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Carboxamidation of carboxylic acids with 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI) without bases

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ABSTRACT

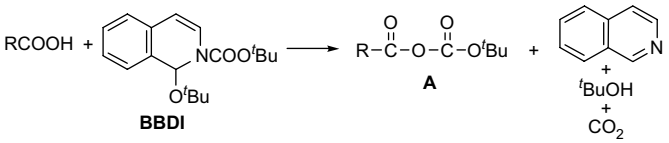
Formation of carboxamides of a variety of carboxylic acids with the coupling reagent BBDI is described. This procedure permits a one pot and simple operation without the need of any bases and no base was required for even use of amine hydrochlorides. In addition, an approach to BBDI-catalyzed carboxamidation is examined.

1. Introduction

Amide moieties constitute major backbones, as well as important functional groups, in numerous natural products and synthetic compounds.[1] The synthesis of carboxylic amide is one of the most fundamental and pivotal protocols for producing natural and synthetically useful compounds such as peptides and medicinal drugs in organic chemistry. To date, a variety of amidation conditions have been developed.[2–5] In general, coupling reactions between activated derivatives of carboxylic acids and amines have been employed. Most procedures require either the presence of some additives such as bases or other catalysts or heating. In some cases, a reagent-derived byproduct such as urea makes product purification difficult. Accordingly, further development of condensing reagents for amidation under mild conditions is desirable. Following our interest in the use of 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI) as a novel butoxycarbonylation reagent in organic synthesis,[6] we recently reported a simple and mild esterification that uses nearly equimolar amounts of *N*-protected amino acids and alcohols using BBDI as a condensing reagent without the need for any additives.[7] In pursuing our interest in the use of BBDI as a *tert*-butoxycarbonylation reagent in organic synthesis, we herein describe the carboxamidation of carboxylic acids with amines in the presence of BBDI with no bases.

2. Results and discussion

Activation of the carboxy group is the most useful method of amide formation. An activated carboxylic acid acylates an amine by a nucleophilic acyl substitution. Among activated carboxylic acids, mixed anhydrides of carbonic acid half esters contain an activating carbonyl group with a reduced electrophilic character due to lone pairs of electrons on vicinal oxygen. Reaction of BBDI with carboxylic acids affords the corresponding mixed anhydrides **A**, which represent a promising active intermediate for carboxamidation. In addition, an amine is difficult to attack *tert*-butoxycarbonyl owing to steric hindrance of *tert*-butyl substituent. In practice, a variety of carboxylic acids were treated with BBDI in dichloromethane for 30 min followed by the addition of various amines (1.2 equiv) for 24 h at room temperature (rt). Similarly, the coupling reagents 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ)[8] and 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (IIDQ)[9] permit the formation of amides from carboxylic acids and amines without the need for bases.[10] In general, almost conventional condensing reagents required additives such as bases.



This procedure allows amidation to proceed in one pot. The reaction mixture was concentrated, ethyl acetate was added, and the organic solvent was washed with diluted HCl and brine. The reagent-derived byproducts are easily removed by a simple aqueous work-up. The results are shown in Table 1. The yields for most reactions are high. However, the yields using bulkier carboxylic acid or amine such as adamantanecarboxylic acid or *tert*-butylamine (entries 9 and 15–18) were relatively low.

Next, carboxamidation of a half methyl ester of adipic acid **4** was examined. The results are shown in Table 2. It was found that the ester moiety remained intact in this reaction.

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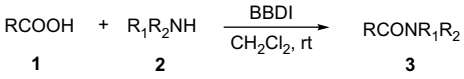
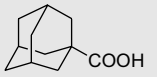
Table 1
Carboxamidation of **1** with amines **2** using BBDI.



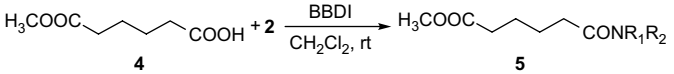
Entry	Carboxylic acid	Amine	Time (h)	3	Yield (%)
1	$PhCH_2CH_2COOH$ **1a**	$PhCH_2NH_2$ **2a**	3	**3a**	85
2	**1a**	**2a**	24	**3a**	95
3	**1a**	$PhNH_2$ **2b**	3	**3b**	90
4	**1a**	$^{i}Pr_2NH$ **2c**	24	**3c**	90
5	**1a**	*tert*-$BuNH_2$ **2d**	24	**3d**	92
6	**1a**	Pyrrolidine **2e**	24	**3e**	89
7	PhCOOH **1b**	**2a**	24	**3f**	92
8	**1b**	**2b**	24	**3g**	77
9	**1b**	**2d**	24	**3h**	69
10	**1b**	**2e**	24	**3i**	87
11	Cinnamic acid **1c**	**2a**	24	**3j**	88
12	**1c**	**2e**	24	**3k**	97
13	Cyclohexanoic acid **1e**	**2a**	24	**3l**	75
14	CH_3CH_2COOH **1f**	**2a**	24	**3m**	93
15	 **1g**	**2a**	24	**3n**	70
16	**1g**	**2b**	24	**3o**	20
17	**1g**	**2d**	24	**3p**	26
18	**1g**	**2e**	24	**3q**	50

It is known that piperine (**7f**) isolated from *Piper* species[11] and its amide analogues have antipyretic, analgesic, insecticidal, and anti-inflammatory activities.[12,25] Therefore, we examined carboxamidation of (2*E*,4*E*)-piperinic acid (**6**) as a conjugated carboxylic acid with several amines using BBDI. The results are summarized in Table 3. Good yields were obtained as shown in Table 4. Raise the temperature from room temperature to reflux significantly increased the yields and reduced the reaction periods.

