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Activation of carboxylic acids as their active esters by means of *tert*-butyl 3-(3,4-dihydrobenzotriazine-4-on)yl carbonate†

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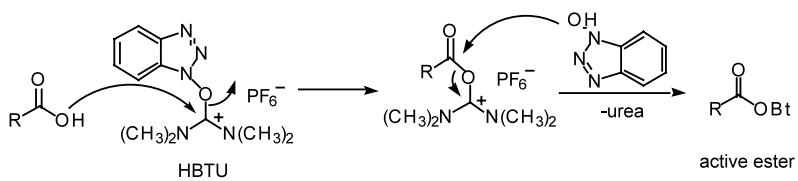
Abstract—Carboxylic acids were activated in the presence of DMAP with *tert*-butyl carbonates (BOC-OX) **1**, which were prepared in situ by reaction of X-OH and di-*tert*-butyl dicarbonate (BOC_2O). The most efficient active carbonate proved to be *tert*-butyl 3-(3,4-dihydrobenzotriazine-4-on)yl carbonate **1a**, leading to efficient formation of benzotriazinonyl esters **3** and **6**, which are intermediates in reactions with primary and secondary amines to afford amides or peptides in good yield. By-products in the formation of **3** or **6** are the environmentally safe *tert*-BuOH and CO_2. The hindered amino acid AIB also forms a dipeptide in good yield.

The formation of an amide bond is a fundamental reaction in chemistry.[2] Despite the efficiency of the use of dicyclohexylcarbodiimide (DCC)[3] as a dehydrating reagent in amide bond formation, many other condensing reagents were developed in order to minimize side products and depress racemization. When DCC is used in coupling reactions, an equimolar amount of urea (DCU) is formed and can cause difficulties in purification of the main product.

In peptide synthesis, auxiliary nucleophiles (additives), usually *N*-hydroxy amine reagents, are frequently used together with the condensing reagents, such as carbodiimides or uronium salts,[4] in order to prevent racemization. Some of the condensing agents that were developed, such as 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU),[4] already carry a *N*-hydroxylamine component, which is subsequently liberated during the reaction of the carboxyl group with the coupling reagent and is used in the next step leading to an active ester (Scheme 1).

We describe herein the use of *tert*-butyl 3-(3,4-dihydrobenzotriazine-4-on)yl carbonate (BOC-ODhbt) **1a** as well as other active carbonates as condensing reagents for activation of carboxylic acids as their active esters **3** and subsequent synthesis of amides and peptides. We found that reaction of carboxylic acids with BOC-ODhbt **1a**[5] in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) afforded the isolable 3-benzotriazinonyl esters **3a**, which in turn can react with primary and secondary amines to give amides **4** (Scheme 2). The carbonate BOC-ODhbt **1a**, a relatively stable solid, can be prepared by reaction of 3-hydroxy-3,4-dihydrobenzotriazine-4-one (HODhbt) and di-*tert*-butyl dicarbonate (BOC_2O) in the presence of triethylamine but the reaction requires several hours, while with DMAP catalyst **1a** is obtained quantitatively within 15 min.[6]

HODhbt is used in peptide synthesis as an auxiliary nucleophile (together with an in situ coupling reagent) because of its ability to prevent racemization.[7,8] However, when DCC is used as the coupling agent, a side



Scheme 1.

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† See Ref. 1.

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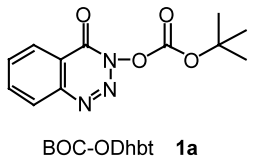
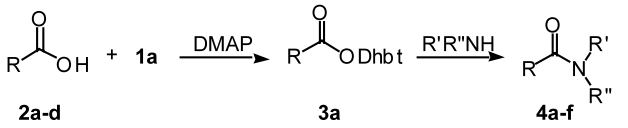


BOC-ODhbt **1a**



2a-d **3a** **4a-f**

a, R: PhCHC(CH 3) (CA)
b, R: Ph (BA)
c, R: (CH 3)3C (PA)
d, R: Ph2CH (DPAA)

R: PhCHC(CH 3)
a, R': H, R": EtO 2CCH 2
b, R': Et, R" : Bn
c, R',R": (CH 2CH 2)2
d, R',R": (CH 2CH 2)2O
e, R',R": diallyl
f, R': OMe, R": Me

Scheme 2.

reaction with HODhbt takes place leading to an azide derivative,[8] which decreases the popularity of HODhbt. Recently, Goodman et al.[9] reported the use of 3-(diethoxyphosphoryloxy) - 3,4 - dihydrobenzotriazin - 4-one (DEPBT) as a condensing reagent for amide bond formation with a resistance to racemization.

