6c** compared with that (pK_a=3.6)[13] of **6a**. Actually, an evolution of gas presumed to be isobutylene was observed in a reaction flask. A high degree of chemoselectivity was also demonstrated by using **6d** of the coexistence of an aliphatic hydroxyl group, as shown in entry 4.

Table 1. *tert*-Butoxycarbonylation of **4a–d** with **1–3**



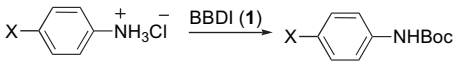
4a-d
a, X = H
b, X = OMe
c, X = NO_2
d, X = CH_2OH

5a-d
a, X = H
b, X = OMe
c, X = NO_2
d, X = CH_2OH

Entry	Reagent	Substrate (X)	Temp	Time (h)	Prod.	Yield (%)[a]
1	**1**	**4a** (H)	Reflux	1	**5a**	99
2	**2**	**4a** (H)	Reflux	2	**5a**	21
3	**3**	**4a** (H)	Reflux	5	**5a**	2
4	**1**	**4b** (OMe)	Reflux	1	**5b**	92
5	**1**	**4c** (NO_2)	rt	3	**5c**	96
6	**2**	**4c** (NO_2)	rt	3	**5c**	21
7	**3**	**4c** (NO_2)	rt	3	**5c**	17
8	**1**	**4d** (CH_2OH)	Reflux	3	**5d**	91

[a] Isolated yields.

Table 2. *tert*-Butoxycarbonylation of **6** with **1**



6a-e
a, X = H
b, X = OMe
c, X = NO_2
d, X = CN
e, X = CH_2CH_2OH

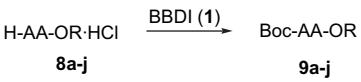
7a-e
a, X = H
b, X = OMe
c, X = NO_2
d, X = CN
e, X = CH_2CH_2OH

Entry	Substrate (X)	Temp	Solvent	Prod.	Yield (%)[a]
1	**6a** (H)	rt	Benzene	**7a**	81
2	**6a** (H)	rt	DME	**7a**	97
3	**6b** (OMe)	rt	DME	**7b**	98
4	**6c** (NO_2)	rt	DME	**7c**	19
5	**6c** (NO_2)	−10 °C	DME	**7c**	38
6	**6d** (CN)	rt	DME	**7d**	75
7	**6e** (CH_2CH_2OH)	rt	DME	**7e**	97

[a] Isolated yields.

The *tert*-butoxycarbonylation of α-amino acids ester hydrochlorides (pK_a=7.6–8.7)[14] as the weaker conjugate acid was next examined. Screening experiments were conducted with L-Met–OMe·HCl **8a** as a model compound using **1** in DME. The use of 3 equiv of **1** gave the best yield (93%, Table 3, entry 1), whereas the use of 2 and 1.2 equiv of **1** resulted in 82% and 33% yields, respectively. The use of diethyl ether (reflux) and chloroform as solvents provided similar results (95% and 92%), respectively, whereas dioxane resulted in a low yield (53%). Moreover, the decrease of the amounts of **1** was examined. Consequently, the treatment of **8a** with **1** (2 equiv) in acetonitrile at 0 °C provided **9a** in 97% yield (entry 3). On the basis of these results, the standard condition for the *tert*-butoxycarbonylation of several α-amino acid ester hydrochlorides **8** with **1** (3 equiv) was in DME at room temperature (A) or in diethyl ether under reflux (B). Thirdly, the use of 2 equiv of **1** in acetonitrile at 0 °C was carried out (C). Thus the *tert*-butoxycarbonylation of various α-amino acids occurs, and the corresponding *N*-Boc L-amino acid esters were obtained in high yields as shown in Table 3. The identification of *N*-Boc L-amino acid esters was confirmed by comparison of ^{1}H NMR and IR data and $[\alpha]_D$

Table 3. *tert*-Butoxycarbonylation of **8** with **1**



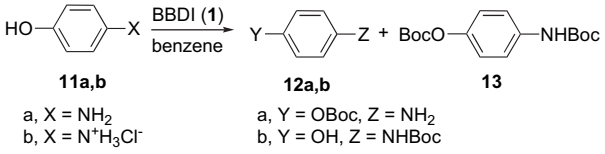
Entry	H–AA–OR·HCl **8**	Method[a]	Boc–AA–OR **9**	Yield (%)[b]
1	Met–OMe·HCl **8a**	A	Boc–Met–OMe **9a**[15]	93
2	Met–OMe·HCl **8a**	B	Boc–Met–OMe **9a**[15]	95
3	Met–OMe·HCl **8a**	C	Boc–Met–OMe **9a**[15]	97
4	Ala–OEt·HCl **8b**	B	Boc–Ala–OEt **9b**[16]	87
5	Leu–OEt·HCl **8c**	B	Boc–Leu–OEt **9c**[16]	91
6	Leu–OEt·HCl **8c**	C	Boc–Leu–OEt **9c**[16]	90
7	Val–OMe·HCl **8d**	A	Boc–Val–OMe **9d**[15]	86
8	Phe–OMe·HCl **8e**	A	Boc–Phe–OMe **9e**[17]	97
9	Pro–OMe·HCl **8f**	A	Boc–Pro–OMe **9f**[18]	98
10	Pro–OMe·HCl **8f**	C	Boc–Pro–OMe **9f**[18]	92
11	Glu(OEt)–OEt·HCl **8g**	B	Boc–Glu(OEt)–OEt **9g**[19]	98
12	Ser–OMe·HCl **8h**	A	Boc–Ser–OMe **9h**[20]	92
13	Cys–OMe·HCl **8i**	A	Boc–Cys–OMe **9i**[21]	87
14	Tyr–OMe·HCl **8j**	A	Boc–Tyr–OMe **9j**[22]	76[c]

[a] Method A: in 1,2-dimethoxyethane at room temperature overnight with 3 equiv of BBDI. Method B: in diethyl ether under reflux overnight with 3 equiv of BBDI. Method C: in acetonitrile at 0 °C for 2 days with 2 equiv of BBDI.
[b] Isolated yield.
[c] A small amount of Boc–Tyr(Boc)–OMe (**10**) was also obtained.

values with the reported data.[15–22] In general, α-amino acid esters are commercially available in the form of hydrochloride salts. Therefore, this procedure without any additive such as a base is a convenient procedure for *N*-*tert*-butoxycarbonylation.

