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ARTICLE

A Multigram-Scale Lower E-Factor Procedure for MIBA-Catalyzed Direct Amidation and Its Application to the Coupling of alpha and beta Aminoacids

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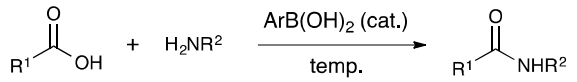
The development of direct and atom-economical amidation methods is of high priority because of the importance of amides and peptides as components of pharmaceuticals and commodity chemicals. This article describes the identification of more economical and more practical conditions for direct amidation of carboxylic acids and amines using the MIBA catalyst (5-methoxy-2-iodophenylboronic acid, **6**) and its application to the coupling of α- and β-amino acid derivatives. It is now possible to use half of the quantity of molecular sieves prescribed in the original procedure, at a higher concentration leading to a reduction of waste and a substantially improved E-factor. This procedure was validated in the multigram scale preparation of prototypical amides, including aminoacids, using toluene as the solvent. Because of substrate inhibition of the catalyst with monoprotected α-aminoacids, the use of doubly-protected N-phthaloyl α-aminoacids or α-azidoacids is required in order to produce dipeptide products in moderate yields. β-Aminoacids do not suffer from this problem, and Boc-β-aminoacids can be coupled successfully. Unlike other boronic acid catalysts, **6** is active under ambient and low-heat conditions, which helps prevent any epimerization of chiral α-aminoacid derivatives.

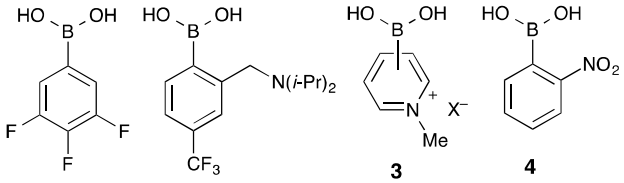
Introduction

Because of the great importance of amide units as components of pharmaceuticals, agrochemicals, and commodity chemicals,[1,2] there is significant interest in the development of simple methods to prepare amide products directly from carboxylic acids and amines.[3,4] In the past decades, a large number of sophisticated methods employing dehydrating-activating reagents have been developed for direct ("in situ") coupling of carboxylic acids and amines.[5-7] Common coupling reagents like carbodiimides, phosphonium or uronium salts tend to be expensive and provide poor atom-economy. Several common reagents are known to be toxic and they are often required in excess. Moreover, they generate large amounts of wasteful by-products that complicate the isolation of the desired amide product. An ideal amidation process between carboxylic acids and amines would be waste-free, catalytic, operationally simple, and occur at or near the ambient temperature. In this regard, boronic acids constitute an attractive class of catalysts for direct amidation reactions.[8,9] The first reported boronic acid catalysts **1**,[10,11] **2**,[12] and **3**[13] function at elevated temperatures. In contrast, we recently reported that *ortho*-iodophenylboronic acid (**5**) is a very efficient catalyst for direct amidation reactions under ambient conditions (Figure 1).[14] Following this discovery, we designed 5-methoxy-2-iodophenylboronic acid (MIBA, **6**) as an improved, second-generation catalyst.[15] The MIBA catalyst was found to give higher yields within shorter reaction times for a wide range of aliphatic and heteroaromatic carboxylic acids and aliphatic amines.[15] To the best of our knowledge, only catalyst **4** (*o*-nitrophenylboronic acid, Figure 1) has been applied to the direct amidation of aminoacid derivatives to address the inherent difficulties associated with peptide synthesis.[16] This method, however, requires an elevated temperature and a stoichiometric amount of boronic acid **4**

when applied to the preparation of dipeptides.



Catalysts active at > 80 °C :



Catalysts active at rt to 50 °C :

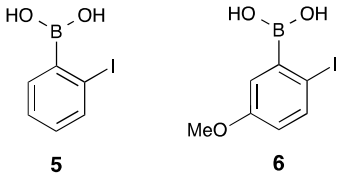


Figure 1. Known Boronic Acid Catalysts for Direct Amidation Reactions.

