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Solventless Mechanosynthesis of N-Protected Amino Esters

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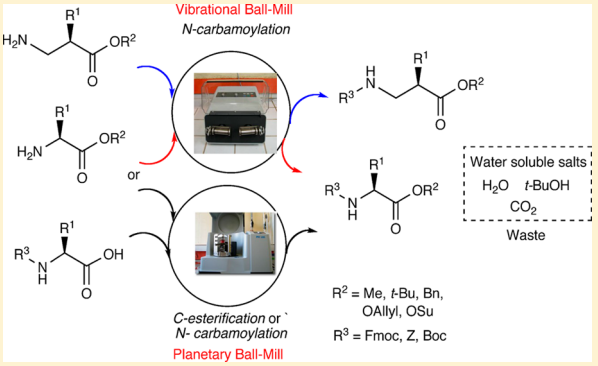
Supporting Information

ABSTRACT: Mechanochemical derivatizations of *N*- or *C*-protected amino acids were performed in a ball mill under solvent-free conditions. A vibrational ball mill was used for the preparation of *N*-protected α- and β-amino esters starting from the corresponding *N*-unmasked precursors via a carbamoylation reaction in the presence of di-*tert*-butyl dicarbonate (Boc_2O), benzyl chloroformate (Z-Cl) or 9-fluorenylmethoxycarbonyl chloroformate (Fmoc-Cl). A planetary ball mill proved to be more suitable for the synthesis of amino esters from *N*-protected amino acids via a *one-pot* activation/esterification reaction in the presence of various dialkyl dicarbonates or chloroformates. The spot-to-spot reactions were straightforward, leading to the final products in reduced reaction times with improved yields and simplified work-up procedures.



INTRODUCTION

The awareness of environmental problems caused by human acitivity has led scientists to change their way of "thinking chemistry", leading to the rapid growth of alternative methods to carried out organic synthesis under environmentally friendly conditions,[1] aiming to diminish the generation of toxic and nontoxic wastes and use safer reagent or solvents. With this perspective, the employment of mechanical energy to conduct organic reactions[2−7] in the absence of solvent is a strong emerging field. Our interest was turned toward the investigation of novel alternatives to solvent-based chemistry, applied to *N*- and *C*-protected amino acids, essential building blocks in the field of peptide synthesis. Usually, peptide syntheses (in solution or solid-phase) are carried out from the *C*- to *N*-direction by the assembly of amino acids through protection/deprotection coupling strategy according to well-established procedures.[8] It is thus necessary to find new methodologies enabling to prepare protected amino acids derivatives in a more straightforward manner and environmentally friendly conditions. Usual procedures not only require dramatic amounts of organic solvents but generally also toxic or dangerous reactants, extended reaction times, and several purification steps.[9−14] Herein we report our findings on the solvent-free synthesis of *N*-protected amino esters under ball milling conditions.

RESULTS AND DISCUSSION

Preparation of *N*-protected amino esters (PG-NH-AA-OR, R = Me, *t*-Bu and PG = protecting group) from the corresponding precursors (NH_2-AA-OR) is usually carried out in solution via carbamoylation reaction in the presence of catalysts,[15] enzymes,[16] or additives[17−19] or through solid-supported methodologies.[20] On the other hand, *N*-protected amino acids (PG-NH-AA-OH) are suitable substrates leading to *N*-protected amino esters (PG-NH-AA-OR) by esterification reaction of the *C*-terminal end with alkyl chloroformates,[21] dialkyl dicarbonates,[22−25] or imidazole carbamates[26] via carbonic carboxylic anhydride intermediates. To avoid the drawbacks of time-consuming solution synthesis and to reduce the environmental impact of reported procedures, new methodologies need to be developed allowing the eco-friendly synthesis of peptide building blocks as *N*- and/or *C*-protected amino acids.

We have recently disclosed in this area new strategies for amide bond formation,[27] preparation of peptides[28,29] and amino acid analogues,[30,31] or for synthesis of *N*-protected amino acids[32] (PG-NH-AA-OH) starting from free amino acids (NH_2-AA-OH), under solvent-free conditions using ball-milling technology. Herein we present how this low-cost, eco-friendly method can be successfully applied to the solid-state synthesis of *N*-protected amino esters (PG-NH-AA-OR) according to two different approaches: (i) via carbamoylation of amino esters (NH_2-AA-OR) or (ii) via esterification of *C*-terminal *N*-protected amino acids (PG-NH-AA-OH) by using, respectively, vibrational or planetary ball-mill apparatus (Scheme 1).

Technical and process parameters[33] such as type of ball mill (vibrational or planetary), oscillation (up to 30 Hz) or rotation frequency (up to 450 rpm), milling time, number of milling stainless steel balls (up to 50, with a diameter of 5 mm), and mode of milling (continuous or cycled) were also explored in some cases.

N-Protection of Amino Esters. A few rare examples of solvent-free procedures were reported for the synthesis of *N*-

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Scheme 1. Mechanochemical Synthesis of *N*-Protected Amino Esters

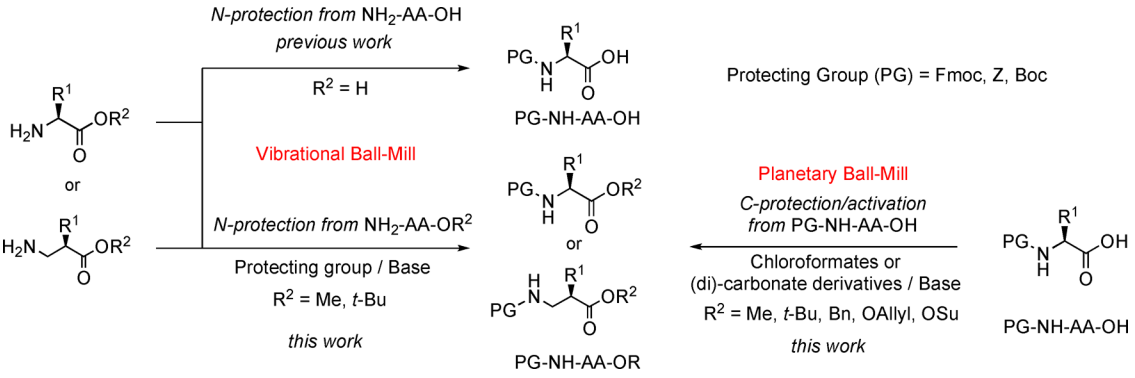
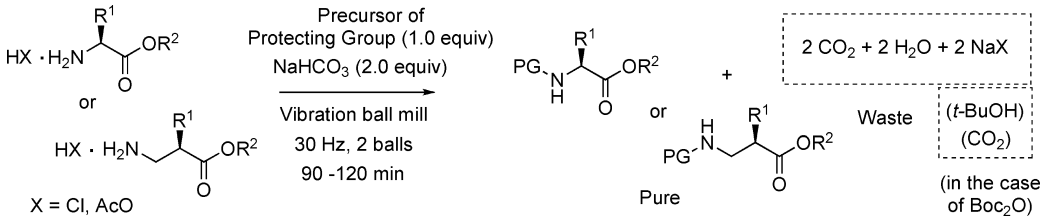


Table 1. *N*-Protection of Amino Esters in a Vibrational Ball Mill[a]



entry	R_2	precursor of protecting group	*N*-protected amino ester[b]		time (min)	yield[c] (%)
1	Me	Fmoc-Cl	Fmoc-Gly-OMe	**1**	90	96
2	Me		Fmoc-Phe-OMe	**2**	90	95
3	Me		Fmoc-Ala-OMe	**3**	90	96
4	Me		Fmoc-Ala-OMe	**3**	90	92[d]
5	*t*-Bu		Fmoc-Leu-O^{t}Bu	**4**	90	87
6	Me	Z-Cl	Z-Gly-OMe	**5**	90	80
7	*t*-Bu		Z-Gly-O-*t*-Bu[e]	**6**	120	96
8	*t*-Bu		Z-Leu-O-*t*-Bu	**7**	90	80
9	*t*-Bu		Z-Leu-O^{t}Bu	**7**	90	67[d]
10	*t*-Bu		Z-Glu(O-*t*-Bu)$_2$	**8**	90	quant
11	Me	Boc_2O	Boc-Phe-OMe	**9**	90	91
12	Me		Boc-Phe-OMe	**9**	90	57[d]
13	Me		Boc-Pro-OMe	**10**	90	81
14	Me		Boc-*β*-Ala-OMe	**11**	120	68
15	Me		Boc-3-Aib-OMe	**12**	120	61
16	Me		Boc-Aib-OMe	**13**	120	68

[a]Typical procedure: vibration ball mill, 10 mL stainless steel jar, 2 stainless steel balls (5 mm diameter) at 30 Hz using *α*-amino ester (1 equiv), $NaHCO_3$ (1 equiv) and Fmoc-Cl, Z-Cl or Boc_2O (1 equiv); [b]Configuration of all substrates is *L* and they are used as hydrochloride salts except when specified; [c]Yields after work-up; [d]1 stainless steel ball (5 mm diameter) was used; [e]The acetic acid salt was used instead of the hydrochloride salt.