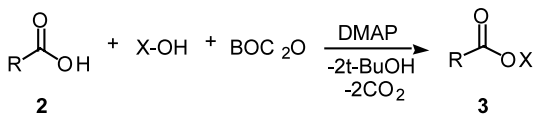
In reactions with carboxylic acids leading to active esters, the active carbonate BOC-ODhbt **1a** combines the functions of a dehydrating (condensing) agent as well as of an auxiliary nucleophile carrier. Reaction of a carboxyl group with BOC-ODhbt proceeds readily in the presence of DMAP to liberate HODhbt and leads to the formation of an active ester. That the DMAP catalyst[10] plays an essential role in the reaction of BOC-ODhbt with carboxylic acids leading to the formation of the active esters was shown by the fact that in the absence of DMAP the reactions proceeded in very poor yield (5%) and required a long time (24 h).

First, reactions of **1a** with simple carboxylic acids **2a–d** were carried out in order to find the best conditions for the formation of the active esters **3**. Reaction of α-methylcinnamic acid (CA) **2a** with preformed and isolated carbonate **1a** in MeCN at room temperature for 1.5 h afforded active ester **3a** in high yield (93–98%).

N-Hydroxy reagents other than HODhbt, such as *N*-hydroxysuccinimde (HOSu), *N*-hydroxyphthalimide (HOPh), and 1-hydroxybenzotriazole (HOBt), as well as other acidic (aromatic) alcohols such as 2-hydroxypyridine (HOPy), 3-hydroxypyridinium oxide (HOPO), 4-nitrophenol (HONPh) and 4-carbethoxyphenol (HOCEPh), were also examined for the preparation of their *tert*-butyl carbonates for coupling reactions leading to active esters **3b–h** and the results are given in Table 1.

Preparation of active esters **3** by reactions of carboxylic acids with active carbonates **1** can be performed in one step by mixing RCO_2H, BOC_2O, auxiliary nucleophile (X-OH) and DMAP (Scheme 3). Since the auxiliary nucleophile (e.g. HODhbt) is a better nucleophile than RCO_2H, it reacts first with BOC_2O to produce an active carbonate **1**, which in the presence of DMAP, reacts further with the carboxyl component to give the desired active ester **3**. This pathway was confirmed by stopping the reaction after a short time (ca. 15 min), which led to isolation of the carbonate **1** as the main product together with a small amount (5–10%) of the active ester **3**.

Reaction of HODhbt with CA (**2a**) and BOC_2O in the presence of DMAP catalyst at room temperature afforded ester **3a**[11] in high yield (entries 1–3, Table 1). The reaction can be carried out without TEA base in



2 **3**

Scheme 3.

Table 1. Reaction of α-methylcinnamic acid **2a** (1 equiv.) with BOC_2O (1.2–1.4 equiv.)/DMAP (0.5 equiv.)/auxiliary nucleophile (X-OH) at room temperature with formation of active esters **3a–h**

Entry	X-OH[a] (equiv.)	Solvent[b]/base[c]	Time	Active ester, yield[d] (%)
1	HODhbt (1.1)	MeCN/–	1 h	**3a**, 99
2	HODhbt (1)	MeCN/–	50 min	**3a**, 96
3	HODhbt (1)	CH_2Cl_2/TEA	1.5 h	**3a**, 94
4	HOSu (1.1)	MeCN/–	45 min	**3b**, 99
5	HOPh (1)	MeCN/TEA	35 min	**3c**, 94
6	HOBt[e] (1)	MeCN/TEA	15 min	**3d**, 82
7	HOPy (1)	Toluene/TEA	2 h	**3e**, 92
8	HOPO (1)	MeCN/TEA	2 h	**3f**, 92
9	HONPh (1)	MeCN/TEA	5 h	**3g**, 90
10	HOCEPh (1)	MeCN/TEA	4 days	**3h**, 88

[a] HODhbt: 3-hydroxy-3,4-dihydrobenzotriazine-4-one; HOSu: *N*-hydroxysuccinimde; HOPh: *N*-hydroxyphthalimide; HOBt: 1-hydroxybenzotriazole; HOPy: 2-hydroxypyridine; HOPO: 3-hydroxypyridinium oxide; HONPh: 4-nitrophenol; HOCEPh: 4-carbethoxyphenol.
[b] Solvents MeCN (HPLC grade), CH_2Cl_2 (AR) or toluene (AR) were used.
[c] 1 equiv. of triethylamine (TEA) was used.
[d] Yields were calculated on the basis of the ^1H NMR spectra integration of the crude reaction mixture.
[e] Mixture of preformed *O*-BOC and *N*-BOC HOBt was used.