2.4. The chemoselectivity of *tert*-butoxycarbonylation

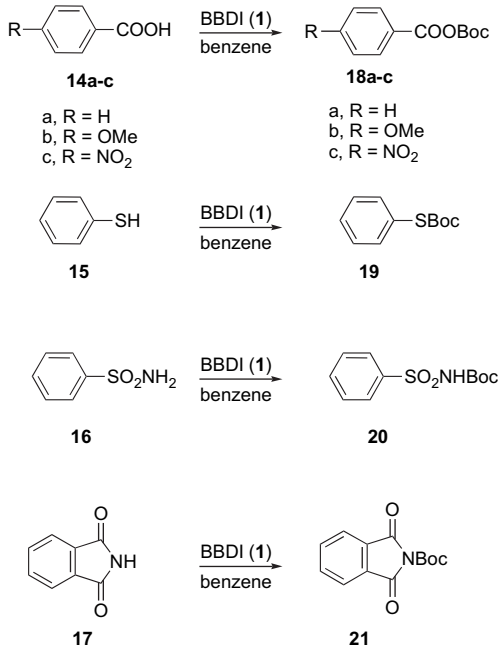
As an application, the chemoselectivity of *tert*-butoxycarbonylation for amino and hydroxyl groups on a benzene ring was investigated using 4-aminophenol (**11a**) and 4-aminophenol hydrochloride (**11b**). When **11a** was reacted with 2 equiv of **1** in benzene under reflux, the *O*-Boc derivative **12a** was obtained in 94% yield together with small amounts of *N*,*O*-(Boc)$_2$ derivative **13**. In contrast, when **11b** was subjected to a reaction with 2 equiv of **1**, the *N*-Boc derivative **12b** was isolated in 93% yield together with small amounts of **13** (Scheme 2). It was found that a higher acidity-containing functional group is preferentially *tert*-butoxycarbonylated.



Scheme 2.

2.5. *tert*-Butoxycarbonylation of various acidic substrates

Further, the *tert*-butoxycarbonylation of several acidic substrates, such as benzoic acid derivatives **14a** (pK_a=11.0),[13] **14b**, **14c**, benzenethiol (**15**) (pK_a=10.2),[13] benzenesulfonamide (**16**) (pK_a=16.1),[13] and phthalimide (**17**) (pK_a=14.6)[23] with **1** without any base was examined. The reaction of **1** (1.2 equiv) with the above substrates in benzene gave the corresponding Boc-derivatives, as shown in Scheme 3 and Table 4. In particular, the *tert*-butoxycarbonylation of **14** was performed under mild conditions for a short time (Table 1, entries 1–3). The Boc-products **18** were somewhat unstable. Therefore, the yield of **18c** was low presumably due to the decomposition of **18c** during silica gel chromatography.



Scheme 3. *tert*-Butoxycarbonylation of various acidic substrates with BBDI.

Although we attempted the *tert*-butoxycarbonylation of *N*-protected amino acids **22**, Boc-compounds **23** were not isolated because of their labilities. However, the Boc anhydrides **23** were regarded to be a promising active intermediate for esterification. In practice, a simple and mild esterification of *N*-protected amino acids via Boc-anhydride **23** using BBDI as a novel condensing reagent in a one-pot method was developed (Table 5).[24] This protocol has several advantages including the use of nearly equimolar amounts of alcohols, no requirement for additives, and no racemization occurs.

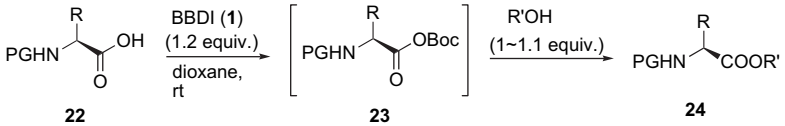
On the other hand, neutral substrates such as alcohols, thiol, and pyrrolidone, when subjected to *tert*-butoxycarbonylation with **1**, gave no Boc-products. Treatment of 1 equiv of methanol (pK_a=29.0)[13] with **1** in benzene under reflux

Table 4. *tert*-Butoxycarbonylation of various acidic substrates with **1**

Entry	Substrate	Condition	Prod.	Yield (%)[a]
1	**14a**	rt/10 min	**18a**	86
2	**14b**	rt/10 min	**18b**	87
3	**14c**	rt/3 min	**18c**	58
4	**15**	Reflux/5 h	**19**	89
5	**16**	Reflux/3 days	**20**	65
6	**17**	Reflux/overnight	**21**	49

[a] Isolated yield.

Table 5. Esterification of *N*-protected amino acids **22** with **1**

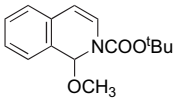


22 **23** **24**

Entry	Substrate	PG	R	R′	Prod.	Yield (%)[a]
1	**22a**	Cbz	Me	Me	**24a**	86
2	**22b**	Cbz	Me	Et	**24b**	95
3	**22c**	Cbz	Ph	Allyl	**24c**	91
4	**22d**	Cbz	$MeSCH_2CH_2$	$PhCH_2$	**24d**	91
5	**22e**	Boc	Me	*p*-MeOPh	**24e**	95
6	**22f**	Fmoc	Ph	Allyl	**24f**	90

[a] Isolated yield.