Boc-protected amines of nucleosides:[34] mainly by using an excess of Boc_2O or a two-step carbonyldiimidazole (CDI)−DMAP-mediated approach, grinding the reaction media with a spatula, but only one step was performed without any solvent.[35] In the case of amino esters, molecular iodine[36] was the catalyst for Boc-protection. Silica−sulfuric acid (SSA)[37] and sulfamic acid (NH_2SO_3H)[38] were used as catalysts for the chemoselective *N*-protection of various aliphatic and aromatic amines with Z- and Boc- groups, respectively, under solvent-free conditions at room temperature.

We disclose herein the solvent-free preparation of diverse *N*-protected *α*-,*β*-amino esters using a vibrational ball mill. The mechanochemical introduction of the most common carbamate-based protecting groups such as Fmoc (9-fluorenylmethoxycarbonyl), Z (benzyloxycarbonyl) or Boc (*tert*-butyloxycarbonyl) derivatives was investigated using a 10 mL stainless steel jar with 2 balls (5 mm diameter) under neat conditions (Table 1).

Except for *β*-amino esters (entries 14 and 15) yields were as high (80% to quantitative) as for the usual synthetic methods in solution.[9,36,39−41] Final products were recovered by a very simple workup, based on a precipitation/filtration procedure without need of chromatographic purification for most of cases, contrary to synthesis in solution, resulting in more environmentally friendly conditions. Starting from our previous findings,[32] equimolar amounts of glycine methyl ester hydrochloride and 9-fluorenylmethoxycarbonyl chloroformate (Fmoc-Cl) were ground without any special precaution in the presence of $NaHCO_3$ (Table 1, entry 1). We were pleased to find that the conversion of reactants was quantitative in only 90 min and no other optimization studies were necessary. The smooth conditions afforded by vibrational ball milling

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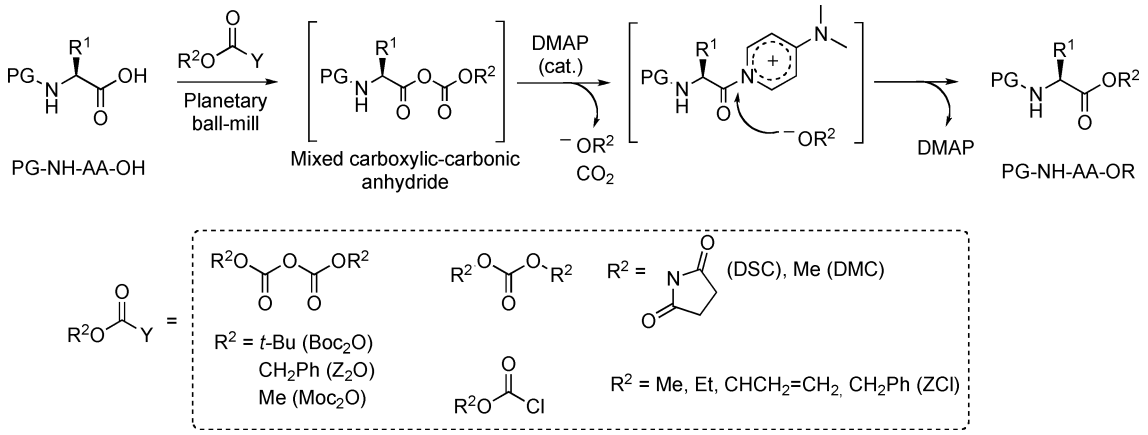
Scheme 2. Simplified Mechanism for Decarboxylative Esterification



prevented formation of byproducts observed during solution-phase synthesis, as dibenzofulvene or its polymer. As a consequence, no striking workup to eliminate side products was necessary, and Fmoc-Gly-OMe was recovered by precipitation after addition of water to the crude. The number of balls in the jar seems to have influence on the yields as shown by parallel experiments performed using one or two balls in the milling jar for the *N*-protection of alanine (Table 1, entries 3 and 4), leucine (entries 8 and 9), and phenylalanine (entries 11 and 12). In the case of Fmoc-Ala-OMe **3** synthesis, yields were similar (entries 3 and 4), while Z-Leu-O-*t*-Bu **7** and Boc-Phe-OMe **9** were obtained in much lower yields in the presence of only one grinding ball instead of two, the conversion of the substrates being incomplete in these cases.

The methodology applied so far to the Fmoc derivatization of amino ester derivatives was extended for the introduction of Z (entries 6−10) and Boc protecting groups (entries 11−16), using, respectively, benzyl chloroformate (Z-Cl) and di-*tert*-butyl dicarbonate (Boc_2O). Z-Cl reacted without any special precaution, although at lower frequencies (e.g., 20 and 25 Hz), incomplete reactions were observed even for prolonged reaction times, probably because of premature Z-Cl hydrolysis leading to the formation of benzyl alcohol, as also confirmed by LC/MS and ^{1}H NMR analyses of the crude. In the case of glycine (entries 1, 6, and 7), the nature of the *C*-terminal ester might influence the kinetic of the process, which proved to be slower when *tert*-butyl esters were used, and independently of the incoming protecting group. Pure *Z*-protected amino esters precipitated from the solution upon acidification with 0.1 N HCl, while Boc-protected amino esters were recovered by extraction. The study was also extended to the protection of *β*-(Table 1, entries 14 and 15) and hindered quaternary amino ester (Table 1, entry 16). The substrates were not completely converted even after longer reaction times (120 min), but the yields remained satisfying, although lower than those obtained for the preparation of *β*-amino esters in solution.[36,39,42] However, an impressive improved yield (three times more than in solution)[43] was obtained with the hindered substrate H-Aib-OMe (Table 1, entry 16), suggesting that mechanochemical activation could be particularly suitable with poorly reactive (hindered) substrates. It is worth noting that in all cases the solvent-free methodology herein reported is environmentally friendly with respect to more classical protocols in solution or on supports for Fmoc,[9] Boc,[12] or Z[13] protection. The only waste was water, sodium chloride, CO_2 and *t*-butyl alcohol (only for Boc-protection), the use of hazardous solvents (THF or dioxane), catalysts ($ZrCl_4$[39] or *β*-cyclodextrin[42]), and reagents (e.g., *N*-hydroxysuccinimide derivatives) was avoided, and chromatographic purifications were not necessary in most cases. Planetary ball milling was also explored for the synthesis of Fmoc-Ala-OMe **3** (Table 1, entry 3), running a similar experiment on 2 mmol scale at 450 rpm during the same time (90 min), using a 12 mL stainless steel jar with 25 balls (5 mm). Interestingly, it resulted in poor conversion of the substrate and recovery of Fmoc-Cl. Together with different stress phenomena with respect to vibrational ball milling (at 30 Hz), a part of the explanation could be that planetary ball milling at 450 rpm would not give enough energy to the reaction. Indeed, 450 rpm corresponded to a frequence of 7.5 Hz, which is much lower than the frequence used in the experiments with the horizontally vibrating ball mill.