Next, carboxamidation of *N*-protected amino acids **8** with amines **2** was examined without any undesirable racemization of chiral center.[13]

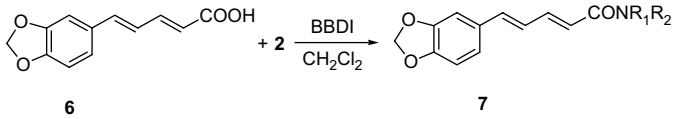
Recently, Brunel reported that little conversion (<5%) was observed in carboxamidation of 3-(2-furyl)acrylic acid (**10**) with methioninemethyl ester hydrochloride (**11a**) by the standard coupling method using a dicyclohexylcarbodiimide (DCC)/additive such as the DMAP, $^{i}Pr_2NEt$, HOBt, or HOAt method.[14] Similar negative results were encountered using more sophisticated coupling reagents such as *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU).[15] Fortunately, the use of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate reagent (BOP)[16] as a coupling reagent led to the expected coupling product **12a** in 75% isolated yield at room temperature in CH_2Cl_2 in the presence of 3 equiv of $^{i}Pr_2NEt$. This method was then successfully applied to the coupling of conjugated carboxylic acids with numerous methyl ester amino acid hydrochlorides in dioxane for 12 h at room temperature. Interestingly, the coupling of

Table 2
Carboxamidation of **4** with amines **2** using BBDI.



Entry	Amine	5	Yield (%)
1	**2a**	**5a**	77
2	**2b**	**5b**	92
3	**2c**	**5c**	77
4	**2d**	**5d**	73
5	**2e**	**5e**	65
6	Piperidine **2f**	**5f**	88

Table 3
Carboxamidation of **6** with amines **2** using BBDI.

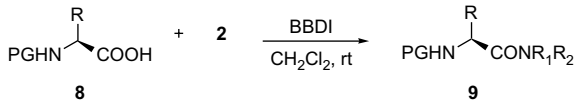


Entry	Amine	Condition	7	Yield (%)
1	**2f**	rt, 24 h	**7f**	72
2	**2a**	Reflux, 5 h	**7a**	87
3	**2e**	rt, 24 h	**7e**	68
4	**2e**	Reflux, 5 h	**7e**	87
5	$^{i}PrNH_2$ **2g**	Reflux, 5 h	**7g**	76
6	$^{i}BuNH_2$ **2h**	rt, 24 h	**7h**	89
7	**2h**	Reflux, 5 h	**7h**	95
8	*n*-Hexanamine **2i**	rt, 24 h	**7i**	71
9	**2i**	Reflux, 5 h	**7i**	94
10	Cyclohexamine **2j**	Reflux, 5 h	**7j**	90

10 with **11a** using BBDI also proceeded to give **12a** in 71% yield. It is remarkable that this condition did not require any base in spite of the use of hydrochloride amines. We consider that the hydrochloride was converted to a free amine, because isoquinoline liberated from BBDI in the *tert*-butoxycarbonylation of carboxylic acid played a role as a base. This procedure was then successfully applied to the coupling of other conjugated carboxylic acids with several methyl ester amino acids hydrochloride as illustrated in Table 5. The yields in Brunel's condition (BOP/3 equiv $^{i}Pr_2NEt$) are shown in parentheses in Table 5. The use of BBDI is better than or equal to that of BOP/3 equiv $^{i}Pr_2NEt$.

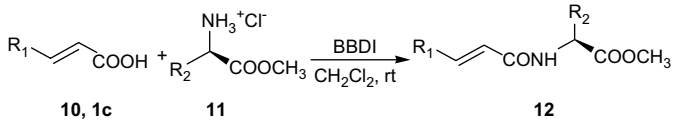
Next, an approach to BBDI-catalyzed carboxamidation of **1a** with **2a** in the presence of Boc_2O was examined under a variety of conditions summarized in Table 6. Treatment of **1a** with BBDI (0.1 equiv) in dichloromethane containing Boc_2O (0.9 equiv) for 30 min (time a), followed by the addition of **2a** (1.2 equiv) for 24 h (time b) at room temperature gave **3a** in 18% yield together with *N*-Boc amine **15** as a byproduct in 82% yield (entry 1). As results, as the amount of BBDI is increased, the yield of **3a** becomes larger and that of **15** is smaller (entries 2–6). In addition, under reflux the yields of **3a** were improved (entries 7–10). Presumably **15** is prepared as follows: BBDI first was protonated to form a cyclic six-membered intermediate **13**, which would be attacked by amine **2a** in place of carboxylate anion (a conjugated base) to transform into **15**. Therefore, it seems that **2a** should be added to the reaction mixture after **1a** has been fully converted to the mixed anhydride **14**. Based on this speculation, *tert*-butoxylation of **1a** with BBDI (0.1 equiv) in dichloromethane containing Boc_2O (0.9 equiv) for 24 h under reflux followed by the addition of **2a** (1.2 equiv) for 3 h (time b) provided **3a** in 86% yield accompanied by **15** in 14% yield (entry 11).

Table 4

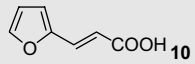
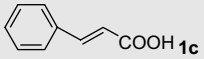


Entry	Amino acid	Amine	Time (h)	9	Yield (%)
1	*N*-Cbz–Ala **8a**	**2a**	5	**9a**	97
2	**8a**	**2e**	5	**9b**	94
3	*N*-Cbz–Phe **8b**	**2a**	5	**9c**	94
4	**8b**	**2e**	5	**9d**	89
5	*N*-Boc–Ala **8c**	**2a**	5	**9e**	91
6	**8c**	**2e**	5	**9f**	81
7	*N*-Boc–Phe **8d**	**2a**	5	**9g**	94
8	**8d**	**2e**	5	**9h**	75
9	**8d**	**2e**	24	**9h**	99