Drawbacks of our current catalytic procedure using boronic acids **5** and **6** include a low reactant concentration and the requirement for a large quantity of heat-activated molecular sieves to remove water and drive the reaction. These impediments limit the synthetic utility of this amidation methodology in larger scale applications. In this Article, we address these concerns with an optimization of the reaction conditions such as solvent, reactant concentration, and the amount of molecular sieves. An optimized procedure for the multigram scale preparation of amides was evaluated, along with a feasibility study for the coupling of aminoacid derivatives to assemble short alpha- (α) and beta- (β) peptides.

Results and discussion

Evaluation of reaction parameters to improve the E-factor.

Optimization of amount of molecular sieves and solvent.

Previous optimization work in our laboratory indicated that to obtain a near-quantitative yield of product within a short reaction time, 1 g of molecular sieves was required in a 0.5 mmol scale reaction (in typical reactions using 50-100 mgs of substrates).[15] However, at that time we did not perform a comprehensive optimization of multiple variables such as the effect of the amount of molecular sieves in combination with substrate concentration and reaction time. Thus, with a view to improve the reaction's Environmental (E) Factor,[17] we aimed to decrease the required amount of molecular sieves and solvent and achieve more practical and economical reaction conditions. To this end, we chose to conduct a model amidation reaction between phenylacetic acid (**7**) and pyrrolidine (**8**) at an exploratory scale of 0.5 mmol at room temperature (Table 1). Pyrrolidine was utilized as a model substrate because it is a challenging secondary amine suitable for a comparison study.

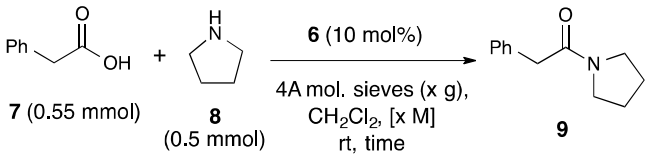


Table 1. Optimization of reactant concentration and amount of molecular sieves in a model amidation reaction catalyzed by **6**.

Entry	conc. (M)[a]	mol. sieves (g)[b]	time (h)	yield (%)[c]
1	0.2	1	18	68
2	0.5	1	18	52
3	0.2	0.6	18	58
4	0.5	0.6	18	49
5	1.0	0.6	18	29
6	1.0	0.5	18	25
7	0.2	0.5	48	65
8	0.5	0.5	48	52
9	1.0	0.5	48	42
10	1.0	0.25	18	11

[a] Relative to the amine. [b] Powdered 4A molecular sieves dried at 300 °C for 12 hours. [c] Isolated yields after aqueous acid-base extractions.

The results of Table 1 confirm that a decrease in the amount of molecular sieves leads to a reduced yield of amide product (entries 1 vs 3). As observed in our previous work,[15] the yield of product **9** is lower at higher substrate concentration (compare entries 1 vs 2, 3-5, 7-9). Increasing the reaction time can partially make up for the lower yield of amide product observed at 1.0 M concentration (compare entries 6 vs 9). Thus, based on the results of Table 1, a reasonable compromise consists in using 1 g of sieves per mmol of substrate at a concentration of 0.5 or 1.0 M for an extended reaction time (entries 8-9). Although the product yield is slightly inferior compared to the original procedure of entry 1, these new conditions are more advantageous on a "green chemistry" standpoint because a smaller quantity of molecular sieves is necessary and less solvent waste is being generated. In effect, considering solvent savings, the E-factor of these new conditions is almost 10 times lower.

Optimization of reaction solvent and temperature.

In previous studies, amidation reactions catalyzed by arylboronic acids were found to perform best in CH_2Cl_2 and toluene as solvents.[15] Because toluene is considered a greener reaction solvent,[18] we decided to compare these two solvents again under the conditions identified above (c.f. Table 1, entry 9), using a reduced amount of 1 g of molecular sieves per mmol of substrate at a concentration of 1 M for a relatively short reaction time of 18 hours. As shown in Table 2, toluene was found to be a better solvent under both ambient and elevated (50 °C) temperature.