which case DMAP catalyst also serves as a base. When HOSu or HOPh was used as the auxiliary nucleophile in the reaction of CA with BOC_2O in the presence of DMAP, active ester **3b** or **3c** was formed in high yield (entries 4 and 5). HOBt, which is commonly used in amide and peptide synthesis as an auxiliary nucleophile, afforded the active ester **3d** in a somewhat lower yield (82%) after a short time (15 min) (entry 6), but isolation of the ester was difficult.[12] In contrast, isolation of HODhbt ester as a solid was simple leading to a high yield of the ester **3a**. Hydroxy pyridines HOPy and HOPO (entries 7 and 8) afforded active esters **3e** and **3f** in high yield (92%) within 2 h, but HOPy gave less clean results than HOPO.[13] While 4-nitrophenol HONPh gave active ester **3g** in 90% yield in 5 h, reaction of the less acidic phenol HOCEPh required days (4 days) to give ester **3h** in 88% yield (entries 9 and 10).

Other carboxylic acids (**2b–d**) were also reacted with BOC_2O/DMAP/HODhbt to afford active esters **3i–k** (Table 2, Scheme 2)). Benzoic acid (BA, **2b**) and even the hindered pivalic acid (PA, **2c**) gave active esters **3i** and **3j**, respectively, in high yields. However, the branched diphenylacetic acid (DPAA) was activated only with difficulty; its reaction with BOC-ODhbt **1a** in MeCN for 1 h afforded the ester **3k** in 62% yield with complete consumption of **1a** and isolation of 13% of mixed anhydride **D** (see Scheme 5). Changing the solvent to CH_2Cl_2 and allowing the reaction to proceed for 3 h raised the yield of the DPAA ester **3k** to 85%. The effect of solvent can be explained by the faster decomposition of the active carbonate by DMAP[14] in the more polar solvent (MeCN) in competition with the slow reaction of the carbonate **1a** with the hindered carboxylic acid.

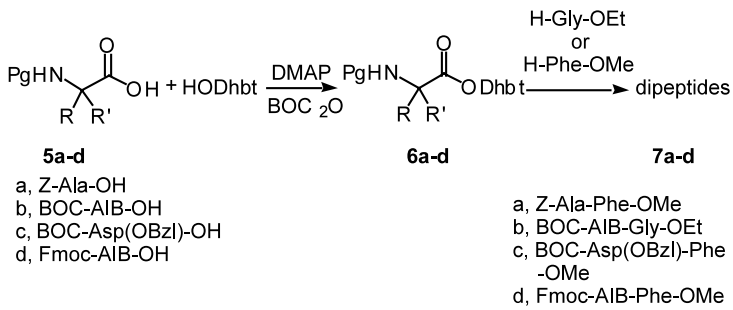
It was important to evaluate amide formation from 3-benzotriazinonyl ester **3a** by examining the reaction of the latter with primary as well as secondary amines (see Scheme 2). The formation of **3a** can be carried out in situ. For example, reaction of CA with BOC_2O/DMAP/HODhbt in MeCN at room temperature for 1 h followed immediately by addition of glycine ethyl ester afforded secondary amide **4a** within 15 min in 93–96% yield with complete consumption of the intermediate active ester (see Table 2). We found that even reactions with secondary amines proceeded at a reasonable rate, affording tertiary amides in over 93% yield. For instance, addition of *N*-ethylbenzylamine (1.2 equiv.) to in situ formed active ester **3a** afforded the tertiary amide **4b** after 3.5 h. Amide formation was faster with diallylamine (2.5 h), with morpholine (1 h) or with pyrrolidine (0.5 h) leading to amides **4c**,[15] **4d** and **4e**, respectively, while the use of the less basic *N*-methoxymethylamine afforded the amide **4f** after 4 h. In order to minimize formation of the *N*-BOC side product resulting from the reaction of the amine with remaining unreacted BOC-ODhbt, an excess of HODhbt should not be used. Reactions of secondary amines with active esters **3b–h** derived from auxiliary nucleophiles X-OH other than of HODhbt were also examined and found to be less efficient.