C-Protection/Activation of N-Protected Amino Acids. Dialkyl dicarbonates were successfully applied as esterification reagents in solution. Takeda[22] used them in the presence of DMAP in THF or *t*-BuOH while Goo*β*en performed a decarboxylative esterification with $Mg(ClO_4)_2$ as catalyst.[23] However, this procedure was unsuitable to access amino acid *tert*-butyl esters because of their instability in the reaction medium. Then, the DMAP-catalyzed benzyl esterification using Boc_2O and benzyl alcohol[24] was also described by Bartoli,[25] who reported a $MgCl_2$-catalyzed process with a combination of alcohol and the corresponding dialkyl dicarbonates (e.g., *t*-BuOH/Boc_2O for the synthesis of *tert*-butyl esters). These methods presented poor mass efficiency requiring a large alcohol excess[25] or/and expensive dialkyl dicarbonate (up to 3 equiv)[22] or catalysis by Lewis acids.[23,25] Starting from our previous findings,[32] we demonstrated that di-*tert*-butyl dicarbonate (Boc_2O) was a very compatible protecting group within ball milling technology. In our ongoing efforts to set up new and straightforward eco-friendly methodologies for organic synthesis, the possibility of realizing the esterification of the *C*-terminal position of amino acids under stoichiometric solventless mechanochemical activation appeared to be promising and appealing. In this respect, various dialkyl dicarbonates [$(ROCO)_2O$ such as Boc_2O, Z_2O, Moc_2O with R = O-*t*-Bu, Bn, Me, respectively], carbonates (RO_2CO, R = succinimide, Me) or alkyl chloroformates (ROCOCl, R = Bn, Me, Et, allyl) were investigated for the esterification of the *C*-terminal of amino acid derivatives (Scheme 2), in the presence

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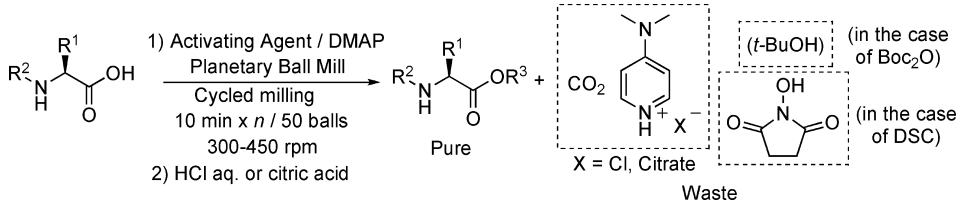
Table 2. *C*-Protection/Activation of *N*-Protected Amino Acids in a Planetary Ball Mill[a]



entry	R_2	activating agent (equiv)/DMAP (equiv)	cycled milling rpm/n[b]	*C*-protected amino ester[c]		yield[d] (%)
1	Z	Boc_2O (1)[e]/0.3	300/6[f]	Z-Phe-O-*t*-Bu	**14**	79
2	Z			Z-Pro-O-*t*-Bu	**15**	67
3	Boc			Boc-Thr(Bn)-O-*t*-Bu	**16**	65
4	Boc			Boc-Tyr(2,6-Cl-Bn)-O-*t*-Bu	**17**	56
5	Z	DSC (1)/0.3	450/6	Z-Phe-OSu	**18**	69
6	Boc			Boc-Thr(Bn)-OSu	**19**	55
7	Boc			Boc-Met-OSu	**20**	35
8	Z	BnOCOCl (1)[e]/1.3	300/6[f]	Z-Phe-OBn	**21**	48
9	Z			Z-Ser(O-*t*-Bu)-OBn	**22**	54
10	Boc			Boc-Met-OBn	**23**	59
11	Z	EtOCOCl (1.2)/1.5	300/9	Z-Phe-OEt	**24**	90
12	Z			Z-Ser(*t*-Bu)-OEt	**25**	87
13	Boc			Boc-Met-OEt	**26**	84
14	Boc			Boc-Cys(SBn)-OEt	**27**	91
15	Z	AllylOCOCl (1.2)/1.5	300/9	Z-Phe-OAllyl	**28**	90
16	Z			Z-Ser(*t*-Bu)-OAllyl	**29**	83
17	Boc			Boc-Met-OAllyl	**30**	82
18	Boc			Boc-Cys(Bn)-OAllyl	**31**	91

[a]Typical procedure: planetary, 12 mL stainless steel jar, 50 stainless steel balls (5 mm diameter) at 300 (or 450) rpm using *N*-protected α-amino acid (250 mg) and activating agent/DMAP (equivalents as stated in the table) were milled for the specified times under cycled milling of 10 min cycles followed by 2 min of standby in between, with reverse rotation. [b]n is the number of cycles. [c]All substrates have the L configuration. [d]Yields after workup. [e]The activating agent was added in two portions of 0.5 equiv each. [f]The second half of activating agent was added after the third cycle.

of DMAP as catalyst, and a selection of data is reported in Table 2.

The common feature of all these decarboxylative esterifications was formation of a mixed carboxylic−carbonic anhydride, converted into an acylpyridinium species by nucleophilic attack of catalytic 4-(dimethylamino)pyridine (DMAP), carbon dioxide evolution providing the driving force of the reaction. Moreover, DMAP catalyzed the nucleophilic addition of the alcohol[44] leading to the desired ester (Scheme 2). *tert*-Butyl esters were prepared first, and *N*-Z-protected phenylalanine (Z-Phe-OH) served as a benchmark for optimization of the method. Synthetic (base, additives, stoichiometry of reactants) and technical parameters (time, rotation speed, number of balls, continuous or cycled milling) needed to be adjusted. Several combinations of bases (K_2CO_3,[32] Et_3N,[21] DMAP[44]) and additives (*t*-BuOH,[24,25] $MgSO_4$, $MgCl_2$,[23] or PPh_3[45]) were also explored. In opposition with synthesis in solution, adding catalysts gave no interesting results, with no or poor conversion of the substrate. Finding inspiration by Takeda's work,[22] *N*-Z-Phe-OH was ball milled with *t*-BuOH (2 equiv) and Boc_2O (1 equiv) in the presence of DMAP. Z-Phe-O-*t*-Bu was obtained in low yield (54%, based on ^{1}H NMR). The yield was increased to the same extent as in solution (66%, based on ^{1}H NMR) by adding an excess of Boc_2O (1.5 equiv), but *N*-Z,*N*-Boc-Phe-O-*t*-Bu was also formed. Using an excess of Boc_2O alone[22−25] was also detrimental leading to *N*-Z,*N*-Boc-Phe-O-*t*-Bu, along with the desired ester (Z-Phe-O-*t*-Bu), even after modulation of the reaction time (30 min to 3 h) and the amount of energy transferred during milling.

Best conversions (and yields) were obtained using stoichiometric amounts of Boc_2O in the presence of DMAP, added in a minimum amount of 0.3 equiv, with lower quantities leading to poor conversions. Vibrational ball mill (up to 30 Hz) or planetary ball mill under continuous or cycled milling at 100−500 rpm were also explored, with or without NaCl as additive.[32]

Vibrational ball mill at 30 Hz using 2 stainless steel balls (5 mm diameter) was ineffective: two experiments were run, following either a one-step procedure where the N-protected amino acid, Boc_2O, and K_2CO_3 were put altogether in the jar and ground for 1 h or a two-step procedure consisting of forming the carboxylate of the amino acid with K_2CO_3 in the first step[32] and then performing the carbamoylation by adding Boc_2O in the second step. In both cases, no conversion of the substrate was observed. Reaction of *N*-Z-Phe-OH under continuous milling in the planetary apparatus, in the presence of a stoichiometric amount of Boc_2O, afforded a moderate yield of *N*-Z-Phe-O-*t*-Bu (54% conversion based on NMR) propably because of Boc_2O degradation, while with an excess of Boc_2O the yield was hampered by the formation of *N*-Z,*N*-Boc-Phe-O-*t*-Bu. Cycled mixing at 300 rpm using 50 balls (stainless steel 5 mm diameter) for two steps of three 10 min cycles, with a 2 min pause between each cycle, were the best milling conditions (Table 2, entry 1), with Boc_2O added twice (0.5 equiv each time to obtain good conversion of the substrate). Environmentally friendly acidic workup with 10% aqueous citric acid allowed elimination of DMAP and afforded the *N*-protected *tert*-butyl amino ester derivatives (PG-NH-AA-OR) in good yields without any further purification (Table 2, entries 1−4).