Table 5



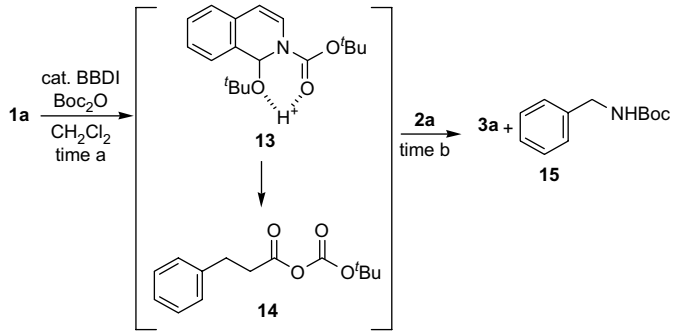
10, 1c **11** **12**

Entry	Acid **10**, **1c**	Amine **11**	**12**	Yield (%)
1	 **10**	Met–OMe·HCl **11a**	**12a**	71 (75)
2	**10**	Val–OMe·HCl **11b**	**12b**	70 (73)
3	**10**	Phe–OMe·HCl **11c**	**12c**	71 (59)
4	**10**	Tyr–OMe·HCl **11d**	**12d**	66 (31)
5	 **1c**	**11a**	**12e**	80 (86)
6	**1c**	**11b**	**12f**	84 (83)

3. Conclusion

In summary, a simple and mild carboxamidation of carboxylic acids using a novel *tert*-butoxycarbonylation reagent, BBDI **1**, easily prepared in quantitative yield by the reaction of isoquinoline with Boc_2O is reported. Although a variety of methods for carboxamidation using coupling reactions between activated derivatives of carboxylic acids and amines have been reported, no use of additives such as a base has not been extensively investigated. In addition, this procedure has several advantages including removal of reagent-derived byproducts by simple work-up, and no requirement for any bases even use of amine hydrochlorides. Furthermore, we developed a novel BBDI-catalyzed amidation of carboxylic acid in the presence of Boc_2O.

Table 6



Entry	BBDI (equiv)	Boc_2O (equiv)	Temp.	Times	**3a**	**15**
				a, b (h)	Yield (%)	Yield (%)
1	0.1	0.9	rt	0.5, 24	18	82
2	0.1	0.9	rt	3, 21	27	70
3	0.2	0.8	rt	5, 3	55	37
4	0.4	0.6	rt	5, 3	67	20
5	0.6	0.4	rt	5, 3	62	14
6	0.8	0.2	rt	5, 3	70	2
7	0.1	0.9	Reflux	5, 19	65	35
8	0.2	0.8	Reflux	5, 3	74	26
9	0.4	0.6	Reflux	5, 3	73	12
10	0.6	0.4	Reflux	5, 3	84	2
11	0.1	0.9	Reflux	24, 3	86	14

4. Experimental section

4.1. General information

Melting points were determined on Mel-Temp or Yanaco micro melting point apparatus. All melting points are uncorrected. Infrared (IR) spectra were recorded on Perkin–Elmer 1600 or Perkin–Elmer 1725 X series FT-IR 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. Optical purities (ees) were determined using TOSOH 8020 series with Chiralcel AS column (*n*-hexane/2-propanol=90:10, 1.0 mL/min). 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, 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.

4.2. General procedure for carboxamidation of carboxylic acids 1 with amines 2 using BBDI (Table 1)

A mixture of **1** (1 mmol) and BBDI (1.2 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 30 min. After addition of amine (1.2 mmol) to the mixture, the whole was stirred for reaction times indicated in Table 1. Ethyl acetate (40 mL) was added to the reaction mixture and then the whole was washed with 5% HCl solution (10 mL×2) 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 **3a**–**q** in yields shown in Table 1.

*4.2.1. N-Benzyl-3-phenylpropionamide (**3a**)*

Colorless prism. Mp 80–82 °C [lit.[17] mp 84–86 °C]. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.50 (t, J=7.9 Hz, 2H), 2.98 (t, J=7.4 Hz, 2H), 4.37 (d, J=5.8 Hz, 2H), 5.73 (br s, 1H), 7.11–7.32 (m, 10H). IR (KBr) cm^{-1}: 1546, 1640, 3294. MS (EI) m/z 239 (M^+).

*4.2.2. N-Phenyl-3-phenylpropionamide (**3b**)*

Colorless needles. Mp 96 °C [lit. [18] mp 97–99 °C]. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.60 (t, J=7.9 Hz, 2H), 2.99 (t, J=8.0 Hz, 2H), 7.02–7.28 (m, 8H), 7.37–7.49 (m, 2H), 7.77 (br s, 1H).

*4.2.3. N,N-Diisopropyl-3-phenylpropionamide (**3c**)*

A colorless liquid. IR (neat) cm^{-1}: 1439, 1638, 2966, 3469. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, J=6.8 Hz, 6H), 1.38 (t, J=6.8 Hz, 6H), 2.58 (t, J=7.7 Hz, 2H), 2.96 (t, J=7.7 Hz, 2H), 3.94 (br s, 1H), 3.89–3.95 (m, 1H), 7.17–7.31 (m, 5H). MS (EI) m/z 233 (M^+), HRMS Calcd for $C_{15}H_{23}NO$ (M^+): 233.1870. Found: 233.1768.

*4.2.4. N-tert-Butyl-3-phenylpropionamide (**3d**)*

Colorless needles. Mp 86–87 °C. IR (neat) cm^{-1}: 1362, 1455, 1552, 1642, 2966, 3312. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 9H), 2.38 (t, J=7.7 Hz, 2H), 2.94 (t, J=7.7 Hz, 2H), 5.08 (br s, 1H), 7.16–7.32 (m, 5H). MS (EI) m/z 205 (M^+). Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.92; H, 9.42; N, 6.81.

*4.2.5. 3-Phenylpropionylpyrrolidine (**3e**)*

A colorless liquid. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.75–1.92 (m, 4H), 2.55 (t, J=8.2 Hz, 2H), 2.98 (t, J=7.4 Hz, 2H), 3.27 (t, J=6.4 Hz, 2H), 3.45 (t, J=6.6 Hz, 2H), 7.14–7.30 (m, 5H). MS (EI) m/z 203 (M^+), HRMS Calcd for $C_{13}H_{17}NO$ (M^+): 203.1310. Found: 203.1315.