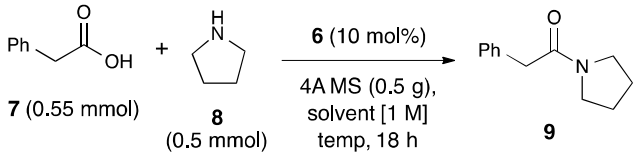


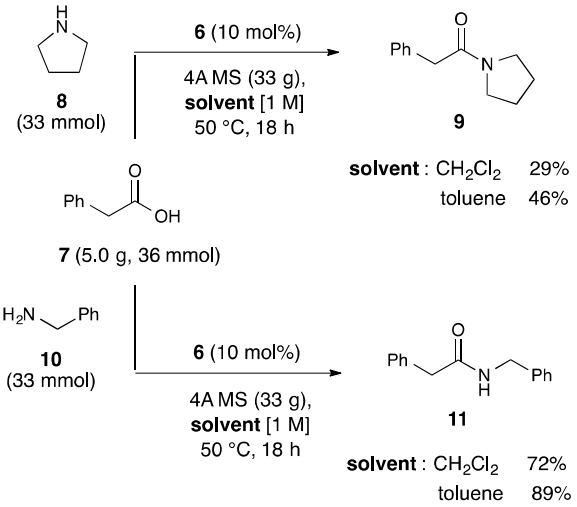
Table 2. Optimization of the reaction solvent in a model amidation reaction catalyzed by **6**.

Entry	solvent[a]	temperature (°C)	yield (%)[b]
1	CH_2Cl_2	25	25
2	CH_2Cl_2	50[c]	33
3	toluene	25	38
4	toluene	50[c]	45

[a] Dry solvent. Molecular sieves: powdered 4A type dried at 300 °C for 12 hours. [b] Isolated yields after aqueous acid-base extractions. [c] Oil bath temperature (CH_2Cl_2 reflux temperature: 40 °C).

Examination of the reaction's scalability.

As described above, toluene as a non-halogenated solvent and a reaction temperature of 50 °C were identified as the optimal conditions for achieving a reasonable yield of the model amide product **9** under a higher concentration with a decreased amount of molecular sieves. With these optimized conditions in hand, the reaction was then performed on a multigram scale (5 g (36 mmol) of **7**), which is significantly higher than the previous largest scale of 5 mmol (~0.7 g of **7**) at which this catalytic amidation was performed.[15] As presented in Scheme 1, the amidation reaction of phenylacetic acid (**7**) proceeded successfully giving 89% and 46% product yields (with benzylamine (**10**) and pyrrolidine (**8**) respectively). Up to 60-80% of catalyst **6** was partially recovered from these experiments using acid-base extractions.

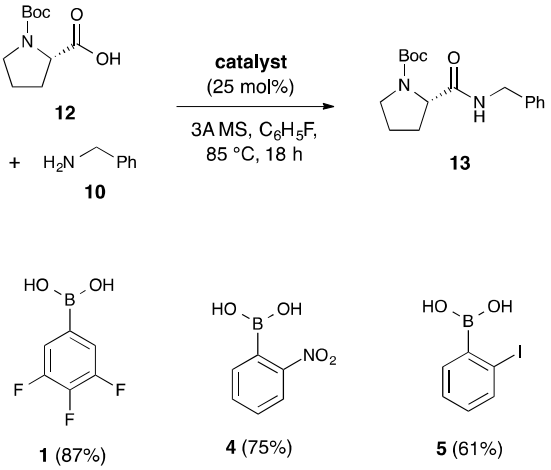


Scheme 1. Scale up of model catalytic direct amidation reactions using 5 g of carboxylic acid. Note. Indicated temperature is oil bath temperature (CH_2Cl_2 reflux temperature: 40 °C).

Application to the synthesis of alpha-peptides.

Evaluation of different arylboronic acid catalysts in direct amide formation with N-*t*-Boc proline.