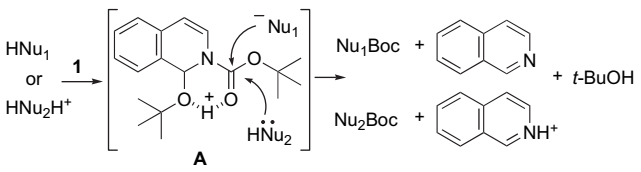
gave a 5/2 mixture of **25** and **1**. The use of a large excess of methanol (15 equiv) in benzene at room temperature provided **25** in 92% yield. Unfortunately, the reactions of propanethiol (pK_a=17.0)[13] and pyrrolidone (pK_a=24.2)[13] gave complex mixtures, which were not identified. Thus, no *tert*-butoxycarbonylation was observed for non-acidic proton-containing substrates.



25

2.6. A mechanism of *tert*-butoxycarbonylation with BBDI

On the basis of these results, a proposed mechanism for this reaction is as follows: Presumably **1** would be first protonated to form a cyclic six-membered intermediate **A**. A subsequent attack of its resulting conjugated base (Nu anion or HNu_2) to the activated carbonyl of **A** followed by cleavage could produce the *tert*-butoxycarbonylation product, isoquinoline or its salt, and *tert*-butyl alcohol. Namely, **1** would act as a weak Lewis base (pseudo base) (Scheme 4).[25] Accordingly, this *tert*-butoxycarbonylation would depend on the strength of the acidity. For the reason that protons of neutral substrates such as alcohols, thiol, and pyrrolidone cannot be captured by **1**, their *tert*-butoxycarbonylation would not take place. It would be difficult to form an **A**-like intermediate in *tert*-butoxycarbonylation using reagents **2** and **3** due to protonation of the more basic nitrogen atoms of **2** and **3**.



Scheme 4. A plausible mechanism of *tert*-butoxycarbonylation with BBDI.

3. Conclusion

In summary, a novel and chemoselective *tert*-butoxycarbonylation reagent, BBDI **1** is reported. This reagent is easily prepared in quantitative yield by the reaction of isoquinoline with Boc_2O. In general, the *tert*-butoxycarbonylation of acidic compounds such as phenols and carboxylic acids using Boc_2O require a base. Interestingly, BBDI easily caused the *tert*-butoxycarbonylation of acidic substrates in the absence of bases. The strength of the acidity of substrates appears to influence the reaction rate, in fact, a higher acidic substrate hastened the reaction compared to a low acidic one. Furthermore, *tert*-butoxycarbonylation of *N*-protected amino acids with BBDI is applicable to their simple and mild esterification using nearly equimolar amounts of alcohols in a one-pot procedure.

4. Experimental

4.1. General information

Melting points were determined on a Mel-Temp melting point apparatus using an open-capillary tube. All melting and boiling points are uncorrected. Infrared (IR) spectra were recorded on a Perkin–Elmer 1600 series FTIR spectrometer. Mass spectra (MS) were recorded on a JEOL JMN-DX 303/JMA-DA 5000 spectrometer. Microanalyses were performed on a Perkin–Elmer CHN 2400 Elemental Analyzer. Optical rotations were measured with a JASCO DIP-360 or JASCO P-1020 digital polarimeter. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on JEOL JNM-EX 270 (270 MHz) or JEOL JNM-AL 400 (400 MHz) spectrometer, using tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. Column chromatography was carried out on Merck Silica gel 60 (230–400 mesh) or KANTO Silica Gel 60N (40–50 μm) for flash chromatography.

4.1.1. 1-*tert*-Butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (1). A mixture of isoquinoline (3.87 g, 30 mmol) and di-*tert*-butyl dicarbonate (7.86 g, 36 mmol) in hexane (30 mL) was stirred at room temperature for 8 h. After concentration in vacuo, the residue was purified by recrystallization from Et_2O–hexane to give **1** (7.87 g, 86%) as colorless prisms. Mp 114–115 °C (Et_2O–hexane). IR (neat) cm^{-1}: 1712. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 9H), 1.52 (s, 9H), 6.10 (d, J=7.5 Hz, 1H), 6.66 (s, 1H), 6.88 (d, J=7.3 Hz, 1H), 7.17–7.33 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 28.7, 74.3, 75.3, 81.8, 109.3, 124.1, 125.0, 126.4, 126.8, 128.0, 130.0, 131.3, 152.1. MS

(EI) *m/z* 303 (M^+). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.38; H, 8.02; N, 4.54.

4.1.2. 1-*tert*-Butoxy-2-*tert*-butoxycarbonyl-1,2-dihydrophthalazine (2). A mixture of phthalazine (3.90 g, 30 mmol) and di-*tert*-butyl dicarbonate (7.86 g, 36 mmol) in benzene (30 mL) was heated under reflux for 6 h. After concentration in vacuo, the residue was purified by recrystallization from hexane or distilled under reduced pressure to give **3** (7.8 g, 86%) as colorless needles. Bp 146–149 °C (1 mmHg), mp 117–118 °C (hexane). IR (neat) cm^{-1}: 1695. ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 9H), 1.60 (s, 9H), 6.82 (br s, 1H), 7.28–7.32, (m, 1H), 7.39–7.47 (m, 2H), 7.46–7.54 (m, 1H), 7.99 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 28.7, 72.2, 74.8, 82.6, 124.0, 125.6, 125.7, 128.6, 131.3, 131.5, 132.4, 143.9. MS (EI) *m/z* 304 (M^+). Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 68.08; H, 7.95; N, 9.20. Found: C, 67.79; H, 7.97; N, 9.30.