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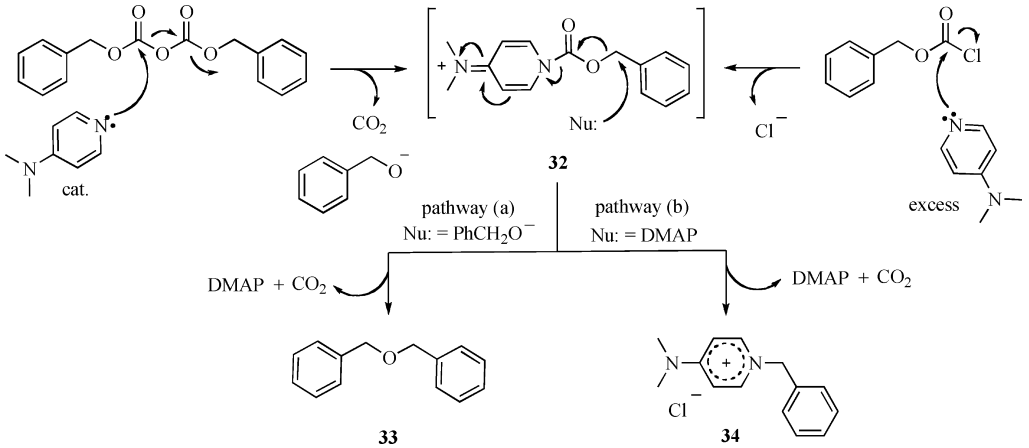
Scheme 3. Possible Side Reaction in the Synthesis of Benzyl Esters



The solvent-free synthesis afforded Z-Phe-O-*t*-Bu in better yields (79%) (Table 2, entry 1) in shorter reaction times (68 min) with respect to solution synthesis (61% yield after 2 days)[22] without using an excess of Boc_2O and avoid silica-gel purification. High-yield Z-Phe-O-*t*-Bu (84%) in solution could be obtained only after further increasing the quantity of dicarbonate and adding large excess of *t*-BuOH.[22] From the point of view of benign chemistry, the above-described procedure thus presents many advantages with respect to literature: (i) the quantity of wastes is reduced, avoiding the use of an excess of expensive Boc_2O, Lewis acids, or solvents or excess of the suitable alcohol to speed up the reaction; (ii) it is particularly suitable for the esterification of amino acids in short reaction times compared to synthesis in solution.

By analogy with the preparation of *tert*-butyl amino esters with (Boc_2O), dibenzyloxy dicarbonate (Z_2O) was used to prepare the corresponding esters. Unfortunately, the main product of the reaction was dibenzyl ether **33** (Scheme 3). One possible explanation may be that catalytic DMAP reacts quickly on Z_2O to form a "Z-DMAP" intermediate **32**, releasing CO_2 and phenylmethanolate, which in turn acts as a nucleophile at the benzylic position (pathway (a), Scheme 3) of **32**, affording dibenzyl ether **33** and regenerating DMAP. In order to avoid the formation of dibenzyl ether **33**, and according to the literature,[46] the reaction was repeated by adding dry CO_2 (about 1.4 g, corresponding to a quarter of the jar volume); no conversion of the substrate was observed, and again, dibenzyl ether **33** was the only product. In addition, we tried to esterify *N*-Z-phenylalanine with both Z_2O and 2 equiv of benzyl alcohol in the milling jar, taking inspiration from literature,[24] where Boc_2O and benzyl alcohol were used for the synthesis of benzyl esters. Dibenzyl ether was once again the main reaction product, confirming the fact that dibenzyl dicarbonate was not suitable for ball milling.

Due to the high reactivity of Z_2O, benzyl chloroformate (Z-Cl) was selected to perform the decarboxylative esterification. Starting from *N*-Z-phenylalanine, the best results were obtained under the same milling conditions as for the preparation of *tert*-butyl esters (Table 2, entry 8) but using a DMAP excess. The two-step cycled milling was executed by addition of Z-Cl in two equivalent portions, so as to consume the chloroformate and reduce the formation of the undesired byproducts. Although dibenzyl ether **33** was still present as a byproduct, its amount was dramatically reduced. In this case, after the addition of dry CO_2 as additive,[46] a similar yield (53% instead of 48%) was obtained. *N*-Phenylmethyl(dimethylamino)pyridinium chloride **34** was also obtained (pathway (b), Scheme 3), probably through a double-nucleophilic attack of DMAP on Z-Cl, as well as toluene, a byproduct probably coming from Z-Cl degradation in the milling jar. Although the elimination of the two byproducts did not represent a problem (the salt being water-soluble and the toluene easily evaporated), column chromatography was necessary to eliminate dibenzyl ether **33**. *N*-Z-Phenylalanine was also reacted with ethyl- (EtOCOCl) and allyl- (AllylOCOCl) chloroformates, the last one never described in solution for the preparation of amino ester derivatives. The corresponding esters were formed in a straightforward manner and without any byproducts (Table 2, entries 11 and 15). The method was general and successfully used for the synthesis of various amino esters, recovered pure after addition of aqueous citric acid and extraction with diethyl ether (Table 2, entries 11−14 and 15−18). Compared to the synthesis of *N*-Z-Phe-OEt (entry 11) in solution, the ball-milling procedure resulted in similar yields, elimination of chlorinated solvent, and reduced quantity of basic catalysts allowing synthesis to be performed at room temperature (instead of 0 °C).

Through a heat transfer lumped mathematical model describing the vibrational milling apparatus starting from its mechano-physical properties,[47] we previously demonstrated that during the mechanochemical solvent-free synthesis of nitrones (at 30 Hz for 30 min) there was a small increase in temperature (from 30 °C at the beginning of the experiment to 44 °C at the end). In order to rule out that a temperature increase into the milling jar could be responsible for the good yields, the temperature of the mixture, after vibrational or planetary milling, was measured using a thermocouple sensor. In the case of *N*-protection (30 Hz for 2 h, vibrational milling), the final temperature was 23 °C, while for planetary milling (450 rpm for 90 min), the value was 25 °C. From this perspective, the *C*-protection was performed under cycled milling mostly to avoid the degradation of precursors of protecting groups instead of controlling a possible temperature increase due to the mechanical energy entry. During the ball milling, the combination of pressure and grinding phenomena (and not necessarily heat!) were responsible for the successful outcome of the reactions, creating conditions otherwise difficult to obtain.

We then turned our attention toward the solvent-free preparation of succinimide esters, one of the most popular

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family of active esters for peptide coupling.[48] They are usually prepared in solution through two reaction pathways: (i) by esterification of the *N*-protected amino acid with *N*-hydroxysuccinimide in the presence of dicyclohexylcarbodiimide (DCC)[48] or (ii) *N,N′*-disuccinimidyl carbonate[49] (DSC) or a succinimidyl carbonate derivative,[50] in basic medium (pyridine or triethylamine). The second approach was selected for the mechanochemical synthesis of succinimide ester derivatives, using DMAP. However, the DSC carbonate was difficult to handle via mechanosynthesis: the reaction mixture became sticky from the beginning of the mixing, preventing the balls from moving into the jar, independent of the milling conditions (reaction time and rotation speed). The use of DSC carbonate in excess was also unsuccessful (the more carbonate used, the stickier the crude was), and the addition of NaCl[32] to make the mixture more powdery did not help. Evoking a liquid-assisted grinding (LAG) in the presence of AcOEt or acetonitrile did not produce any improvement. For these reasons, only moderate yields of succinimide esters were obtained (Table 2, entries 5−7). However, the workup remained simple and fast: *N*-hydroxysuccinimide precipitated by addition of AcOEt, and it was filtered. The residual unreacted amino acid was removed by washings with aqueous citric acid, followed by a saturated solution of $NaHCO_3$, leading to the desired compounds without any other purification steps. An attempt to synthesize Z-Phe-OSu (Table 2, entry 5) in the presence of Boc_2O with an excess of hydroxysuccinimide (HOSu) (like for the synthesis of *tert*-butyl esters with Boc_2O/*t*-BuOH in excess)[24] was also performed, but neither the succinimidyl nor the *tert*-butyl ester was obtained, confirming our previous trials. We then became interested in the possibility of preparing the methyl ester derivatives from N-protected amino acids. Highly reactive dimethyldicarbonate (Moc_2O), dimethyl carbonate (DMC), and methyl chloroformates (MeOCOCl), known to produce very good results in solution, were tested in the presence of DMAP or 1,8-diazabicycloundec-7-ene (DBU).[51,52] In particular, dimethyl carbonate (DMC) has recently attracted interest as a valuable green methylating agent[51−56] as it showed stability, nontoxicity, and biodegradability. Unfortunately, our attempts with any of these methylation sources were unsuccessful, principally due to their degradation during the milling, always affording unreacted starting material. Moc_2O degraded itself as soon as added in the jar. Although methyl chloroformate seemed to be the most promising reactant, leading to Z-L-Phe-OMe (300 rpm, 9 cycles of 10 min) in good yield (60% determined by ^1H NMR), when the reaction was tested with other amino acids, the mixture became sticky and prevented the balls from moving, thus stopping the reaction.