Activation of *N*-protected amino acids **5** as stable active esters **6** by means of HODhbt/BOC_2O/DMAP (Scheme 4) was successful when the reaction was car-

Table 2. Reaction of RCO_2H **2a–d** with BOC_2O (1.2–1.4 equiv.)/DMAP (0.5 equiv.)/HODhbt at room temperature with formation of active esters **3a,i–k** and amides **4a–f**

RCO_2H[a] (1 equiv.)	HODhbt (equiv.)	Solvent[b]/base[c]	Time	Active ester, yield[d] (%)	Amide,[e] yield[d] (%)
CA (**2a**)	1	MeCN/–	50 min	**3a**, 96	**4a–f**, 93–96
BA (**2b**)	1.1	MeCN/TEA	40 min	**3i**, 95	
PA (**2c**)	1.1	MeCN/TEA	30 min	**3j**, 98	
DPAA (**2d**)	1.1)	MeCN/TEA	1 h	**3k**, 62	
DPAA (**2d**)	1.1	CH_2Cl_2/TEA	3 h	**3k**, 85	

[a] CA: α-methylcinnamic acid; BA: benzoic acid; PA: pivalic acid; DPAA: diphenylacetic acid.
[b] Solvents MeCN (HPLC grade) or CH_2Cl_2 (AR) were used.
[c] 1 equiv. of triethylamine (TEA) was used.
[d] Yields were calculated on the basis of the ^1H NMR spectra integration of the crude reaction mixture.
[e] **4a**: Ethyl *N*-(α-methylcinnamyl)glycinate; **4b**: *N*-benzyl-*N*-ethyl-α-methylcinnamamide; **4c**: *N*,*N*-diallyl-α-methylcinnamamide; **4d**: *N*-α-Methylcinnamyl morpholine **4e**: *N*-α-methylcinnamoyl pyrrolidine; **4f**: *N*-methoxy-*N*-methyl-α-methylcinnamamide.



Scheme 4.

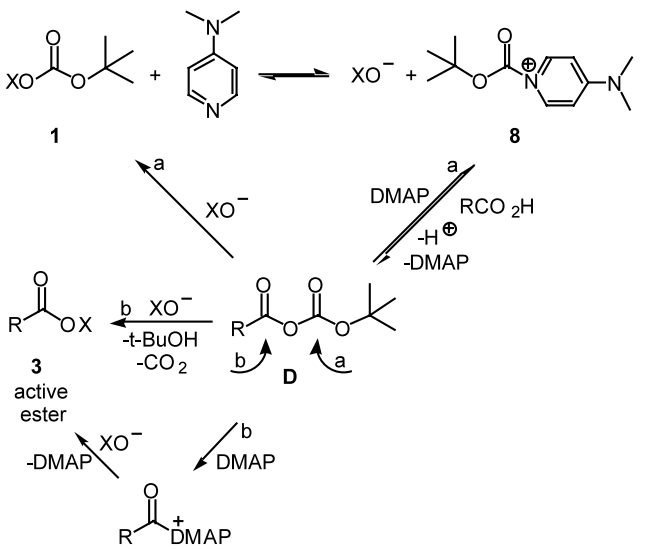
Table 3. Reaction of amino acids **5a–d** with BOC_2O (1.4 equiv.)/DMAP (0.5 equiv.)/HODhbt at room temperature with formation of active esters **6a–d** and dipeptides **7a–d**

Entry	RCO_2H (1 equiv.)	HODhbt (equiv.)	Solvent[a]/base[b]	Time (h)	Active ester, yield[c] (%)	Dipeptide,[d] yield[c] (%)
1	Z-Ala-OH (**5a**)	1.1	MeCN/TEA	2.5	**6a**	**7a**, 10
2	Z-Ala-OH (**5a**)	1.1	CH_2Cl_2/TEA	2.5	**6a**, 85	**7a**, 95
3	BOC-AIB-OH (**5b**)	1	CH_2Cl_2/TEA	3	**6b**, 92	**7b**, 94
4	BOC-Asp(OBzl)-OH (**5c**)	1	CH_2Cl_2/TEA	3	**6c**, 75	**7c**, 80
5	Fmoc-AIB-OH (**5d**)	1	CH_2Cl_2/TEA	3	**6d**, 75	**7d**, 75

[a] Solvents MeCN (dry) or CH_2Cl_2 (dry) were used.
[b] 2 equiv. of triethylamine (TEA) were used.
[c] Calculated by NMR integration.
[d] **7a**: Z-Ala-Phe-OMe; **7b**: BOC-AIB-Gly-OEt; **7c**: BOC-Asp(OBzl)-Phe-OMe; **7d**: Fmoc-AIB-Phe-OMe.