4.1.3. 3-*tert*-Butoxy-4-*tert*-butoxycarbonyl-3,4-dihydroquinazoline (3). A mixture of quinazoline (3.90 g, 30 mmol) and di-*tert*-butyl dicarbonate (7.86 g, 36 mmol) in benzene (30 mL) was heated under reflux for 30 h. After concentration in vacuo, the residue was purified by recrystallization from hexane to give **3** (5.9 g, 65%) as colorless prisms. Mp 134–135 °C (hexane). IR (neat) cm^{-1}: 1716. ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.57, (s, 9H), 6.49 (br s, 1H), 7.20–7.30, (m, 2H), 7.36–7.47 (m, 2H), 8.12 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 28.2, 73.1, 74.9, 83.8, 126.0, 126.1, 126.2, 126.8, 129.0, 140.0, 141.5, 151.1. MS (EI) *m/z* 304 (M^+). Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 68.08; H, 7.95; N, 9.20. Found: C, 68.08; H, 8.04; N, 9.26.

4.2. General procedure for *tert*-butoxycarbonylation of phenols 4 by BBDI 1 (Table 1)

A mixture of **1** (1.52 g, 5 mmol) and phenol **4a** (5 mmol) in benzene (10 mL) was heated under reflux or stirred at room temperature for reaction times as indicated in Table 1. The reaction mixture was washed with 5% HCl solution (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give **5a–d** in yields as shown in Table 1.

4.2.1. *tert*-Butyl phenyl carbonate (5a). A colorless liquid. Bp 88–90 °C (1 mmHg) [lit.[26] bp 74–78 °C (0.5 mmHg)]. IR (neat) cm^{-1}: 1758. ^1H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 9H), 6.97–7.50 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 83.5, 121.3, 125.7, 129.4, 151.1, 151.9. MS (EI) *m/z* 194 (M^+).

4.2.2. *tert*-Butyl 4-methoxyphenyl carbonate (5b). A colorless plates. Mp 66–67 °C (hexane). IR (KBr) cm^{-1}: 1752. ^1H NMR (400 MHz, $CDCl_3$) δ 1.55 (s, 9H), 3.79 (s, 3H), 6.86–6.89 (d, *J*=9.2 Hz, 2H), 7.07–7.09 (d, *J*=8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 55.6, 83.3, 114.3, 122.1, 144.7, 152.3, 157.2. MS (EI) *m/z* 224 (M^+). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.21; H, 7.24.

4.2.3. *tert*-Butyl 4-nitrophenyl carbonate (5c). A white powder. Mp 78–79 °C (hexane) [lit.[27] mp 78.5–79.5 °C]. IR (KBr) cm^{-1}: 1346, 1757. ^1H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 9H), 7.37 (d, *J*=9.2 Hz, 2H), 8.27 (d, *J*=9.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 84.8, 121.9, 125.2, 145.1, 150.5, 155.7. MS (EI) *m/z* 240 (M^++1).

4.2.4. *tert*-Butyl 4-(hydroxymethyl)phenyl carbonate (5d).[28] A white powder. Mp 39–40 °C (pentane). IR (KBr) cm^{-1}: 1762, 3270. ^1H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 9H), 2.01 (br s, 1H), 4.64 (s, 2H), 7.14 (d, *J*=8.7 Hz, 2H), 7.35 (d, *J*=8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 64.0, 83.6, 121.3, 128.0, 138.4, 150.4, 151.9. MS (EI) *m/z* 224 (M^+).

4.3. General procedure for the *tert*-butoxycarbonylation of aniline hydrochlorides 6 by 1 (Table 2)

A solution of **1** (6 mmol) in DME (10 mL) was added to a stirred suspension of aniline hydrochloride **6** (5 mmol) in DME (10 mL), with stirring at room temperature for 16 h. After removing DME under reduced pressure, the residue was dissolved in AcOEt, washed with 5% HCl solution (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give **7** in yields as shown in Table 2.

4.3.1. *tert*-Butyl *N*-phenylcarbamate (7a). A colorless needles. Mp 137–138 °C (Et_2O–hexane) [lit.[29] mp 135–136 °C]. IR (KBr) cm^{-1}: 1687, 3313. ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H), 6.49 (br s, 1H), 6.99–7.06 (m, 1H), 7.25–7.37 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 80.5, 118.5, 123.0, 128.9, 138.3, 152.7. MS (EI) *m/z* 193 (M^+).

4.3.2. *tert*-Butyl *N*-(4-methoxyphenyl)carbamate (7b). A colorless needles. Mp 96–97 °C (hexane) [lit.[30] 91.5–92.5 °C]. IR (KBr) cm^{-1}: 1695, 3366. ^1H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H), 3.78 (s, 3H), 6.36 (br s, 1H), 6.83 (d, *J*=8.2 Hz, 2H), 7.26 (d, *J*=9.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 55.5, 80.2, 114.2, 120.6, 131.4, 153.2, 155.7. MS (EI) *m/z* 223 (M^+).

4.3.3. *tert*-Butyl *N*-(4-nitrophenyl)carbamate (7c). A yellow needless. Mp 111–112 °C. [lit.[31] 108–109 °C]. IR (KBr) cm^{-1}: 1543, 1600, 1735, 1746, 3397. ^1H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 9H), 6.90 (br s, 1H), 7.53 (d, *J*=9.2 Hz, 2H), 8.18 (d, *J*=9.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 81.9, 117.5, 125.2, 142.7, 144.5, 151.8. MS (EI) *m/z* 238 (M^+). Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.49; H, 5.92; N, 11.75.

4.3.4. *tert*-Butyl *N*-(4-cyanophenyl)carbamate (7d). A colorless needles. Mp 118–119 °C [lit.[32] 113–114 °C]. IR (KBr) cm^{-1}: 1500, 1522, 1694, 2227, 2996, 3370. ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H), 6.86 (br s, 1H), 7.49 (d, *J*=8.7 Hz, 2H), 7.57 (d, *J*=8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 81.6, 105.6, 118.0, 119.0, 133.2, 142.6, 152.0.