CONCLUSION

Two different methodologies to prepare *N*-protected amino esters were developed under solvent-free conditions via mechanosynthesis: the *N*-protection approach using free amino esters as substrates was straightforward and more adaptable to mechanochemistry. In the case of the *C*-terminal esterification via carbonates or chloroformates, the success of the reaction was strictly dependent on the nature and stability of the activating agent in milling conditions. In all cases, the pure products were recovered in good to excellent yields after simple and clean workup procedures reducing the environmental impact with respect to the syntheses in solution. The transformations here reported are attractive for the synthetic chemist and especially useful for applications in combinatorial chemistry and drug discovery.

EXPERIMENTAL SECTION

General Remarks. All reagents were commercially available and used without any further purification. NMR spectra were recorded at room temperature with the appropriate deuterated solvent ($CDCl_3$, CD_3OD, or DMSO-d_6). Chemical shifts (δ) of ^1H NMR and ^{13}C NMR spectra are reported in ppm relative to residual solvent signals ($CHCl_3$ in $CDCl_3$: δ = 7.27 ppm for ^1H and $CDCl_3$: δ = 77.04 ppm for ^{13}C NMR. *J* values are given in hertz. ^1H and ^{13}C NMR spectra were registered at 300 or 400 MHz. The identity of analytically pure final products was assessed by comparison of their ^1H NMR data previously described in the literature and by their fragmentation in LC/MS. Analytical high-performance liquid chromatography (HPLC) was performed with a variable wavelength diode detector using a CHROMOLITH RP18 column (50 × 4,6 mm), flow 5 mL/min, linear gradient CH_3CN in water 0−100% (+ 0.1% TFA) in 4.5 min. LC-MS analysis were performed using an Onyx C_{18} HPLC column (25 × 4.6 mm), flow 3 mL/min linear gradient CH_3CN in water 0−100% (+ 0.1% HCO_2H) in 2.5 min. The ball milling experiments were performed in a MM200 vibrational ball (Retsch GmbH, Haan, Germany) using 10 mL mill steel jar (2 stainless steel balls, 5 mm Ø), or PM100 planetary mill (Retsch GmbH, Haan, Germany) 12 mL steel jar (12, 24, 36, or 50 stainless steel balls, 5 mm Ø). All compounds displayed identical spectral data compared to authentic commercial sample.

General Experimental Procedures and Characterizations. *General Procedure for the Synthesis of N-Fmoc- (Table 1, Entries 1−4) and N-Z-α-Amino Esters (Table 1, Entries 6−10).* The amino ester hydrochloride (0.238 mmol), $NaHCO_3$ (0.476 mmol), and the suitable protecting group (Fmoc-Cl or Z-Cl) (0.238 mmol) were introduced into a 10 mL stainless grinding jar with two stainless balls (5 mm diameter). The reaction mixture was ground at 30 Hz with a vibrational ball mill for 90 min (120 min from the *tert*-butyl esters). CH_2Cl_2 was then added to the crude product, and the water-soluble side products were filtered on cotton. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give the pure compound after drying over P_2O_5.

Fmoc-Gly-OMe **1**. CAS [121616-32-8] (70.5 mg, 95% yield). ^1H NMR (300 MHz, $CDCl_3$)[57] δ (ppm): 3.78−4.44 (m, 6H), 5.42 (m, 2H), 7.36−7.79 (m, 8H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 40.3, 44.8, 50.0, 64.8, 117.7, 122.7, 124.7, 125.4, 138.9, 141.4, 153.9, 168.2. MS ESI-(+): *m*/*z* 312 $[M + H]^+$, 334 $[M + Na]^+$, 623 $[2M + H]^+$, 179 $[C_{14}H_{11}]^+$, 134.

Fmoc-Phe-OMe **2**. CAS [129397-81-5][58] (90.2 mg, 95% yield). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.93−5.37 (m, 10H), 7.82−7.16 (m, 13H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 36.2, 45.2, 50.3, 52.8, 64.9, 117.9, 123.0, 124.6, 125.0, 125.7, 126.6, 127.3, 139.3, 140.4, 141.7, 153.5, 169.9. MS ESI-(+): *m*/*z* 402 $[M + H]^+$, 424 $[M + Na]^+$, 803 $[2M + H]^+$, 825 $[2M + Na]^+$, 224, 180 $[C_{14}H_{11} + H]^+$.

Fmoc-Ala-OMe **3**. CAS [146346-88-5][59] (74.8 mg, 96%). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.46 (d, 3H, *J* = 7.1 Hz), 3.79 (s, 3H), 4.25 (t, 1H, *J* = 7.0 Hz), 4.38−4.43 (m, 3H), 5.43 (d, 1H, *J* = 6.6 Hz), 7.43 (t, 4H, *J* = 7.3 Hz), 7.63 (d, 2H, *J* = 6.6 Hz), 7.79 (d, 2H, *J* = 7.4 Hz). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 16.7, 45.2, 47.7, 50.6, 65.0, 118.1, 123.5, 125.1, 125.8, 139.4, 141.8, 153.7, 171.6. MS ESI-(+): *m*/*z* 326 $[M + H]^+$, 348 $[M + Na]^+$, 651 $[2M + H]^+$, 179 $[C_{14}H_{11} + H]^+$, 148, 104.

Fmoc-Leu-O-t-Bu **4**. CAS [129460-20-4] (78.1 mg, 87%). ^1H NMR (300 MHz, $CDCl_3$)[60] δ (ppm): 0.78 (d, 3H, *J* = 5.4 Hz), 0.81 (d, 3H, *J* = 5.4 Hz), 1.41 (s, 9H), 1.62 (pseudo-s, 2H), 4.01−4.05 (m, 1H), 4.40−4.60 (m, 3H), 4.81−4.95 (m, 2H), 7.33−7.69 (m, 8H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 22.2, 23.2, 25.2, 28.2, 42.3, 47.4, 53.2, 67.0, 82.0, 120.1, 125.3, 127.2, 127.8, 141.4, 143.9, 144.1, 156.1, 172.81. MS ESI-(+): *m*/*z* 224 $[M + H]^+$, 417 $[M + H_2O]^+$, 432 $[M + Na]^+$, 354 $[M - t\text{-Bu} + H]^+$, 217.

Z-Gly-OMe **5**. CAS [1212-53-9] (42.4 mg, 80%). ^1H NMR (300 MHz, $CDCl_3$)[61] δ (ppm): 3.75 (s, 3H), 3.98 (d, 2H, *J* = 5.6 Hz), 5.13

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(s, 2H, CH_2O), 5.38 (s_{broad}, 1H, NH), 7.3 (s, 5H, ArH). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 42.7, 52.4, 67.2, 128.2, 128.3, 128.6, 136.3, 156.4, 170.6. MS ESI-(+): m/z 410 $[M + H]^+$, 246 $[M + Na]^+$, 180.

Z-Gly-O-t-Bu **6**. CAS [16881-32-6] (61 mg, 96% yield). ^1H NMR (300 MHz, $CDCl_3$)[62] δ (ppm): 1.39 (s, 9H), 3.79 (d, 2H, J = 5.4 Hz), 5.04 (s, 2H), 5.22 (pseudo-s, 1H), 7.26 (s, 5H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 28.2, 43.4, 66.9, 82.2, 128.08, 128.13, 128.5, 140.9, 156.3, 169.1. MS ESI-(+): m/z 266 $[M + H]^+$, 288 $[M + Na]^+$, 210 $[M - t\text{-Bu} + H]^+$, 166 $[M - Boc + H]^+$, 132.

Z-Leu-O-t-Bu **7**. CAS [16881-37-1][16] (61.3 mg, 80% yield). ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 0.84−0.90 (m, 6H), 1.64−1.25 (m, 11H), 3.89−3.92 (m, 1H, CH_α), 5.04 (s, 2H, CH_2O), 7.31−7.35 (m, 5H), 7.61 (d, 1H, J = 7.9 Hz). $^{13}C\{1H\}$ NMR (300 MHz, DMSO-d_6) δ (ppm): 21.2, 22.7, 24.2, 27.6, 39.5, 52.9, 65.3, 80.3, 127.6, 127.7, 127.9, 142.5, 156.1, 171.9. MS ESI-(+): m/z 322 (9) $[M + H]^+$, 344 $[M + Na]^+$, 266 $[M - t\text{-Bu} + H]^+$, 222 $[M - Boc + H]^+$, 132.