ried out in the less polar dry solvent CH_2Cl_2 rather than in polar MeCN (Table 3, entries 1 and 2 for Ala-OH). Subsequent addition of *O*-protected amino acid (free amine) afforded dipeptides **7**[16] in 95% yield. Activation of *N*-BOC protected α-aminoisobutyric acid (BOC-AIB-OH), which is considered a very hindered α-amino acid, was also successful. Using the conditions described above afforded AIB-ODhbt ester **6b** in 92% yield after 3 h (entry 3). Other *N*-protected amino acids were activated by reaction with BOC_2O/DMAP/HODhbt and were used further in the preparation of dipeptides in slightly lower yields (entries 4 and 5).

We believe that the reaction of carboxylic acids with BOC-ODhbt **1a** and with other active carbonates in the presence of DMAP leading to active esters of type **3** involves the formation of a *tert*-butyl mixed anhydride (see **D** in Scheme 5). Based on previous studies,[17] it appears reasonable that first DMAP reacts with the carbonate **1** to release auxiliary nucleophile X-OH (e.g. HODhbt) as its anion XO^- and to form intermediate **8**. The latter reacts further with the carboxylic acid to form a mixed anhydride **D**. The released XO^- can react



Scheme 5. Pathway for reaction of carboxylic acids with active carbonates **1** (derived from reaction of X-OH, BOC_2O and DMAP) leading to active esters (e.g. **3a**).

with anhydride **D** at the carboxylic carbonyl group (path b), with or without the mediation of DMAP, to afford the active ester **3** with release of *tert*-butyl alcohol and carbon dioxide. Reaction of the alcohol anion XO^- with mixed anhydride **D** at the undesirable carbonic carbonyl site (path a) will lead back to carbonate **1** which reenters the cycle. Similarly, reaction of DMAP with **D** on the carbonic carbonyl (path a) gives back BOC-pyridinium **8**, while at site b it will ultimately produce **3**.

Normally, when mixed anhydrides (e.g. **D**) are used in reaction with nucleophiles, for instance with amines or even with RCO_2H, attack at either carbonyl moiety (see 'a' and 'b' in **D**) can take place, and thus leads to side products. The advantage of Scheme 5, using active carbonates **1**, is that side reactions are avoided by the fact that intermediates such as **8**, **D**, **1**, and DMAP reenter the cycle to ultimately produce active ester **3**. The only side products are the environmentally safe *tert*-butyl alcohol and CO_2.

In summary, *tert*-butyl carbonate **1a**, which can be prepared in situ by reaction of HODhbt with BOC_2O/DMAP, is useful in activation of simple carboxylic acids and amino acids as their active esters **3a** and **6a** and in subsequent formation of amides and peptides with easily separable *tert*-BuOH and CO_2 as by-products. HODhbt ester **3a** reacts readily with primary or secondary amines. Activation of hindered *N*-BOC-AIB-OH was also successful.