Recently, Whiting and coworkers reported the use of catalytic amounts of 3,4,5-trifluorophenylboronic, TFPBA, (**1**) and *o*-nitrophenylboronic acid, *o*-NPBA, (**4**) in the model direct amidation of *N-tert*-butyloxycarbonyl(Boc)-proline (**12**) with benzylamine (Scheme 2).[16]



Scheme 2. Comparison of different catalysts in the amidation of Boc-proline as reported by Whiting and co-workers.[16]

Under these conditions, catalysts **1** and **4** displayed the highest catalytic reactivity and were both superior to our first-generation IBA catalyst (**5**) under the same

reaction conditions in refluxing fluorobenzene (85 °C). The desired product **13** was obtained without any racemization. Considering the results from the Whiting group with o-nitrophenylboronic acid (**4**),[16] and our previous studies,[15] we set out to re-evaluate the MIBA catalyst (**6**) in a range of different reaction conditions with the objective of achieving optimal conditions in the formation of peptide bonds. Thus, the comparison between catalysts **4** and **5** was expanded to include our improved second-generation catalyst,[14] MIBA (**6**), in CH_2Cl_2 or fluorobenzene as solvents, with both 3A and 4A and molecular sieves as drying agent. It was also important to compare these catalysts under different temperatures because of the likelihood that they operate under different mechanisms. The results are presented in Table 3.

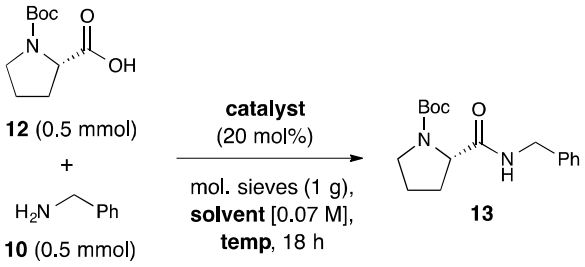


Table 3. Comparison of product yields for different molecular sieves and catalysts **4-6** in a direct amidation reaction between (Boc)-proline and benzylamine.

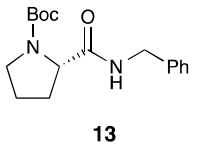
Entry	catalyst	mol. sieves[a]	solvent[b]	temp. (°C)[c]	yield (%)[d]
1	**4**	3A	C_6H_5F	85	74
2	**4**	4A	C_6H_5F	85	67
3	**4**	3A	CH_2Cl_2	50	51
4	**4**	4A	CH_2Cl_2	50	42
5	**5**	3A	C_6H_5F	85	48
6	**5**	4A	C_6H_5F	85	54
7	**5**	3A	CH_2Cl_2	50	60
8	**5**	4A	CH_2Cl_2	50	69
9	**6**	3A	C_6H_5F	85	64
10	**6**	4A	C_6H_5F	85	74
11	**6**	3A	CH_2Cl_2	50	82
12	**6**	**4A**	**CH_2Cl_2**	**50**	**91**

[a] Powdered 4A molecular sieves dried at 300 °C for 12 hours. [b] Dry solvent. [c] Oil bath temperature (Reflux temp.: CH_2Cl_2 40 °C; C_6H_5F: 85 °C). [d] Isolated yields after aqueous acid-base extractions.

Compared to catalysts **4** and **5**, the activity of the electron-rich 5-methoxy-2-iodophenylboronic acid **6** was enhanced in CH_2Cl_2 as a solvent and 4A molecular sieves as a dehydrating agent (entry 4 vs 8 and 12). However, as observed by Whiting and co-workers,[16] the reactivity of **5** (and **6**) was reduced in refluxing fluorobenzene, and catalyst **4** was superior in these conditions (entries 1, 5, 9). In contrast, the activity of o-nitrophenylboronic acid (**4**) is inferior in CH_2Cl_2, at 50 °C, with both 3A and 4A molecular sieves (entries 3-4). Although temperature plays a role, these results support the idea that the choice of solvent and molecular sieves is crucial in optimizing the catalytic activity. We conclude that MIBA catalyst **6** is a superior catalyst when used in CH_2Cl_2 as a solvent with 4A molecular sieves as the dehydrating agent (Table 3, entry 12).