Z-Glu(O-t-Bu)$_2$ **8**. CAS [16881-41-7][63] (94 mg, quant). ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.39 (s, 18H), 1.60−1.80 (m, 1H), 1.80−2.00 (m, 1H), 2.27−2.28 (m, 2H), 3.90−4.00 (m, 1H), 5.04 (s, 2H), 7.31−7.36 (m, 5H), 7.63 (d, 1H, J = 7.9 Hz). $^{13}C\{1H\}$ NMR (300 MHz, DMSO-d_6) δ (ppm): 27.1, 28.6, 28.7, 32.2, 54.6, 66.4, 80.9, 81.6, 128.7, 128.8, 129.3, 138.0, 157.1, 172.2, 172.4. MS ESI-(+): m/z 394 $[M + H]^+$, 416 $[M + Na]^+$, 809 $[2M + Na]^+$, 338 $[M - t\text{-Bu} + H]^+$, 282 $[M - (^tBu)_2 + H]^+$, 238 $[M - Boc\text{-}t\text{-Bu} + H]^+$.

General Procedure for the Synthesis of N-Boc-α- and β-Amino Esters (Table 1, Entries 11−16). The amino ester hydrochloride (50 mg, 1 equiv), $NaHCO_3$ (2 equiv), and Boc_2O (1 equiv) were introduced into a 5 mL stainless grinding jar with two stainless balls (5 mm diameter). The reaction mixture was ground at 30 Hz for 90 min in a vibrational ball mill. The crude was extracted with H_2O/Et_2O, and the organic phase was dried over $MgSO_4$, filtered, and concentrated to give the pure compound after drying over P_2O_5.

Boc-Phe-OMe **9**. CAS [51987-73-6][64] (58,2 mg, 91% yield). ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.32 (s, 9H), 2.81−3.03 (m, 2H), 3.60 (s, 3H), 4.14−4.22 (m, 1H), 7.18−7.30 (m, 5H). $^{13}C\{1H\}$ NMR (300 MHz, DMSO-d_6) δ (ppm): 28.1, 36.5, 51.8, 55.2, 78.3, 126.4, 128.2, 129.1, 137.6, 146.2, 155.4, 172.6. MS ESI-(+): m/z 230 $[M + H]^+$, 252 $[M + Na]^+$, 174 $[M - t\text{-Bu} + H]^+$, 130 $[M - Boc + H]^+$.

Boc-Pro-OMe **10**. CAS [51987-73-6] (55,5 mg, 81% yield). ^1H NMR (300 MHz, $CDCl_3$)[64] δ (ppm): 1.36 (2s, 9H), 1.71−2.22 (m, 4H), 3.37−3.48 (m, 2H), 3.65 (s, 3H), 4.13−4.26 (m, 1H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 23.8, 24.4, 28.4, 28.5, 30.0, 30.9, 46.4, 46.6, 52.0, 52.1, 58.8, 59.2, 79.86, 79.91, 153.9, 154.5, 173.6, 173.8. MS ESI-(+): m/z 230 $[M + H]^+$, 252 $[M + Na]^+$, 174 $[M - t\text{-Bu} + H]^+$, 130 $[M - Boc + H]^+$.

Boc-β-Ala-OMe **11**. CAS [42116-55-2] (50,1 mg, 68% yield). ^1H NMR (300 MHz, $CDCl_3$)[65] δ (ppm): 1.41 (s, 9H, O-*t*-Bu), 2.50 (t, 2H, J = 6.1 Hz, CH_2CO), 3.33−3.42 (m, 2H, CH_2N), 3.69 (s, 3H, OMe). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 28.5, 34.5, 36.2, 51.8, 79.4, 155.9, 172.9. MS ESI-(+): m/z 204 $[M + H]^+$, 226 $[M + Na]^+$, 148 $[M - t\text{-Bu} + H]^+$.

Boc-3-Aib-OMe **12**. CAS [182486-32-4] (43.7 mg, 61% yield). ^1H NMR (300 MHz, $CDCl_3$)[66] δ (ppm): 1.17 (d, 3H, J = 7.2 Hz, CH_3), 1.43 (s, 9H, O-*t*-Bu), 2.67−2.71 (m, 1H, CHCO), 3.24−3.31 (m, 2H, CH_2N), 3.70 (s, 3H, OMe). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 14.8, 28.5, 40.1, 43.1, 51.9, 85.3, 156.0, 175.9. MS ESI-(+): m/z 218 $[M + H]^+$, 240 $[M + Na]^+$, 162 $[M - t\text{-Bu} + H]^+$.

Boc-Aib-OMe **13**. CAS [84758-55-4] (48.9 mg, 68% yield). ^1H NMR (300 MHz, $CDCl_3$)[67] δ (ppm): 1.42 (s, 9H), 1.48 (s, 6H), 3.72 (s, 3H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 25.5, 28.4, 52.6, 56.3, 79.9, 154.7, 175.5. MS ESI-(+): m/z 218 $[M + H]^+$, 240 $[M + Na]^+$, 203 $[M - Me + H]^+$.

General Procedure for the Synthesis of N-Protected tert-Butyl Esters (Table 2, Entries 1−4). The *N*-protected amino acid (250 mg, 1 equiv), Boc_2O (0.5 equiv), and DMAP (0.3 equiv) were added together in a 12 mL stainless steel jar with 50 stainless steel balls (diameter 5 mm). The mixture was milled in a planetary ball mill at 300 rpm for 3 cycles of 10 min each, with a 2 min pause in between, with reverse rotation. Then, Boc_2O (0.5 equiv) was added to the jar and the mixture was milled again for 3 cycles of 10 min (2 min pause in between, with reverse rotation). Aqueous citric acid (10% aq, 10 mL) was added, and the crude was mixed with a spatula. The mixture was extracted with diethyl ether (3 × 5 mL). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under vacuum.

Z-Phe-O-t-Bu **14**. CAS [7670-20-4] (236.6 mg, 79% yield). ^1H NMR (300 MHz, $CDCl_3$)[22] δ (ppm): 1.40 (s, 9H, O-*t*-Bu), 2.22 (d, 2H, J = 6.0 Hz), 4.53−4.60 (m, 1H, CH_α), 5.06 (s, 2H, CH_2O), 7.03−7.36 (m, 10H, ArH). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 28.1, 38.6, 55.3, 66.9, 82.5, 127.1, 128.2, 128.3, 128.5, 128.6, 129.7, 136.2, 136.5, 155.8, 170.7. MS ESI-(+): m/z 356 $[M + H]^+$, 378 $[M + Na]^+$, 300 $[M - t\text{-Bu} + H]^+$, 256 $[M - CO_2\text{-}t\text{-Bu} + H]^+$.

Z-Pro-O-t-Bu **15**. CAS [16881-39-3] (205.1 mg, 67% yield). ^1H NMR (300 MHz, $CDCl_3$)[68] δ (ppm): 1.36/1.46 (2*s*, 9H), 1.81−1.95 (m, 3H), 2.15−2.21 (m, 1H), 3.48−3.61 (m, 2H), 4.21−4.29 (m, 1H), 5.07−5.21 (m, 2H), 7.28−7.37 (m, 5H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 23.5, 24.3, 27.9, 28.1, 30.0, 31.0, 46.5, 47.0, 59.7, 60.0, 66.9, 81.3, 81.3, 127.8, 127.9, 128.0, 128.5, 128.5, 136.8, 137.0, 154.6, 154.9, 171.9, 172.1. MS ESI-(+): m/z 306 $[M + H]^+$, 328 $[M + Na]^+$, 250 $[M - t\text{-Bu} + H]^+$, 206 $[M - CO_2t\text{-Bu} + H]^+$.

Boc-Thr(Bzl)-O-t-Bu **16**. CAS [174872-58-3][69] (200.3 mg, 65% yield). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.29 (d, 3H, J = 6.3 Hz, CH_3), 1.49 (pseudo-s, 18H, 2 × $C(CH_3)_3$), 4.04−4.10 (m, 1H, CH_α), 4.14−4.46 (1H, CH−O), 4.32−4.63 (m, 2H, CH_2O), 5.28 (d, 1H, J = 9.5 Hz, NH), 7.30−7.37 (m, 5H, ArH). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm)16.5, 16.4,28.2, 28.5,58.8, 71.0, 71.2, 75.2, 75.5, 79.7, 81.9, 82.2, 127.7, 127.8, 128.4, 128.7, 138.2, 156.4, 170.3. MS ESI-(+): m/z 366 $[M + H]^+$, 388 $[M + Na]^+$, 254 $[M - t\text{-Bu} + H]^+$, 210 $[M - CO_2 - t\text{-Bu} + H]^+$; HRMS ESI-(+) calcd for $C_{20}H_{31}NO_5$ $[M + Na]^+$ 388.2100, found 388.2098.