*4.2.6. N-Benzylbenzamide (**3f**)*

Colorless needles. Mp 103–104 °C [lit.[17] mp 105–107 °C]. IR (KBr) cm^{-1}: 1641, 3301. ^1H NMR (270 MHz, $CDCl_3$): δ 4.62 (d, J=5.6 Hz, 2H), 6.59 (br s, 1H), 7.25–7.52 (m, 8H), 7.74–7.81 (m, 2H). MS (EI) m/z 211 (M^+).

*4.2.7. Benzanilide (**3g**)*

Colorless prisms. Mp 162 °C [lit.[19] mp 162–164 °C]. IR (KBr) cm^{-1}: 1439, 1535, 1600, 1656, 3345. ^1H NMR (270 MHz, $CDCl_3$): δ 7.09–7.18 (m, 1H), 7.30–7.54 (m, 5H), 7.60–7.70 (m, 2H), 7.82–7.97 (m, 3H). MS (EI) m/z 197 (M^+).

*4.2.8. N-tert-Butylbenzamide (**3h**)*

Colorless needles. Mp 126–128 °C [lit.[20] mp 123–124 °C]. ^1H NMR (270 MHz, $CDCl_3$): δ 1.47 (s, 9H), 6.03 (br s, 1H), 7.34–7.48 (m, 3H), 7.69–7.73 (m, 2H). MS (EI) m/z 177 (M^+).

*4.2.9. N-Benzoylpyrrolidine (**3i**)*

A colorless liquid. IR (neat) cm^{-1}: 1420, 1575, 1626, 2877, 2972, 3477. ^1H NMR (270 MHz, $CDCl_3$): δ 1.81–2.04 (m, 4H), 3.42 (t, J=6.6 Hz, 2H), 3.65 (t, J=6.7 Hz, 2H), 7.34–7.46 (m, 3H), 7.49–7.67 (m, 2H). MS (EI) m/z 175 (M^+). HRMS Calcd for $C_{11}H_{13}NO$ (M^+): 175.0997. Found: 175.0998.

*4.2.10. trans-Cinnamoylbenzylamine (**3j**)*

Colorless needles. Mp 109–111 °C [lit.[21] mp 106–109 °C]. IR (KBr) cm^{-1}: 1221, 1542, 1615, 1653, 3028, 3266. ^1H NMR (270 MHz, $CDCl_3$): δ 4.53 (d, J=5.8 Hz, 2H), 6.28 (br s, 1H), 6.75 (d, J=15.6 Hz, 1H), 7.22–7.37 (m, 3H), 7.43–7.47 (m, 2H), 7.65 (d, J=15.6 Hz, 1H). MS (EI) m/z 237 (M^+).

*4.2.11. trans-Cinnamoylpyrrolidine (**3k**)*

Colorless needles. Mp 98 °C [lit.[22] mp 47–49 °C]. ^1H NMR (270 MHz, $CDCl_3$): δ 1.84–2.08 (m, 4H), 3.59–3.65 (m, 4H), 6.73 (d, J=15.5 Hz, 1H), 7.32–7.41 (m, 3H), 7.49–7.55 (m, 2H), 7.70 (d, J=15.4 Hz, 1H). MS (EI) m/z 201 (M^+).

*4.2.12. N-Benzylcyclohexanecarboxamide (**3l**)*

Colorless needles. Mp 107–109 °C [lit.[23] mp 103–104 °C]. IR (KBr) cm^{-1}: 1552, 1642, 2853, 2923, 3286. ^1H NMR (270 MHz, $CDCl_3$): δ 1.09–1.46 (m, 5H), 1.54–1.94 (m, 5H), 2.00–2.23 (m, 1H), 4.38 (d, J=5.8 Hz, 2H), 6.15 (br s, 1H), 7.11–7.37 (m, 5H). MS (EI) m/z 217 (M^+).

*4.2.13. N-Benzylpropanamide (**3m**)*

Colorless needles. Mp 48–49 °C [lit.[24] mp 49–50 °C]. IR (KBr) cm^{-1}: 1548, 1639, 3295. ^1H NMR (270 MHz, $CDCl_3$): δ 1.18 (t, J=7.6 Hz, 3H), 2.24 (q, J=7.6 Hz, 2H), 4.43 (d, J=5.7 Hz, 2H), 5.80 (br s, 1H), 7.24–7.37 (m, 5H). MS (EI) m/z 163 (M^+).

*4.2.14. N-Benzyl-1-adamantanecarboxamide (**3n**)*

Colorless needles. Mp 171–172 °C. IR (KBr) cm^{-1}: 1533, 1634, 2905, 3345. ^1H NMR (270 MHz, $CDCl_3$): δ 1.62–1.95 (m, 12H), 2.04 (br s, 3H), 4.43 (d, J=5.6 Hz, 2H), 5.89 (br s, 1H), 7.24–7.37 (m, 5H). MS (EI) m/z 269 (M^+). Anal. Calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.43; H, 8.36; N, 9.20.

*4.2.15. N-Phenyl-1-adamantanecarboxamide (**3o**)*

Colorless needles. Mp 199–200 °C [lit.[25] mp 205–206 °C]. ^1H NMR (270 MHz, $CDCl_3$): δ 1.65–1.84 (m, 6H), 1.89–2.11 (m, 9H), 7.05–7.11 (m, 1H), 7.26–7.33 (m, 3H), 7.52–7.55 (m, 2H). MS (EI) m/z 255 (M^+).