Stereochemical integrity in the coupling of α-aminoacids.

Regardless of the amidation method employed, epimerization is always a possible threat in the coupling of optically enriched α-amino acid derivatives. Whiting and co-workers assessed catalysts **1** and **4** under their optimal conditions (fluorobenzene, 85 °C) for their ability to preserve the optical purity of both a carboxyl and amine partner in the direct formation of amides **13** and **14** (Table 4).[16] We employed the same substrates to evaluate boronic acid **6** in the optimal conditions for this catalyst (CH_2Cl_2, 50 °C). The combined results shown in Table 4 highlight the advantage provided by catalyst **6** in avoiding racemization. On the contrary, although catalyst **1** was effective for the coupling of N-Boc proline (entry 7), both catalysts **1** and **4** led to partial racemization in the formation of amide **14** using phenylalanine methyl ester (entries 5-6). It is unclear whether the lack of epimerization with MIBA catalyst (**6**) is due to its use at a lower temperature or to a different activation mechanism. Regardless, it is the most advantageous catalyst both in terms of activity (higher yields) (c.f., Table 3), and lack of epimerization.



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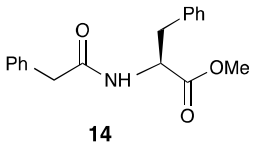

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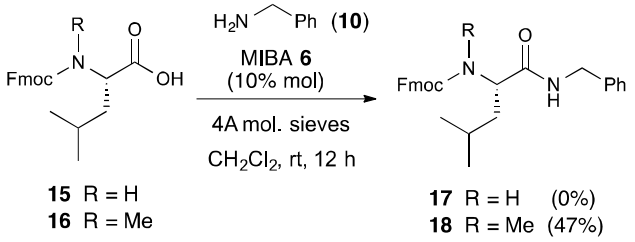
Table 4. Study of possible racemization in the direct formation of amides from chiral amino acids.

Entry[a]	product	temp. (°C)[c]	catalyst	ee (%)[d]
1	**13**	85	**1**	99
2	**13**	85	**4**	79
3	**13**	50	**6**	99
4	**14**	85	**1**	64
5	**14**	85	**4**	67
6	**14**	50	**6**	99

[a] Reaction conditions: for entries 1, 2, 4, 5: see reference 16. For entries 3 and 6: N-Boc proline (**13**) or phenylacetic acid (**14**) (0.55 mmol, 1.1 equiv), boronic acid (20 mol%), and benzyl amine (**10**) or phenylalanine methyl ester hydrochloride (0.50 mmol, 1.0 equiv) pre-neutralized with *i*-Pr_2NEt(1.0 equiv) were stirred at 50 °C for 18 h in dry CH_2Cl_2 containing the drying agent (1 g per mmol). [c] Oil bath temperature (Reflux temp.: CH_2Cl_2 40 °C; C_6H_5F: 85 °C). [d] Measured by chiral HPLC.

Design of suitable alpha-aminoacid substrates.

Our preliminary results for the coupling of monoprotected α-amino acids containing a free and relatively acidic NH (i.e., aminoacids other than proline) were unsuccessful. For example, the reaction of Fmoc-leucine (**15**) with benzylamine catalyzed by MIBA (**6**) failed to provide the desired amide product **16**, whereas, Fmoc-*N*-methyl leucine (**16**) gave a moderate yield of amide product **18** (Scheme 3).



Scheme 3. Coupling of Fmoc leucine (**15**) and Fmoc N-methyl leucine (**16**) with benzylamine catalyzed by **6**.