4.3.5. *tert*-Butyl *N*-[4-(2-hydroxyethyl)phenyl]carbamate (7e). A white powder. Mp 109–110 °C (hexane). IR (KBr) cm^{-1}: 1699, 3364, 3413. ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, *J*=5.6 Hz, 1H), 1.51 (s, 9H), 2.82 (t, *J*=6.5 Hz,

2H), 3.82 (q, J=6.3 Hz, 2H), 6.45 (br s, 1H), 7.14 (d, J=8.7 Hz, 2H), 7.30 (d, J=8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 38.4, 63.7, 80.5, 118.9, 130.0, 133.1, 136.8, 152.9. MS (EI) m/z 237 (M^+). Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 66.01; H, 8.03; N, 5.88.

4.4. General procedure for the *N*-*tert*-butoxycarbonylation of amino acid esters 8 by 1

Method A: A solution of **1** (15 mmol) in DME (20 mL) was added to a stirred suspension of amino acid ester hydrochloride **8** (5 mmol) in DME (10 mL), with stirring at room temperature for overnight. After removing DME under reduced pressure, the residue was dissolved in AcOEt, washed with 5% HCl solution (10 mL×2) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give **9**. Method B: A stirred mixture of **1** (15 mmol) and amino acid alkyl ester hydrochloride (5 mmol) in Et_2O (30 mL) was refluxed for overnight. The reaction mixture was washed with 5% HCl solution (10 mL×2) and brine (10 mL), dried over $MgSO_4$ and then evaporated. The residue was purified by flash column chromatography on silica gel to give **9**. Method C: A stirred mixture of **1** (10 mmol) and amino acid alkyl ester hydrochloride (5 mmol) in acetonitrile (30 mL) was stirred for 48 h. The reaction mixture was washed with 5% HCl solution (10 mL×2) and brine (10 mL), dried over $MgSO_4$ and then evaporated. The residue was purified by flash column chromatography on silica gel to give **9**. Yields are shown in Table 3.

4.4.1. Boc–Met–OMe (9a). A colorless liquid. $[\alpha]_D^{26}$ −34.0 (c 2.6, MeOH) [lit.[15] $[\alpha]_D^{amb}$ −34.0 (c 1.0, MeOH)]. IR (neat) cm^{-1}: 1715, 1745, 3359. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.84–1.99 (m, 1H), 2.08–2.18 (m, 1H), 2.10 (s, 3H), 2.54 (t, J=7.6 Hz, 2H), 3.76 (s, 3H), 4.34–4.46 (br, 1H), 5.08–5.20 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 28.3, 30.0, 32.2, 52.4, 52.7, 80.0, 155.3, 172.8. MS (EI) m/z 263 (M^+).

4.4.2. Boc–Ala–OEt (9b). A colorless liquid. $[\alpha]_D^{26}$ −39.8 (c 2.5, MeOH) [lit.[16] $[\alpha]_D$ −42.5 (c 1.0, MeOH)]. IR (neat) cm^{-1}: 1715, 1738, 3367. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J=7.0 Hz, 3H), 1.38 (d, J=7.2 Hz, 3H), 1.45 (s, 9H), 4.20 (q, J=7.1 Hz, 2H), 4.23–4.36 (m, 1H), 5.10 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.6, 28.3, 31.1, 49.2, 61.2, 79.7, 155.1, 173.3. MS (EI) m/z 217 (M^+).

4.4.3. Boc–Leu–OEt (9c). A colorless liquid. $[\alpha]_D^{25}$ −34.6 (c 2.3, MeOH) [lit.[17] $[\alpha]_D$ −37.0 (c 1.0, MeOH)]. IR (neat) cm^{-1}: 1716, 1740, 3365. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (dd, J=6.5, 3.1 Hz, 6H), 1.28 (t, J=7.1 Hz, 3H), 1.44 (s, 9H), 1.48–1.78 (m, 3H), 4.18 0 (q, J=7.2 Hz, 2H), 4.24–4.33 (m, 1H), 4.90 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.9, 22.8, 24.8, 28.3, 41.9, 52.1, 61.1, 79.7, 155.4, 173.5. MS (EI) m/z 260 (M^++1).

4.4.4. Boc–Val–OMe (9d). A colorless liquid. $[\alpha]_D^{25}$ −21.9 (c 2.2, MeOH) [lit.[15] $[\alpha]_D^{amb}$ −22.7 (c 2.0, MeOH)]. IR (neat) cm^{-1}: 1715, 1746, 3369. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (dd, J=25.8, 7.0 Hz, 6H), 1.45 (s, 9H), 2.06–2.16 (m, 1H), 3.74 (s, 3H), 4.22 (dd, J=9.2, 4.8 Hz, 1H), 5.03 (br d, J=8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 18.9, 28.3, 31.3, 52.0, 58.5, 79.8, 155.7, 172.9. MS (EI) m/z 231 (M^+).

4.4.5. Boc–Phe–OMe (9e). A colorless liquid. $[\alpha]_D^{25}$ −6.0 (c 2.5, MeOH) [lit.[17] $[\alpha]_D^{20}$ −3.0 (c 2.0, MeOH)]. IR (neat) cm^{-1}: 1716, 1746, 3368. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.97–3.16 (m, 2H), 3.70 (s, 3H), 4.52–4.65 (m, 1H), 5.03 (br d, J=7.6 Hz, 1H), 7.11–7.24 (m, 2H), 7.27–7.31 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 38.3, 52.2, 54.4, 79.9, 127.0, 128.5, 129.3, 136.0, 155.1, 172.3. MS (EI) m/z 279 (M^+).

4.4.6. Boc–Pro–OMe (9f). A colorless liquid. $[\alpha]_D^{27}$ −54.5 (c 1.1, CH_2Cl_2) [lit.[18] $[\alpha]_D^{25}$ −52.47 (c 0.99, CH_2Cl_2)]. IR (neat) cm^{-1}: 1702, 1752. ^{1}H NMR (400 MHz, $CDCl_3$, major/minor) δ 1.41/1.47 (2×s, 9H), 1.85–2.03 (m, 3H), 2.14–2.30 (m, 1H), 3.36–3.60 (m, 2H), 3.72 (s, 3H), 4.22/4.33 (dd, J=8.5, 4.1 Hz, 0.6H/J=8.7, 3.4 Hz, 0.4H). ^{13}C NMR (100 MHz, $CDCl_3$, major/minor) δ 23.6/24.2, 28.2/28.3, 30.8/29.8, 46.2/46.5, 51.8/52.0, 59.0/58.6, 79.7, 153.7/154.3, 173.7/173.4. MS (EI) m/z 229 (M^+).