Boc-Tyr(2,6-dichlorobenzyl)-O-t-Bu **17**. CAS [1253041-18-7][70] (159.1 mg, 56% yield). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.43 (s, 18H), 3.02 (d, 2H, J = 5.9 Hz), 4.40−4.46 (m, 1H), 4.99 (pseudo-d, 1H, J = 8.1 Hz), 5.25 (s, 2H), 6.94−7.62 (m, 7H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 27.9, 28.3, 37.7, 54.9, 65.3, 79.6, 81.9, 114.9, 128.5, 129.1, 130.4, 130.6, 132.2, 137.0, 155.2, 157.9, 171.0. MS ESI-(+): m/z 496 $[M + H]^+$, 518 $[M + Na]^+$, 340 $[H\text{-AA-OH}]^+$. HRMS ESI-(+): calcd for $C_{25}H_{31}NO_5Cl_2$ $[M + H]^+$ 496.1658, found 496.1660.

General Procedure for the Synthesis of N-Protected Succinimidyl Esters (Table 2, Entries 5−7). The *N*-protected amino acid (250 mg, 1 equiv), DSC (1 equiv), and DMAP (0.3 equiv) were added in a 12 mL stainless steel jar with 50 stainless steel balls (diameter 5 mm). The mixture was milled at 450 rpm for 6 cycles of 10 min each, with a 2 min pause in between, with reverse rotation. Aqueous citric acid (10% aq, 10 mL) was added, and the crude was mixed with a spatula. The mixture was then extracted with diethyl ether (3 × 5 mL). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ dried over $MgSO_4$, filtered, and concentrated under vacuum.

Z-Phe-OSu **18**. CAS [3397-32-8] (228.7 mg, 69% yield). ^1H NMR (300 MHz, $CDCl_3$)[71] δ (ppm): 2.86 (s, 4H), 3.27 (dd, 1H, J = 5.7 Hz, J = 13.9 Hz), 3.36 (dd, 1H, J = 5.7 Hz, J = 13.9 Hz), 5.02−5.16 (m, 4H), 7.28−7.40 (m, 10H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 25.6, 38.0, 52.9, 67.4, 127.5, 128.2, 128.3, 128.5, 128.6, 128.8, 129.4, 129.7, 134.3, 135.9, 155.3, 167.5, 168.5. MS ESI-(+): m/z 300 $[M + H]^+$, 322 $[M + Na]^+$, 256.

Boc-Thr(Bzl)-OSu **19**. CAS [32886-43-4][50] (179.4 mg, 55% yield). Two rotamers were present in the spectrum. ^1H NMR (300 MHz, acetone-d_6) δ (ppm):1.23/1.31 (2d, 6H, J = 6.3 Hz, 2 × CH_3 two rotamers), 1.38 (pseudo-s, 9H), 2.62 (s, 2H), 2.87 (s, 2H), 4.15−4.30 (m, 1H), 4.55−4.69 (m, 3H), 7.20−7.37 (m, 5H). $^{13}C\{1H\}$ NMR (300 MHz, acetone-d_6) δ (ppm): 15.3, 16.9, 26.1, 26.3, 28.4, 42.9, 57.9, 71.5, 72.0, 75.8, 79.5, 80.0, 128.2, 128.8, 128.9, 139.5, 156.4, 167.9, 170.3, 171.6, 172.5. MS ESI-(+): m/z 407 $[M + H]^+$, 425 $[M + Na]^+$, 351 $[M - t\text{-Bu} + H]^+$, 307 $[M - Boc + H]^+$. HRMS ESI-(+): calcd for $C_{20}H_{26}N_2O_7$ $[M + H]^+$ 407.1818, found 407.1822.

Boc-Met-OSu **20**. CAS [3845-64-5][50] (121.2 mg, 35% yield). ^1H NMR (300 MHz, acetone-d_6) δ (ppm): 1.35 (s, 9H), 2.09−2.25 (m,

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4H), 2.58−2.73 (m, 3H), 2.88 (s, 1H), 4.69−4.76 (m, 1H). $^{13}C\{1H\}$ NMR (300 MHz, acetone-d_6) δ (ppm): 14.9, 26.2, 32.0, 42.9, 51.8, 73.4, 79.8, 156.1, 169.3, 170.2, 171.5, 174.8. MS ESI-(+): m/z 306 $[M + H]^+$, 328 $[M + Na]^+$, 250 $[M - t\text{-Bu} + H]^+$. HRMS ESI-(+): calcd for $C_{14}H_{22}N_2O_6S$ $[M + Na]^+$ 369.1096, found 369.1091.

General Procedure for the Synthesis of N-Protected Benzyl Esters (Table 2, Entries 8−10). The *N*-protected amino acid (250 mg, 1 equiv), Z-Cl (0.5 equiv), and DMAP (1.3 equiv) were added in a 12 mL stainless steel jar with 50 stainless steel balls (diameter 5 mm). The mixture was milled in a planetary mill at 300 rpm for 3 cycles of 10 min each, with a 2 min pause in between. Then, Z-Cl (0.5 equiv) was added into the jar and the mixture was milled again for 3 cycles of 10 min (2 min pause in between, with reverse rotation). Aqueous citric acid (10% aq., 10 mL) was added and the crude mixed with a spatula. The mixture was extracted with diethyl ether (3 × 5 mL). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under vacuum.

Z-Phe-OBn ***21***. CAS [60379-01-3] (155.4 mg, 48% yield). ^1H NMR (300 MHz, $CDCl_3$)[72] δ (ppm): 3.13 (pseudo-s, 2H), 4.73 (q, 1H, J = 5.9 Hz), 5.07−5.27 (m, 5H), 7.01−7.39 (m, 15H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 38.3, 54.9, 67.1, 67.4, 127.2, 128.2, 128.3, 128.65, 128.69, 128.74, 129.5, 135.2, 135.6, 136.4, 155.7, 171.5. MS ESI-(+): m/z 390 $[M + H]^+$, 412 $[M + Na]^+$, 346.

Z-Ser(O-t-Bu)-OBn ***22***. CAS [20700-93-0][73] (175.3 mg, 54% yield). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.08 (s, 9H), 3.58 (dd, 1H, J = 3.1 Hz, J = 8.9 Hz), 3.85 (dd, 1H, J = 2.6 Hz, J = 8.9 Hz), 4.43 (dt, 1H, J = 2.8 Hz, J = 8.9 Hz), 5.05−5.18 (m, 1H), 7.34−7.36 (m, 5H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 27.3, 54.8, 62.1, 67.1, 128.25, 128.27, 128.31, 128.4, 128.6, 135.7, 136.4, 156.3, 170.7. MS ESI-(+): m/z 386 $[M + H]^+$, 408 $[M + Na]^+$, 330 $[M - t\text{-Bu} + H]^+$, 286 $[M - CO_2 - t\text{-Bu} + H]^+$. HRMS ESI-(+): calcd for $C_{22}H_{27}NO_5$ $[M + H]^+$ 386.1967, found 386.1973.

Boc-Met-OBn ***23***. CAS [87746-57-4] (201.6 mg, 59% yield). ^1H NMR (300 MHz, $CDCl_3$)[74] δ (ppm): 1.43 (s, 9H), 1.89−1.99 (m, 1H), 2.04 (s, 3H), 2.09−2.14 (m, 1H), 2.45−2.51 (m, 2H), 4.42−4.48 (m, 1H), 5.12−5.23 (m, 2H), 7.35 (s, 5H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 15.6, 28.4, 29.9, 32.3, 52.9, 67.3, 80.2, 128.5, 128.6, 128.7, 135.4, 155.4, 172.3. MS ESI-(+): m/z 340 $[M + H]^+$, 462 $[M + Na]^+$, 284 $[M - t\text{-Bu} + H]^+$, 240 $[M - CO_2 - t\text{-Bu} + H]^+$, 146.

General Procedure for the Synthesis of N-Protected Ethyl (Table 2, Entries 11−14) and Allyl Esters (Table 2, Entries 15−18). The *N*-protected amino acid (250 mg, 1 equiv), the suitable alkyl chloroformate (ethylchloroformate or allylchloroformate, 1.2 equiv), and DMAP (1.5 equiv) were added to a 12 mL stainless steel jar with 50 stainless steel balls (diameter 5 mm). The mixture was milled at 300 rpm for 9 cycles of 10 min each, with a 2 min pause in between, with reverse rotation. Aqueous citric acid (10% aq., 10 mL) was added and the crude was mixed with a spatula. The mixture was extracted with diethyl ether (3 × 5 mL) (except for Boc-L-Cys(Bzl)-OAllyl **31**, which precipitated when aqueous citric acid was added and it was filtered and dried under vacuum). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under vacuum.