It is well documented that boronic acids have a facility to form 5-membered complexes with bidentate substrates such as α-hydroxy carboxylic acids and α-aminoacid derivatives (e.g., **19**-**20**, Figure 2).[19,20] Notably, this sort of condensation process has been employed in the design of chiral oxazaborolidinone catalysts (**20**). Thus, it is not surprising that in the reaction of Fmoc-alanine (**15**), a complex **21** between **15** and catalyst **6** could form (Figure 2). This complexation leads to inhibition of the catalyst by the substrate and can explain the failure of monoprotected, primary aminoacids such as **15** to undergo the boronic acid catalyzed direct amidation.

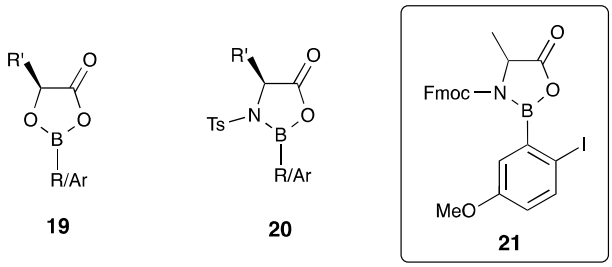
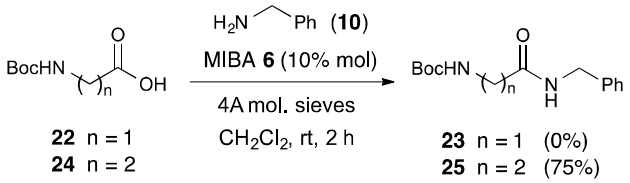


Figure 2. Complexation between α-hydroxy and α-amino carboxylic acids with boronic acids.

The same failure was observed with a Boc-protected primary α-aminoacid, glycine (**22**, Scheme 4). In contrast, the corresponding β-aminoacid β-alanine (**24**) was successfully coupled with benzylamine, indicating that inhibition by boronic acid complexation is not a major issue with monoprotected β-aminoacids probably because of the lesser stability of the resulting 6-membered complexes.



Scheme 4. Coupling of Boc-glycine and Boc-β-alanine with benzylamine catalyzed by **6**.

For this direct amidation to become applicable to the preparation of α-peptides, the inhibitory complexation of the catalyst must be prevented. Initially, the use of additives such as diols that could break the undesired complex (*cf*, **21**) and provide a way to cycle the catalyst was attempted, however in vain. We then turned our efforts towards engineering suitable α-aminoacid substrates to avoid the monoprotected derivatives that provide a free NH unit responsible for covalent complexation of the catalyst. Thus, we considered the use of doubly protected α-amino acids such as N-phthaloyl α-aminoacids and amine surrogates like α-azidoacids (Figure 3). Being devoid of a free NH, complexation of the boronic acid should be prevented, thus allowing the catalytic amidation to proceed through the expected acylborate intermediate.

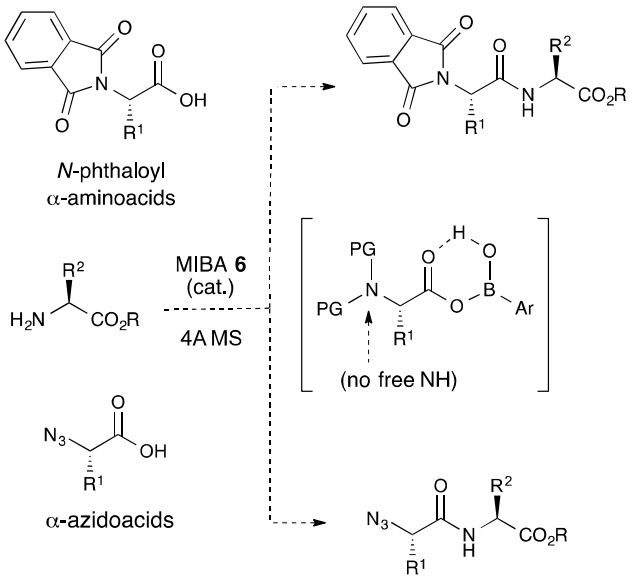
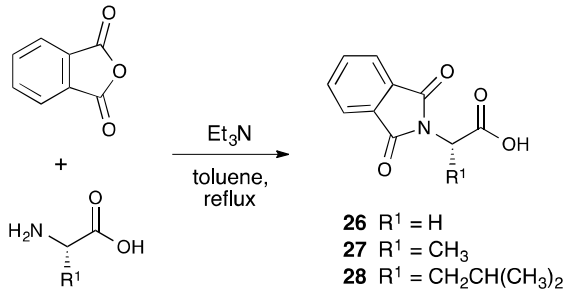


Figure 3. Substrate modifications to avoid inhibitory complexation of the boronic acid catalyst.