*4.2.16. N-tert-Butyl-1-adamantanecarboxamide (**3p**)*

Colorless needles. Mp 188–189 °C. IR (KBr) cm^{-1}: 1535, 1638, 1904, 3336. ^1H NMR (270 MHz, $CDCl_3$): δ 1.33 (s, 9H), 1.62–1.84 (m, 12H), 2.03 (br s, 3H), 5.37 (br s, 1H). MS (EI) m/z 235 (M^+). Anal. Calcd for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 5.95. Found: C, 76.76; H, 11.06; N, 5.95.

*4.2.17. N-(Adamantylcarbonyl)pyrrolidine (**3q**)*

Colorless needles. Mp 109–110 °C. IR (KBr) cm^{-1}: 1402, 1604, 1887, 2906, 3198. ^1H NMR (270 MHz, $CDCl_3$): δ 1.38–2.11 (m, 19H), 3.58 (br s, 4H). MS (EI) m/z 233 (M^+). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.28; H, 10.27; N, 6.02.

4.3. General procedure for carboxamidation of adipic acid 4 with amines 2 using BBDI (Table 2)

A mixture of **4** (1 mmol) and BBDI (1.2 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 30 min. After addition of amine **2** (1.2 mmol) to the mixture, the whole was stirred for 24 h. Ethyl acetate (40 mL) was added to the reaction mixture and then the whole was washed with 5% HCl solution (10 mL×2) 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**–**f** in yields shown in Table 2.

*4.3.1. 6-Oxo-6-(benzylamino)-hexanoic acid methyl ester (**5a**)*

Colorless needles. Mp 44–45 °C. ^1H NMR (270 MHz, $CDCl_3$): δ 1.57–1.86 (m, 6H), 2.23 (t, J=6.6 Hz, 2H), 2.34 (t, J=6.6 Hz, 2H), 3.66 (s 3H), 4.43 (d, J=5.6 Hz, 2H), 5.89 (br s, 1H), 7.14–7.23 (m, 5H). MS (EI) m/z 249 (M^+). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.33; H, 7.77; N, 5.50.

*4.3.2. 6-Oxo-6-(phenylamino)-hexanoic acid methyl ester (**5b**)*

Colorless needles. Mp 45 °C. IR (KBr) cm^{-1}: 1173, 1538, 1664, 1725, 2951, 3312. ^1H NMR (270 MHz, $CDCl_3$): δ 1.83–1.91 (m, 4H), 2.26–2.43 (m, 4H), 3.67 (s, 3H), 7.09 (t, J=7.3 Hz, 1H), 7.30 (t, J=7.9 Hz, 2H), 7.52 (d, J=7.7 Hz, 2H), 7.67 (br s, 1H). MS (EI) m/z 235 (M^+). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.42; H, 7.28; N, 5.90.

*4.3.3. 6-Oxo-6-(diisopropylamino)-hexanoic acid methyl ester (**5c**)*

A colorless liquid. IR (neat) cm^{-1}: 1635, 1739, 2966, 3474. ^1H NMR (400 MHz, $CDCl_3$): δ 1.19, (d, J=3.6 Hz, 6H), 1.37 (d, J=6.7 Hz, 6H), 1.65–1.67 (m, 4H), 2.28–2.37 (m, 4H), 3.48 (br s, 1H), 3.66 (s, 1H), 3.94–3.97 (m, 1H). MS (EI) m/z 243 (M^+). HRMS Calcd for $C_{13}H_{25}NO_3$ (M^+): 243.1834. Found: 243.1848.

*4.3.4. 6-Oxo-6-(tert-butylamino)-hexanoic acid methyl ester (**5d**)*

Colorless needles. Mp 53–55 °C. IR (KBr) cm^{-1}: 1544, 1640, 1736, 2962, 3332. ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 9H), 1.61–1.68 (m, 4H), 2.11 (t, J=6.7 Hz, 2H), 2.33 (t, J=7.2 Hz, 2H), 3.67 (s, 3H), 5.28 (br s, 1H). MS (EI) m/z 215 (M^+). Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.57; H, 10.08; N, 6.45.

*4.3.5. 6-Oxo-6-(pyrrolidino)-hexanoic acid methyl ester (**5e**)*

A pale yellow liquid. IR (neat) cm^{-1}: 1453, 1623, 1734, 2954, 3447. ^1H NMR (270 MHz, $CDCl_3$): δ 1.60–1.74 (m, 4H), 1.80–2.01 (m, 4H), 2.20–2.38 (m, 4H), 3.38–3.48 (m, 4H), 3.67 (s, 3H). MS (EI) m/z 213 (M^+). HRMS Calcd for $C_{11}H_{19}NO_3$ (M^+): 312.1365. Found: 213.1350.

*4.3.6. 6-Oxo-6-(piperidino)-hexanoic acid methyl ester (**5f**)*

A pale yellow liquid. IR (neat) cm^{-1}: 1436, 1634, 1733, 2938, 3480. ^1H NMR (270 MHz, $CDCl_3$): δ 1.45–1.72 (m, 10H), 2.30–2.38 (m, 4H), 3.33–3.42 (m, 2H), 3.50–3.58 (m, 2H), 3.66 (s, 3H). MS (EI) m/z 227 (M^+). HRMS Calcd for $C_{12}H_{21}NO_3$ (M^+): 227.1521. Found: 227.1508.

4.4. General procedure for carboxamidation of piperinic acid 6 with amines 2 using BBDI (Table 3)

A mixture of **6** (0.5 mmol) and BBDI (0.6 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 30 min. After addition of amine **2** (0.6 mmol) to the mixture, the whole was stirred at reflux or at

room temperature for 24 h indicated in Table 3. Ethyl acetate (40 mL) was added to the reaction mixture and then the whole was successively washed with 5% HCl solution (5 mL×2), 10% K_2CO_3 (5 mL×2), 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 **7a–f** in yields shown in Table 3.