4.4.7. Boc–Glu(OEt)–OEt (9g). A colorless needles. Mp 46–47 °C (pentane). $[\alpha]_D^{27}$ −18.2 (c 1.3, Acetone) [lit.[19] mp 46–47 °C, $[\alpha]_D$ −16.4 (c 1.0, Acetone)]. IR (KBr) cm^{-1}: 1682, 1694, 1732, 3352. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J=7.1 Hz, 3H), 1.29 (t, J=7.1 Hz, 3H), 1.44 (s, 9H), 1.88–2.01 (m, 1H), 2.12–2.24 (m, 1H), 2.30–2.44 (m, 2H), 4.14 (q, J=7.1 Hz, 2H), 4.20 (q, J=7.1 Hz, 2H), 4.23–4.37 (m, 1H), 5.12 (br d, J=7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.1, 27.7, 28.2, 30.3, 52.9, 60.6, 61.4, 79.9, 155.5, 172.2, 172.7. MS (EI) m/z 304 (M^++1).

4.4.8. Boc–Ser–OMe (9h). A colorless liquid. $[\alpha]_D^{26}$ +9.1 (c 1.3, $CHCl_3$) [lit.[20] $[\alpha]_D^{20}$ +9.0 (c 1.0, $CHCl_3$)]. IR (neat) cm^{-1}: 1717, 1747, 3399. ^{1}H NMR (400 MHz, $CDCl_3$) 1.45 (s, 9H), 3.08 (br s, 1H), 3.78 (s, 3H), 3.87–3.90 (m, 1H), 3.95–3.97 (m, 1H), 4.38 (br s, 1H), 5.59 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 52.5, 55.6, 63.2, 80.2, 155.8, 171.4. MS (EI) m/z 220 (M^++1).

4.4.9. Boc–Cys–OMe (9i). A colorless liquid. $[\alpha]_D^{26}$ +27.5 (c 1.0, $CHCl_3$) [lit.[21] $[\alpha]_D^{21}$ +28.5 (c 318 mM, $CHCl_3$)]. IR (neat) cm^{-1}: 1712, 1747, 3368. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.84 (br s, 1H), 2.95–2.99 (m, 2H), 3.79 (s, 3H), 4.61–4.80 (br s, 1H), 5.45 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3, 28.2, 52.6, 54.8, 80.3, 155.1, 170.8. MS (EI) m/z 235 (M^+).

4.4.10. Boc–Tyr–OMe (9j). Colorless prisms. Mp 102–104 °C (Et_2O–hexane), $[\alpha]_D^{27}$ +12.0 (c 2.2, EtOH) [lit.[31] mp 101–103 °C, $[\alpha]_D^{25}$ +10.6 (c 2, EtOH)]. IR (KBr) cm^{-1}: 1690, 1716, 1761, 3389. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.91–3.07 (m, 2H), 3.71 (s, 3H), 4.47–4.60 (m, 1H), 5.04 (br d, J=8.1 Hz, 1H), 6.55 (br s, 1H), 6.72 (d, J=8.1 Hz, 2H), 6.95 (d, J=8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 37.5, 52.3, 54.6, 80.3, 115.5, 127.3, 130.3, 155.2, 155.4, 172.7. MS (EI) m/z 295 (M^+).

4.4.11. Boc–Tyr(Boc)–OMe (10). Colorless needles. Mp 90–91 °C (hexane). $[\alpha]_D^{20}$ −0.6 (c 2.3, MeOH). IR (KBr)

cm^{-1}: 1716, 1758, 3455. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.55 (s, 9H), 3.02–3.14 (m, 2H), 3.71 (s, 3H), 4.51–4.62 (m, 1H), 4.98 (br d, J=8.1 Hz, 1H), 7.06–7.16 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 28.2, 37.6, 52.2, 54.3, 80.0, 83.5, 121.3, 130.2, 133.5, 150.1, 151.8, 155.0, 172.1. MS (EI) m/z 395 (M^+). Anal. Calcd for $C_{20}H_{29}NO_7$: C, 60.74; H, 7.39; N, 3.54. Found: C, 60.64; H, 7.24; N, 3.63.

4.5. *tert*-Butyl 4-aminophenyl carbonate (12a)

A mixture of **1** (3.03 g, 10 mmol) and 4-aminophenol (**11a**) (0.55 g, 5 mmol) in benzene (15 mL) was heated under reflux for 8 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give **12a** (0.98 g, 94%) as colorless needles, *tert*-butyl 4-*tert*-butoxycarbonylaminophenyl carbonate (**13**) (0.08 g, 5%) as a brown powder.

12a: Mp 113–114 °C (Et_2O–hexane) [lit.[6] mp 113.5–114.5 °C]. IR (KBr) cm^{-1}: 1744, 3384, 3475. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 9H), 3.63 (br s, 2H), 6.64 (d, J=8.7 Hz, 2H), 6.94 (d, J=8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 83.1, 115.5, 121.9, 143.3, 144.1, 152.5. MS (EI) m/z 209 (M^+).

13: Mp 137–138 °C (hexane) [lit.[6] mp 135–137 °C]. IR (KBr) cm^{-1}: 1704, 1754. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H), 1.55 (s, 9H), 6.53 (br s, 1H), 7.08 (d, J=8.7 Hz, 2H), 7.34 (d, J=8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 28.3, 80.6, 83.4, 119.3, 121.6, 135.9, 146.4, 152.0, 152.7. MS (EI) m/z 309 (M^+).