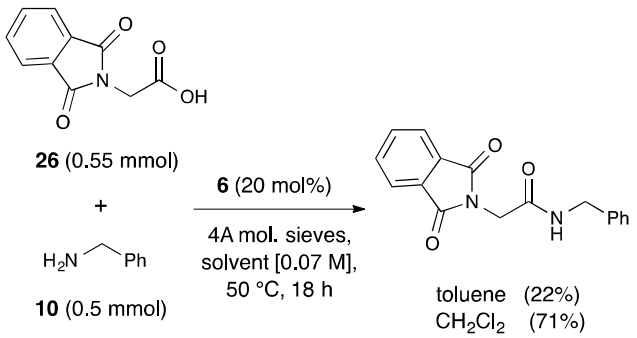
Synthesis of α-dipeptides from *N*-phthaloyl α-aminoacids.

To test the viability of N-phthaloyl α-aminoacids, we planned to prepare a few simple model residues like Gly, Ala, and Val, and attempt their coupling with α-aminoesters. The requisite *N*-phthaloyl amino acids were easily prepared from phthallic anhydride as shown in Scheme 5.



Scheme 5. Synthesis of double *N*-protected α-amino acid.

As discussed above, the optimal reaction solvent in the boronic acid catalyzed amidation varies depending on the particular combination of substrates employed.[15] Therefore, it was necessary to first identify the preferred solvent (typically, CH_2Cl_2 and toluene) for the coupling of newly prepared N-phthaloyl aminoacids. In the event, the MIBA-catalyzed amidation between N-phthaloyl glycine (**26**) and benzylamine (**10**) revealed a clear preference for CH_2Cl_2 as the most effective solvent (Scheme 6).



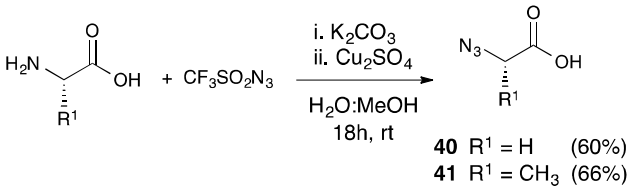
Scheme 6. Optimization of solvent for amidation of doubly protected N-phthaloyl α-amino acids. Note. Indicated temperature is oil bath temperature (CH_2Cl_2 reflux temperature: 40 °C).

The corresponding three aminoesters (Gly, Ala, Val) were selected as the amine fragment, with *tert*-butoxy protection because of the orthogonality of deprotection methods (TFA for the *t*-butoxy ester and hydrazine for the N-phthaloyl). Then, different combinations of both aminoacid fragments were subjected to the optimized reaction conditions to prepare the corresponding α-dipeptides. Because it is a study of substrate scope, the original reaction conditions at low concentration were employed. To ensure reaction completion in the case of slower amino acid substrates, an arbitrary reaction time of 48 h was chosen. The results are summarized in Figure 4. It was shown possible to couple *N*-terminal to *C*-terminal protected amino acids in good to moderate yields at a reflux temperature (40 °C) in CH_2Cl_2. Even highly hindered residues, exemplified by valine (**28** and **31**), were successfully employed to make amide products using this simple and atom-economical process. However, increased steric bulk in both the *N*-phthaloyl aminoacid or the aminoester had a major negative impact on the yield. The yields decreased continually from 60% for the Gly-Gly dipeptide **32** to 28% to the most hindered Val-Val dipeptide **39**.

Synthesis of α-dipeptides from α-azido carboxylic acids.