Z-Phe-OEt ***24***. CAS [28709-70-8] (247.9 mg, 90% yield). ^1H NMR (300 MHz, $CDCl_3$)[75] δ (ppm): 1.26 (t, 3H, J = 7.1 Hz), 3.15 (pseudo-t, 2H, J = 5.5 Hz), 4.20 (q, 2H, J = 7.1 Hz), 4.65−4.71 (m, 1H), 5.14 (s, 2H), 5.27 (d, 1H, J = 7.8 Hz), 7.13−7.42 (m, 10H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 14.2, 38.4, 54.9, 61.6, 67.1, 127.2, 128.2, 128.3, 128.65, 128.68, 129.5, 135.9, 136.4, 155.7, 171.6. MS ESI-(+): m/z 328 $[M + H]^+$, 350 $[M + Na]^+$, 284.

Z-Ser(O-t-Bu)-OEt ***25***. CAS [130192-13-1][76] (238.4 mg, 87% yield). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.13 (s, 9H), 1.28 (t, 3H, J = 7.1 Hz), 3.58 (dd, 1H, J = 3.1 Hz, J = 8.9 Hz), 3.83 (dd, 1H, J = 2.8 Hz, J = 8.9 Hz), 4.21 (q, 2H, J = 7.1 Hz), 4.45 (dt, 1H, J = 2.9 Hz, J = 8.9 Hz), 5.14 (s, 2H), 5.63 (d, 1H, J = 8.7 Hz), 7.32−7.39 (m, 5H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 14.3, 27.4, 54.8, 61.5, 62.2, 67.1, 73.5, 128.3, 128.6, 136.5, 156.3, 170.7. MS ESI-(+): m/z 324 $[M + H]^+$, 346 $[M + Na]^+$, 268 $[M - t\text{-Bu} + H]^+$, 224. HRMS ESI-(+): calcd for $C_{17}H_{25}NO_5$ $[M + Na]^+$ 346.1630, found 346.1635.

Boc-Met-OEt ***26***. CAS [76220-80-9] (232.1 mg, 84% yield). ^1H NMR (300 MHz, $CDCl_3$)[77] δ (ppm): 1.27 (t, 3H, J = 7.1 Hz), 1.43 (s, 9H), 1.84−1.96 (m, 1H), 2.08 (s, 3H), 2.08−2.17 (m, 1H), 2.52 (t, 2H, J = 7.0 Hz), 4.19 (q, 2H, J = 7.1 Hz), 4.36 (pseudo-s, 1H), 5.13 (pseudo-s, 1H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm):14.3, 15.6, 28.4, 30.1, 32.4, 52.9, 61.6, 80.1, 155.4, 172.4. MS ESI-(+): m/z 278 $[M + H]^+$, 300 $[M + Na]^+$, 221 $[M - t\text{-Bu} + H]^+$, 219 $[M - (CH_2)_2SCH_3 + H]^+$, 178 $[M - Boc + H]^+$.

Boc-Cys(Bzl)-OEt ***27***. CAS [110694-58-1][78] (246.1 mg, 91% yield). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.27 (t, 3H, J = 7.1 Hz), 1.46 (s, 9H), 2.84 (m, 2H, CH_2−S), 3.73 (s, 2H), 4.18 (q, 2H, J = 7.1 Hz), 4.53 (pseudo-s, 1H), 5.31 (pseudo-d, 1H, J = 7.6 Hz), 7.22−7.35 (m, 5H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 14.3, 28.4, 33.8, 36.8, 53.3, 61.8, 80.2, 127.3, 128.7, 129.1, 137.9, 155.5, 171.2. MS ESI-(+): m/z 340 $[M + H]^+$, 362 $[M + Na]^+$, 284 $[M - t\text{-Bu} + H]^+$, 240 $[M - Boc + H]^+$, 223. HRMS ESI-(+): calcd for $C_{17}H_{25}NO_4S$ $[M + Na]^+$ 362.1402, found 362.1404.

Z-Phe-OAllyl ***28***. CAS [64286-85-7] (257.6 mg, 90% yield). ^1H NMR (300 MHz, $CDCl_3$)[64] δ (ppm): 3.14 (t, 2H, J = 5.6 Hz, CH_2Ar), 4.62 (d, 2H, J = 5.8 Hz, allyl CH_2−O), 4.67−4.72 (m, 1H, CH_α), 5.11 (s, 2H, OCH_2Ph), 5.19−5.28 (m, 3H, allyl CH_2 and NH), 5.80−5.93 (m, 1H, allyl CH), 7.10−7.37 (m, 10H, ArH). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 38.4, 54.9, 66.2, 67.1, 119.2, 127.3, 128.2, 128.3, 128.67, 128.74, 129.5, 131.5, 135.8, 136.4, 155.8, 171.3. MS ESI-(+): m/z 340 $[M + H]^+$, 362 $[M + Na]^+$, 296.

Z-Ser(O-t-Bu)-OAllyl ***29***. (236.1 mg, 83% yield, colorless oil). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.12 (s, 9H), 3.58 (dd, 1H, J = 3.1 Hz, J = 8.9 Hz), 3.85 (dd, 1H, J = 2.8 Hz, J = 8.9 Hz), 4.48 (dt, 1H, J = 2.9 Hz, J = 8.9 Hz), 4.65 (d, 2H, J = 5.6 Hz), 5.14 (s, 2H), 5.21−5.36 (m, 2H), 5.63 (d, 1H, J = 8.8 Hz), 5.83−5.96 (m, 1H), 7.30−7.38 (m, 7H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 27.4, 54.8, 62.2, 66.0, 67.2, 73.6, 118.5, 128.3, 128.7, 131.8, 136.5, 156.3, 170.5. MS ESI-(+): m/z 336 $[M + H]^+$, 358 $[M + Na]^+$, 280 $[M - t\text{-Bu} + H]^+$, 236. HRMS ESI-(+): calcd for $C_{18}H_{25}NO_5$ $[M + Na]^+$ 358.1630, found 358.1629.

Boc-Met-OAllyl ***30***. CAS [887646-46-0] (232.1 mg, 84% yield): ^1H NMR (300 MHz, $CDCl_3$)[79] δ (ppm): 1.42 (s, 9H), 1.84−2.02 (m, 1H), 2.07 (s, 3H), 2.08−2.18 (m, 1H), 2.52 (t, 2H, J = 7.4 Hz), 4.40 (pseudo-s, 1H), 4.62 (dd, 2H, J = 1.2 Hz, J = 5.8 Hz), 5.15 (pseudo-s, 1H), 5.27 (qd, 2H, J = 1.2 Hz, J = 10.4 Hz), 5.83−5.96 (m, 1H). $^{13}C\{1H\}$ NMR (300 MHz, $CDCl_3$) δ (ppm): 15.6, 26.9, 28.4, 30.1, 32.3, 52.9, 66.1, 80.1, 119.0, 131.6, 155.4, 172.1. MS ESI-(+): m/z 290 $[M + H]^+$, 234 $[M - t\text{-Bu} + H]^+$, 190 $[M - Boc + H]^+$.

Boc-Cys(Bzl)-OAllyl ***31***. CAS [848779-96-4][80] (255.6 mg, 91% yield). ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.39 (s, 9H), 2.57−2.73 (m, 2H), 3.71 (s, 2H), 4.19 (q, 1H, J = 5.1 Hz), 4.57 (d, 1H, J = 4.8 Hz), 5.19−5.33 (m, 2H), 5.75−5.89 (m, 1H), 7.19−7.34 (m, 5H). $^{13}C\{1H\}$ NMR (300 MHz, DMSO-d_6) δ (ppm): 26.4, 28.2, 31.9, 35.2, 53.4, 64.9, 78.5, 117.6, 126.9, 128.4, 128.9, 132.3, 138.1, 155.4, 170.2. MS ESI-(+): m/z 352 $[M + H]^+$, 374 $[M - t\text{-Bu} + H]^+$, 252 $[M - Boc + H]^+$, 235. HRMS ESI-(+): calcd for $C_{18}H_{25}NO_4S$ $[M + Na]^+$ 374.1402, found 374.1400.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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