4.6. *tert*-Butyl *N*-(4-hydroxyphenyl)carbamate (12b)

A solution of **1** (3.03 g, 10 mmol) in DME (15 mL) was added to a stirred suspension of 4-aminophenol hydrochloride (**11b**) (0.73 g, 5 mmol) in DME (10 mL), with stirring at room temperature for 16 h. After removing DME under reduced pressure, the residue was dissolved in AcOEt, washed with 5% HCl solution (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give **12b** (0.97 g, 93%) as colorless needles and **13** (0.08 g, 5%) as a brown powder.

12b: Mp 142–143 °C (Et_2O–hexane) [lit.[33] mp 144–145 °C]. IR (KBr) cm^{-1}: 1698, 3362. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H), 5.59 (br s, 1H), 6.35 (br s, 1H), 6.73 (d, J=8.7 Hz, 2H), 7.16 (d, J=8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 80.4, 115.7, 121.4, 130.9, 152.1, 153.6. MS (EI) m/z 209 (M^+).

4.7. General procedure for the *tert*-butoxycarbonylation of acidic substrates by 1 (Table 4)

To a solution of **1** (5 mmol) in benzene (15 mL) were added acidic substrates (5 mmol) at room temperature, and the resulting mixture was stirred at room temperature for **14a–c** or refluxed for **15–17**. The reaction times were shown in Table 4. The reaction mixture was washed with 5% HCl solution (10 mL), dried, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give the products **18–21**. The yields are shown in Table 4.

4.7.1. Benzoic *tert*-butylcarbonic anhydride (18a).

A colorless liquid. IR (neat) cm^{-1}: 1742, 1800. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 9H), 7.45–7.49 (m, 2H), 7.61–7.64 (m, 1H), 8.05–8.07 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.4, 85.6, 128.0, 128.6, 130.4, 134.2, 147.2, 161.8. MS (EI) m/z 222 (M^+). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.71; H, 6.39.

4.7.2. 4-Methoxybenzoic *tert*-butylcarbonic anhydride (18b).

A colorless liquid. IR (neat) cm^{-1}: 1736, 1795. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 9H), 3.87 (s, 3H), 6.94 (d, J=8.9 Hz, 2H), 8.01 (d, J=9.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.4, 55.5, 85.3, 113.9, 120.2, 132.6, 147.4, 161.4, 164.4. MS (EI) m/z 252 (M^+). Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.71; H, 6.40.

4.7.3. 4-Nitrobenzoic *tert*-butylcarbonic anhydride (18c).

A pale yellow needles. Mp 94–96 °C. IR (neat) cm^{-1}: 1747, 1799. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 9H), 8.25 (d, J=9.2 Hz, 2H), 8.33 (d, J=8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.4, 86.8, 123.8, 131.5, 133.5, 146.2, 151.2, 160.1. MS (EI) m/z 268 (M^++1). Anal. Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 54.12; H, 4.89; N, 5.13.

4.7.4. *O*-*tert*-Butyl *S*-phenyl thiocarbonate (19).[34]

A colorless liquid. IR (neat) cm^{-1}: 1728, 1698. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 7.36–7.42 (m, 3H), 7.51–7.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 85.4, 128.6, 129.0, 129.2, 134.8, 167.7. MS (EI) m/z 210 (M^+). Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71. Found: C, 62.80; H, 6.84.

4.7.5. *tert*-Butyl (benzenesulfonyl)carbamate (20).

A colorless needles. Mp 128–130 °C (Et_2O–hexane). IR (KBr) cm^{-1}: 1722, 1732, 3241. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (9H, s), 7.45 (1H, br), 7.53–7.65 (3H, m), 8.00–8.04 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 84.2, 128.1, 128.9, 133.7, 138.9, 149.1. MS (EI) m/z 256 (M^++1). Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44. Found: C, 51.47; H, 5.64; N, 5.29.

4.7.6. *tert*-Butoxycarbonyl phthalimide (21).

A colorless needles. Mp 91–93 °C (Et_2O–hexane) [lit.[35] 97.4 °C]. IR (KBr) cm^{-1}: 1721, 1768, 1802. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.64 (9H, s), 7.74–7.86 (2H, m), 7.93–7.99 (2H, m). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 27.9, 85.4, 124.3, 131.2, 135.1, 146.7, 164.2. MS (EI) (m/z) 247 (M^+). Anal. Calcd $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.32; H, 5.20; N, 5.78.

4.8. General procedure for esterification of *N*-protected amino acids 22 with BBDI 1

BBDI **1** (1.2 mmol) was added to a solution of *N*-protected amino acid **22** (1 mmol) in dioxane (5 mL) with sitirring at room temperature. The reaction mixture was stirred for 30 min. To the reaction mixture was alcohol (1 or 1.1 mmol) (amounts of alcohol of entries 2, 4, and 6 in Table 5 were used 1 mmol and others were used 1.1 mmol), and after the addition, the reaction mixture was stirred for 5 h, and then

concentrated. After the addition of ethyl acetate, the organic phase was washed twice with 5% HCl and brine. The organic layers were dried ($MgSO_4$) and the solvent evaporated to give the crude compound, which was purified by chromatography on a short column using a mixture of *n*-hexane and ethyl acetate as eluant to yield *N*-protected amino acid ester **24**. Yields and reaction times are shown in Table 5.

4.8.1. *N*-Cbz–Ala methyl ester (24a). Colorless needles. Mp 47–48.5 °C [lit.[15] 45–46 °C]. $[\alpha]_D^{23}$ −33.0 (*c* 1.2, MeOH) [lit.[36] $[\alpha]_D^{25}$ −32.7 (*c* 1.3, MeOH)]. IR (KBr) cm^{-1}: 1685, 1755, 3340. ^1H NMR (270 MHz, $CDCl_3$) δ 1.41 (3H, d, *J*=7.1 Hz), 3.74 (3H, s), 4.30–4.46 (1H, m), 5.11 (2H, s), 5.24–5.38 (1H, m), 7.22–7.46 (5H, m). MS (EI) *m/z* 237 (M^+).