*4.4.1. 1-E,E-Piperinoyl-piperidine (**7f**)*

Colorless needles. Mp 132–133 °C [lit.[11] mp 132–133 °C]. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.47–1.72 (m, 6H), 3.20–3.69 (br d, 4H), 5.97 (s, 2H), 6.43 (d, J=14.7 Hz, 1H), 6.64–6.80 (m, 3H), 6.88 (dd, J=1.6, 8.1 Hz, 1H), 6.97 (d, J=1.5 Hz, 1H), 7.35–7.45 (m, 1H).

*4.4.2. 1-E,E-Piperinoylbenzylamine (**7a**)*

Colorless needles. Mp 182 °C [lit.[26] mp 177–178 °C]. ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.54 (d, J=5.6 Hz, 2H), 5.83 (br s, 1H), 5.93 (d, J=14.1, 1H), 5.97 (s, 2H), 6.61–6.79 (m, 3H), 6.89 (dd, J=1.6, 8.1 Hz, 1H), 6.98 (d, J=1.4 Hz, 1H), 7.33 (m, 6H).

*4.4.3. 1-E,E-Piperinoylpyrrolidine (**7e**)*

Pale yellow neeedles. Mp 144–146 °C. [lit.[27] mp 147 °C]. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.82–2.08 (m, 4H), 3.46–3.59 (m, 4H), 5.97 (s, 2H), 6.25 (d, J=14.9 Hz, 1H), 6.73–6.81 (m, 3H), 6.89 (dd, J=1.5, 8.1 Hz, 1H), 6.98 (d, J=1.3 Hz, 1H), 7.45 (dd, J=8.9, 14.8 Hz, 1H).

*4.4.4. 1-E,E-Piperinoyl-isopropylanime (**7g**)*

Pale yellow needles. Mp 173–175 °C [lit.[26] mp 169–169.4 °C]. IR (KBr) cm^{-1}: 1253, 1446, 1489, 1543, 1614, 1644, 2973, 3272. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.19 (d, J=6.8 Hz, 6H), 4.11–4.26 (m, 1H), 5.66 (br d, J=6.1 Hz, 1H), 5.91 (d, J=14.9 Hz, 1H), 5.96 (s, 2H), 6.66–6.78 (m, 3H), 6.86 (dd, J=1.5, 8.1 Hz, 1H), 6.95 (d, J=1.5 Hz, 1H), 7.34 (dd, J=10.1, 15.0 Hz, 1H). MS (EI) m/z 259 (M^+).

*4.4.5. 1-E,E-Piperinoyl-isobutylamine (**7h**)*

Colorless needles. Mp 171 °C [lit.[26] mp 161.2–161.7 °C]. IR (KBr) cm^{-1}: 1255, 1446, 1504, 1616, 1645, 2960, 3291. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.93 (d, J=6.8 Hz, 6H), 1.75–1.92 (m, 1H), 3.18 (t, J=6.8 Hz, 2H), 5.89 (br s, 1H), 5.96 (s, 2H), 5.97 (d, J=14.8 Hz, 1H), 6.60–6.81 (m, 3H), 6.86 (dd, J=1.7, 8.0 Hz, 1H), 6.95 (d, J=1.6 Hz, 1H), 7.35 (dd, J=9.8, 15.0 Hz, 1H). MS (EI) m/z 273 (M^+).

*4.4.6. 1-E,E-Piperinoyl-hexylamine (**7i**)*

Pale yellow needles. Mp 139–140 °C [lit.[26] mp 149.5–149.8 °C]. IR (KBr) cm^{-1}: 1261, 1501, 1539, 1604, 1643, 3296. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.88 (t, J=6.8 Hz, 3H), 1.26–1.40 (m, 6H), 1.48–1.60 (m, 2H), 3.34 (q, J=7.2 Hz, 2H), 5.58 (br s, 1H), 5.91 (d, J=14.8 Hz, 1H), 6.70–6.83 (m, 3H), 6.88 (dd, J=1.5, 8.3 Hz, 1H), 6.97 (d, J=1.6 Hz, 1H), 7.34 (dd, J=10.2, 14.9 Hz, 1H).

*4.4.7. 1-E,E-Piperinoyl-cyclohexylamine (**7j**)*

Colorless needles. Mp 207–208 °C [lit.[26] mp 196.4–197.3 °C]. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.09–1.26 (m, 2H), 1.30–1.49 (m, 2H), 1.57–1.80 (m, 4H), 1.91–2.03 (m, 4H), 5.48 (br d, J=7.5 Hz, 1H), 5.89 (d, J=14.9 Hz, 1H), 5.97 (s, 2H), 6.60–6.80 (m, 3H), 6.87 (dd, J=1.5, 8.1 Hz, 1H), 6.96 (d, J=1.6 Hz, 1H), 7.33 (dd, J=10.22, 14.8 Hz, 1H). MS (EI) m/z 299 (M^+).

4.5. General procedure for carboxamidation of *N*-protected α-amino acid 8 with amines 2 using BBDI (Table 4)

A mixture of **8** (1 mmol) and BBDI (1.2 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 30 min. After addition of amine **2** (1.2 mmol) to the mixture, the whole was stirred at room temperature for times indicated in Table 4. Ethyl acetate (40 mL) was added to the reaction mixture and then the whole was successively washed with 5% HCl solution (5 mL×2), 10% K_2CO_3 (5 mL×2), 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 **9a–h** in yields shown in Table 4.

*4.5.1. N-Cbz–Ala benzylamide (**9a**)*

Colorless needles. Mp 140–141 °C. $[\alpha]_D^{22}$ −8.1 (c 1.3, $CHCl_3$). >99% ee (Chiralcel AS). IR (KBr) cm^{-1}: 1256, 1533, 1641, 1688, 3296. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.37 (d, J=7.1 Hz, 3H), 4.25–4.44 (m, 3H), 4.92–5.11 (m, 2H), 5.58 (br d, J=6.9 Hz, 1H), 6.76 (br s, 1H), 7.14–7.36 (m, 10H). Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 68.98; H, 6.44; N, 8.94.