Acknowledgements

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5. All new compounds were characterized by ^1H and ^{13}C NMR and high resolution mass spectroscopy. Data for **3-*(tert*-butoxycarbonyloxy)-3,4-dihydrobenzotriazin-4-one 1a**: White solid; mp 102–104°C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.40 (dm, 1H), 8.24 (dm, 1H), 8.02 (tm, 1H), 7.85 (tm, 1H), 1.62 (s, 9H); ^{13}C NMR δ 150.20 (C), 149.84 (C), 144.16 (C), 135.37 (CH), 132.62 (CH), 128.90 (CH), 125.62 (CH), 122.17 (C), 88.07 (C), 27.41 ($3CH_3$); MS (CI/NH_3) m/z (%) = 281 (MNH_4^+, 8), 264 (MH^+, 100), 164 (13); HRMS m/z calcd for $C_{12}H_{14}N_3O_4$ 264.0984, found 264.0995.
6. No symmetrical carbonate was formed in contrast to the reactions of other alcohols with BOC_2O/DMAP.[17]
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11. Typical procedure for the preparation of active esters **3**: To a solution of BOC_2O (1.2 equiv.) dissolved in 4 mL of MeCN were added consecutively α-methylcinnamic acid (0.5 mmol, 1 equiv.), HODhbt (1–1.1 equiv.), and DMAP (0.5 equiv.). At the end of the reaction (50 min–1 h, see Table 1), chloroform or dichloromethane (10 mL) was added and the solution was washed with 2% HCl (20 mL), saturated $NaHCO_3$ solution and water, dried with $MgSO_4$ and evaporated to give active esters **3a** in over 96% yield (see also Table 1). Data for **3-hydroxy-3,4-dihydrobenzotriazin-4-onyl α-methylcinnamate 3a**: White solid; mp 96–98°C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.41 (dm, 1H), 8.25 (dm, 1H), 8.09 (q, $J=2$ Hz, 1H), 8.02 (tm, 1H), 7.85 (tm, 1H), 7.52–7.35 (m, 5H), 2.33 (d, $J=2$ Hz, 3H); ^{13}C NMR δ 164.57 (C), 150.50 (C), 144.40 (C), 143.63 (CH), 135.31 (CH), 134.81 (C), 132.63 (CH), 130.02 (2CH), 129.40 (CH), 128.97 (CH), 128.60 (2CH), 125.76 (CH), 123.94 (C), 122.34 (C), 14.24 (CH_3); MS (CI/NH_3) m/z (%) = 325 (MNH_4^+, 2), 308 (MH^+, 100), 182 (53), 165 (71), 137 (99), 120 (74); HRMS m/z calcd for $C_{17}H_{14}N_3O_3$ 308.1035, found 308.1035.
12. Reaction of HOBt with BOC_2O gave mainly the *N*-BOC in addition to the *O*-BOC derivative, which may interfere with ester formation. See: Singh, J.; Fox, R.; Wong, M.; Kissick, T. P.; Moniot, J. L.; Geugoutas, J. Z.; Malley, M. F.; Kocy, O. *J. Org. Chem.* **1988**, *53*, 205.
13. Reaction of HOPy with BOC_2O also gave an *N*-BOC product (carbamate), which may lead to side reactions.
14. In the same manner that BOC_2O is decomposed by DMAP. See: Basel, Y.; Hassner, A. *Synthesis* 2001, 550.
15. Typical procedure for preparation of amides **4**: To a solution of BOC_2O (1.2 equiv.) dissolved in 4 mL of MeCN were added consecutively α-methylcinnamic acid (0.5 mmol, 1 equiv.), HODhbt (1 equiv.), Et_3N (1 equiv.) and DMAP (0.5 equiv.). After 1 h diallylamine (1.2 equiv.) was added and the reaction was allowed to proceed for 2.5 h. Chloroform or dichloromethane (10 mL) was then added and the solution was washed with 2% HCl (20 mL), a saturated $NaHCO_3$ solution and water, dried with $MgSO_4$ and evaporated to give amide **4c** in 93–96% yield (see also Table 2). Data for ***N,N*-diallyl-α-methylcinnamamide 4c**: Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.23 (m, 5H), 6.58 (q, $J=2$ Hz, 1H), 5.80 (ddt, $J=16$, 8, 5.5 Hz, 2H), 5.25 (dd, $J=8$, 1.5 Hz, 2H), 5.19 (dd, $J=16$, 1.5 Hz, 2H), 4.04 (d, $J=5.5$ Hz, 4H), 2.11 (d, $J=2$ Hz, 3H); ^{13}C NMR δ 173.82 (C), 135.95 (C), 133.09 (C), 133.06 (CH), 129.03 (2CH), 128.97 (2CH), 128.27 (2CH), 127.54 (CH), 117.63 (2CH), 50.16 (br, CH_2), 47.08 (br, CH_2), 16.19 (CH_3); MS (dci/IBu) m/z (%) = 242 (MH^+, 33), 144 (100), 117 (64), 115 (35). HRMS m/z calcd for $C_{16}H_{20}NO$ 242.1544, found 242.1530.
16. Typical procedure for preparation of dipeptides **7**: To a solution of BOC_2O (1.4 equiv.) dissolved in 4 mL of dry CH_2Cl_2 were added consecutively Z-Ala-OH (0.5 mmol, 1 equiv.), HODhbt (1 equiv.), triethylamine (2 equiv.) and DMAP (0.5 equiv.). After 3.5 h, H-Gly-OEt or H-Phe-OMe (1.2 equiv.) was added and the reaction was allowed to proceed for 1 h in the case of H-Gly-OEt or 2 h in the case of H-Phe-OMe. Chloroform or dichloromethane (10 mL) was then added and the solution was washed with water, 2% HCl (20 mL), a saturated $NaHCO_3$ solution and water, dried with $MgSO_4$ and evaporated to give the dipeptide (see also Table 3).
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