4.8.2. *N*-Cbz–Ala ethyl ester (24b). Colorless liquid. $[\alpha]_D^{27}$ −32.6 (*c* 1.5, MeOH) [lit.[36] $[\alpha]_D^{25}$ −32.2 (*c* 1.0, MeOH)]. IR (neat) cm^{-1}: 1723, 3341. ^1H NMR (270 MHz, $CDCl_3$) δ 1.26 (3H, t, *J*=7.1 Hz), 1.40 (3H, d, *J*=7.3 Hz), 4.18 (2H, q, *J*=7.0 Hz), 4.27–4.38 (1H, m), 5.10 (2H, s), 5.32–5.49 (1H, m), 7.19–7.43 (5H, m). MS (EI) *m/z* 251 (M^+). HRMS *m/z* Calcd for $C_{13}H_{17}NO_4$ (M^+) 251.1158. Found: 251.1142.

4.8.3. *N*-Cbz–Phe allyl ester (24c). Colorless liquid. $[\alpha]_D^{21}$ −14.8 (*c* 1.3, MeOH) [lit.[37] $[\alpha]_D^{25}$ −15.6 (*c* 2.03, MeOH)]. IR (KBr) cm^{-1}: 1714, 1728, 3340. ^1H NMR (270 MHz, $CDCl_3$) δ 3.04–3.19 (2H, m), 4.59 (2H, d, *J*=5.8 Hz), 4.60–4.71 (1H, m), 5.08 (2H, s), 5.21–5.35 (3H, m), 5.77–5.91 (1H, m), 7.07–7.19 (2H, m), 7.24–7.38 (8H, m). MS (EI) *m/z* 339 (M^+). HRMS *m/z* Calcd for $C_{20}H_{21}NO_4$ (M^+) 339.1471. Found: 339.1458.

4.8.4. *N*-Cbz–Met benzyl ester (24d). Colorless needles. Mp 37–38 °C. $[\alpha]_D^{21}$ −30.6 (*c* 1.0, MeOH). IR (KBr) cm^{-1}: 1689, 1738, 3312. ^1H NMR (270 MHz, $CDCl_3$) δ 1.84–2.20 (5H, m), 2.40–2.52 (2H, m), 4.37–4.58 (1H, m), 5.09 (2H, s), 5.10–5.21 (2H, m), 5.47–5.60 (1H, m), 7.28–7.51 (10H, m). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 15.1, 29.5, 31.5, 53.0, 66.8, 67.0, 127.8, 127.9, 128.1, 128.3, 128.4, 134.9, 135.0, 136.0, 155.7, 171.6. MS (EI) *m/z* 373 (M^+). HRMS *m/z* Calcd for $C_{20}H_{23}NO_4S$ (M^+) 373.1348. Found: 373.1328.

4.8.5. *N*-Boc–Ala *p*-methoxyphenyl ester (24e). Colorless needles. Mp 82–83 °C. $[\alpha]_D^{30}$ −63.4 (*c* 1.1, MeOH). IR (KBr) cm^{-1}: 1687, 1774, 3386. ^1H NMR (270 MHz, $CDCl_3$) δ 1.46 (9H, s), 1.54 (3H, d, *J*=7.0 Hz), 3.80 (3H, s), 4.47–4.60 (1H, m), 5.05–5.11 (1H, m), 6.86–6.91 (2H, m), 6.98–7.04 (2H, m). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 18.2, 28.2, 49.3, 55.4, 79.8, 114.3, 121.9, 143.9, 155.0, 157.2, 172.2. MS (EI) *m/z* 295 (M^+). Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.09; H, 7.16; N, 4.70.

4.8.6. *N*-Fmoc–Phe allyl ester (24f). Colorless needles. Mp 105–106 °C [lit.[38] mp 92–95 °C]. $[\alpha]_D^{27}$ +15.2 (*c* 0.9, $CHCl_3$) [lit.[38] $[\alpha]_D^{20}$ +15.9 (*c* 0.8, $CHCl_3$)]. IR (KBr) cm^{-1}: 1690, 1735, 3343. ^1H NMR (270 MHz, $CDCl_3$) δ 3.05–3.19 (2H, m), 4.19 (1H, t, *J*=6.8 Hz), 4.29–4.46 (2H, m), 4.60 (2H, d, *J*=5.6 Hz), 4.65–4.73 (1H, m), 5.22–5.32 (3H, m), 5.78–5.93 (1H, m), 6.92–7.11 (2H, m), 7.20–7.43 (7H, m), 7.49–7.59 (2H, m), 7.74 (2H, d, *J*=7.2 Hz). MS (EI) *m/z* 427 (M^+). Anal. Calcd for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89; N, 3.28. Found: C, 75.75; H, 5.92; N, 3.18.

4.8.7. 2-*tert*-Butoxycarbonyl-1-methoxy-1,2-dihydroisoquinoline (25). To a solution of **1** (3.03 g, 10 mmol) in benzene (15 mL) was added absolute methanol (6 mL, 148 mmol) with stirring for 6 h at room temperature. After concentration in vacuo, the residue was purified by distilled under reduced pressure to give **25** (2.40 g, 92%) as a colorless prism. Mp 61–62 °C (pentane). IR (KBr) cm^{-1}: 1718. ^1H NMR (400 MHz, $CDCl_3$) δ 1.56 (9H, s), 3.30 (3H, s), 6.01 (1H, br s), 6.44 (1H, br), 7.00 (1H, br s), 7.19–7.35 (4H, m). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 28.1, 54.5, 81.6, 82.3, 107.3, 124.2, 124.9, 126.6, 127.5, 128.2, 129.0, 130.4, 152.5. MS (EI) (*m/z*) 261 (M^+). Anal. Calcd $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.92; H, 7.51; N, 5.28.

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