*4.5.2. N-Cbz–Ala pyrrolidine amide (**9b**)*

Colorless prisms. Mp 131–132 °C. $[\alpha]_D^{24}$ −17.3 (c 1.2, MeOH) [lit.[28] mp 128–131 °C. $[\alpha]_D^{20}$ −16.8 (c 1.0, MeOH)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (d, J=7.3 Hz, 3H), 1.76–2.02 (m, 4H), 3.34–3.65 (m, 4H), 4.44–4.56 (m, 1H), 5.08 (s, 2H), 5.79 (br s, 1H), 7.27–7.39 (m, 5H). Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found: C, 64.93; H, 7.39; N, 9.90.

*4.5.3. N-Cbz–Phe benzylamide (**9c**)*

Colorless needles. Mp 162–164 °C [lit.[29] mp 161–162 °C]. $[\alpha]_D^{22}$ +8.0 (c 0.9, $CHCl_3$). >99% ee (Chiralcel AS). ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.99–3.17 (m, 2H), 4.25–4.43 (m, 3H), 5.03 (s, 2H), 5.40 (br s, 1H), 6.07 (br s, 1H), 7.03–7.06 (m, 2H), 7.10–7.38 (m, 13H). MS (EI) m/z 338 (M^+). HRMS m/z Calcd for $C_{24}H_{24}N_2O_3$ (M^+): 338.1787. Found: 338.1779.

*4.5.4. N-Cbz–Phe pyrrolidine amide (**9d**)*

A colorless liquid. $[\alpha]_D^{22}$ +20.3 (c 2.0, $CHCl_3$) [lit.[30] $[\alpha]_D^{25}$ +21.6 ($CHCl_3$)]. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.43–1.84 (m, 4H), 2.49–2.65 (m, 1H), 2.92–3.11 (m, 2H), 3.20–3.46 (m, 3H), 4.57–4.70 (m, 1H), 4.95–5.16 (m, 2H), 6.00–6.21 (br s, 1H), 7.11–7.38 (m, 10H). MS (EI) m/z 352 (M^+). HRMS Calcd for $C_{21}H_{24}N_2O_3$ (M^+): 352.1787. Found: 352.1787.

*4.5.5. N-Boc–Ala benzylamide (**9e**)*

Colorless needles. Mp 104–106 °C [lit.[31] mp 104 °C]. $[\alpha]_D^{22}$ −24.5 (c 1.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (d, J=7.2 Hz, 3H), 1.41 (s, 9H), 4.18 (br s, 1H), 4.44 (s, 2H), 5.00 (br s, 1H), 6.53 (br s, 1H), 7.25–7.35 (m, 5H). MS (EI) m/z 278 (M^+). Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 63.47; H, 8.08; N, 9.80.

*4.5.6. N-Boc–Ala pyrrolidine amide (**9f**)*

Colorless needles. Mp 63–65 °C. $[\alpha]_D^{24}$ −6.8 (c 1.1, $CHCl_3$) [lit.[32] mp 67–69 °C. $[\alpha]_D^{25}$ −14.5 (c 2.1, $CHCl_3$)]. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.31 (d, J=6.7 Hz, 3H), 1.43 (s, 9H), 1.81–2.05 (m, 4H), 3.34–3.66 (m, 4H), 4.37–4.51 (m, 1H), 5.51 (br d, J=7.7 Hz, 1H). Anal. Calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15; N, 11.56. Found: C, 59.18; H, 9.35; N, 11.32.

*4.5.7. N-Boc–Phe benzylamide (**9g**)*

Colorless needles. Mp 134–135 °C. $[\alpha]_D^{26}$ +4.2 (c 1.3, $CHCl_3$) [lit.[33] mp 131–132 °C. $[\alpha]_D^{20}$ +3.93 (c 1.0, $CHCl_3$)]. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.35 (s, 9H), 2.93–3.11 (m, 2H), 4.08–4.51 (m, 3H), 5.24–5.38 (m, 1H), 6.46–6.68 (br s, 1H), 7.00–7.11 (m, 2H), 7.13–7.30 (m, 8H). Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 70.91; H, 7.45; N, 7.87.

*4.5.8. N-Boc–Phe pyrrolidine amide (**9h**)*

Pale yellow needles. Mp 94–97 °C. $[\alpha]_D^{25}$ +37.8 (c 1.8, $CHCl_3$) [lit.[32] mp 93–95 °C. $[\alpha]_D^{25}$ +39.3 (c 1.0, $CHCl_3$)]. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.41 (s, 9H), 1.47–1.76 (m, 4H), 2.47–2.63 (m, 1H), 2.87–3.08 (m, 2H), 3.23–3.47 (m, 3H), 4.50–4.65 (m, 1H), 5.52 (br d, J=8.7 Hz, 1H), 7.15–7.32 (m, 5H). Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.60; H, 8.33; N, 8.61.

4.6. General procedure for carboxamidation of 3-(2-furyl)acrylic acid (10) or *trans*-cinnamic acid (1c) with α-amino acid ester hydrochloride 11 using BBDI (Table 5)

A mixture of **10** or **1c** (1.1 mmol) and BBDI (1.05 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 1 h. After addition of hydrochloride salt **11** (1.05 mmol) to the mixture, the whole was stirred at room temperature for 24 h. Ethyl acetate (40 mL) was added to the reaction mixture and then the whole was successively washed with 5% HCl solution (10 mL×2), 10% K_2CO_3 (10 mL×2), 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 **12a**–**f** in yields shown in Table 5.

4.6.1. Furylacryloyl-methionine methyl ester (*12a*)

Pale yellow needles. Mp 101–102 °C [lit.[14] mp 103 °C]. $[\alpha]_D^{26}$ +22.6 (*c* 1.2, $CHCl_3$). IR (KBr) cm^{-1}: 1228, 1616, 1741, 3274. ^1H NMR (270 MHz, $CDCl_3$): δ 1.98–2.11 (m, 4H), 2.17–2.30 (m, 1H), 2.49–2.58 (m, 2H), 3.78 (s, 3H), 4.82–4.90 (m, 1H), 6.37 (d, *J*=15.3 Hz, 1H), 6.44–6.46 (m, 2H), 6.55–6.59 (m, 1H), 7.41 (d, *J*=15.7 Hz, 1H), 7.44 (m, 1H). MS (EI) *m*/*z* 283 (M^+).

4.6.2. Furylacryloyl-valine methyl ester (*12b*)

Pale yellow needles. Mp 159–160 °C [lit.[14] mp 146 °C]. $[\alpha]_D^{27}$ +45.4 (*c* 1.2, $CHCl_3$). IR (KBr) cm^{-1}: 1216, 1536, 1563, 1618, 1735, 3290. ^1H NMR (270 MHz, $CDCl_3$): δ 0.88–0.99 (m, 6H), 2.16–2.28 (m, 1H), 3.67 (s, 3H), 4.70–4.75 (m, 1H), 6.35 (br s, 1H), 6.42 (d, *J*=14.8 Hz, 1H), 6.42–6.45 (m, 1H), 6.54 (m, 1H), 7.42 (d, *J*=15.3 Hz, 1H), 7.43 (m, 1H). MS (EI) *m*/*z* 251 (M^+). HRMS Calcd for $C_{13}H_{17}NO_4$ (M^+): 251.1158. Found: 251.1161.

4.6.3. Furylacryloyl-phenylalanine methyl ester (*12c*)

Pale yellow needles. Mp 103 °C [lit.[14] mp 109 °C]. $[\alpha]_D^{26}$ +173.4 (*c* 0.7, $CHCl_3$). IR (KBr) cm^{-1}: 1539, 1565, 1619, 1655, 1732, 3311. ^1H NMR (270 MHz, $CDCl_3$): δ 3.11–3.26 (m, 2H), 3.77 (s, 3H), 4.99–5.06 (m, 1H), 6.16 (br s, 1H), 6.31 (d, *J*=15.3 Hz, 1H), 6.43–6.45 (m, 1H), 6.54–6.55 (m, 1H), 7.09–7.12 (m, 2H), 7.21–7.31 (m, 3H), 7.41 (d, *J*=15.2 Hz, 1H), 7.42 (m, 1H). MS (EI) *m*/*z* 299 (M^+). HRMS Calcd for $C_{17}H_{17}NO_4$ (M^+): 299.1158. Found: 299.1157.

4.6.4. Furylacryloyl-tyrosine methyl ester (*12d*)

Colorless prisms. Mp 135–137 °C [lit.[14] mp 90 °C]. $[\alpha]_D^{26}$ −73.0 (*c* 0.9, MeOH). ^1H NMR (270 MHz, $CDCl_3$): δ 3.01–3.17 (m, 2H), 3.74 (s, 3H), 4.95–5.01 (m, 1H), 6.20 (br d, *J*=7.9 Hz, 1H), 6.30 (d, *J*=15.3 Hz, 1H), 6.42–6.45 (m, 1H), 6.54 (d, *J*=3.3 Hz, 1H), 6.58 (s, 1H), 6.73 (d, *J*=8.6 Hz, 2H), 6.95 (d, *J*=8.6 Hz, 2H), 7.40 (d, *J*=17.9 Hz, 1H), 7.42 (s, 1H). MS (EI) *m*/*z* 315 (M^+). Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.55; H, 5.26; N, 4.39.

4.6.5. trans-Cinnamoyl-methionine methyl ester (*12e*)

Colorless needles. Mp 87–88 °C [lit.[14] mp 137 °C]. $[\alpha]_D^{27}$ +43.9 (*c* 1.4, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$): δ 1.98–2.14 (m, 4H), 2.17–2.34 (m, 1H), 2.57 (t, *J*=7.6 Hz, 2H), 3.76 (s, 3H), 4.85–4.92 (m, 1H), 6.49 (d, *J*=15.6 Hz, 1H), 6.75 (br s, 1H), 7.29–7.40 (m, 3H), 7.46–7.54 (m, 2H), 7.62 (d, *J*=15.6 Hz, 1H). MS (EI) *m*/*z* 293 (M^+). Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.18; H, 6.47; N, 4.75.

4.6.6. trans-Cinnamoyl-valine methyl ester (*12f*)

Colorless prisms. Mp 130 °C [lit.[14] 130 °C]. $[\alpha]_D^{26}$ +44.5 (*c* 1.3, $CHCl_3$). IR (KBr) cm^{-1}: 1212, 1533, 1620, 1655, 1742, 2964, 3323. ^1H NMR (270 MHz, $CDCl_3$): δ 0.97 (dd, *J*=6.9, 8.4 Hz, 6H), 2.17–2.29 (m, 1H), 3.79 (s, 3H), 4.71–4.76 (m, 1H), 6.17 (br d, *J*=8.6 Hz, 1H), 6.48 (d, *J*=15.5 Hz, 1H), 7.33–7.39 (m, 3H), 7.48–7.53 (m, 2H) 7.64 (d, *J*=15.5 Hz, 1H). MS (EI) *m*/*z* 261 (M^+). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.06; H, 7.32; N, 5.31.

4.7. Catalytic carboxamidation of 3-phenylpropanoic acid (1a) with benzylamine (2a) using BBDI (Table 6)

A mixture of **1a** (1 mmol) and a combination of Boc_2O and BBDI of amounts shown in Table 6 in CH_2Cl_2 (2 mL) was stirred in conditions described in Table 6. After addition of **2a** (1.2 mmol) to the mixture, the whole was stirred in conditions described in Table 6. Ethyl acetate (40 mL) was added to the reaction mixture and then the whole was successively washed with 5% HCl solution (10 mL×2) 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 **3a** and **15** in yields shown in Table 6.

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