As described above, in addition to N-phthaloyl α-aminoacids, α-azidoacids were also considered as a viable masked form of α-aminoacids. As with the N-phthaloyl α-aminoacids, we planned to prepare just a few simple residues for a preliminary study of boronic acid catalyzed coupling with α-aminoesters. The requisite α-azido acids **40** and **41** were easily prepared

according to literature procedures as shown in Scheme 7.



Scheme 7. Synthesis of α-azido acids.

Before embarking into a study of substrate scope, we briefly compared the most common solvents for the boronic acid catalyzed amidation by using α-azidoalanine and glycine *t*-butyl ester as model substrates (Scheme 8). This comparison revealed that toluene would be the favored solvent for the coupling of α-azido acids.

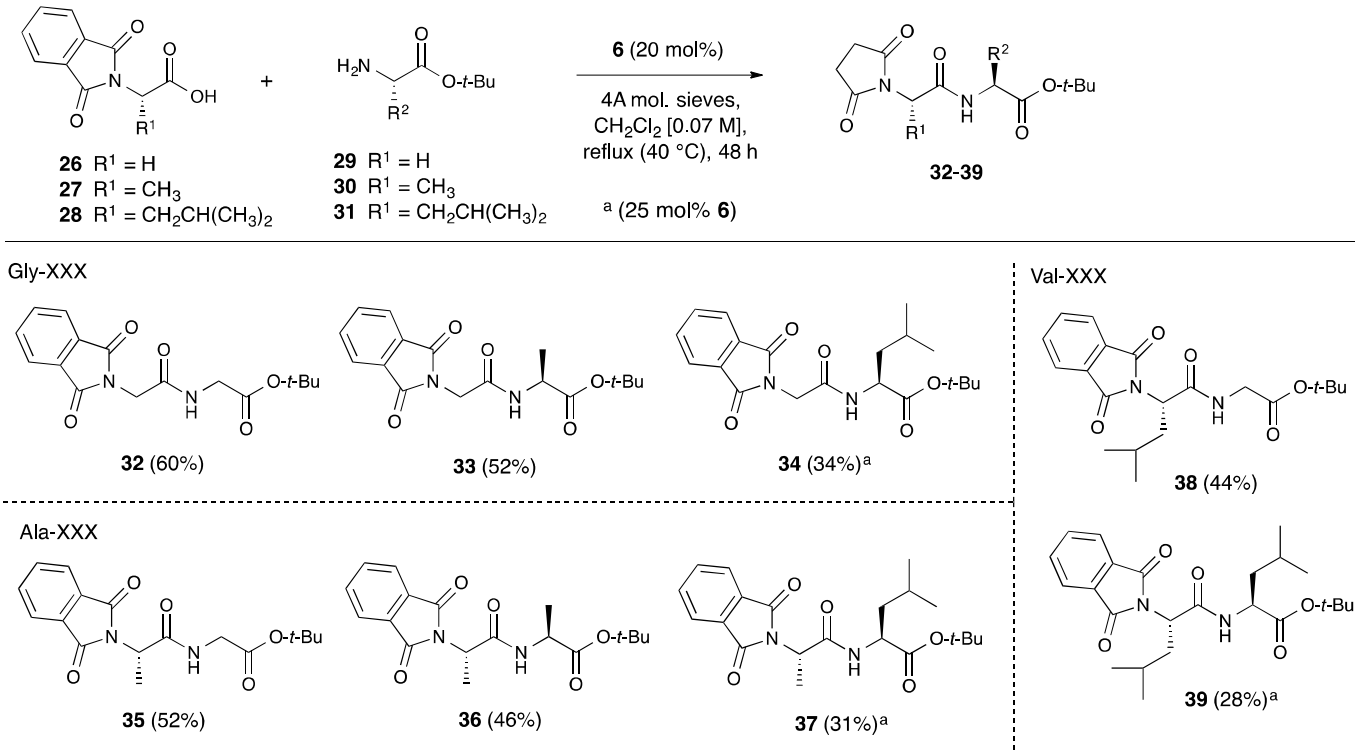
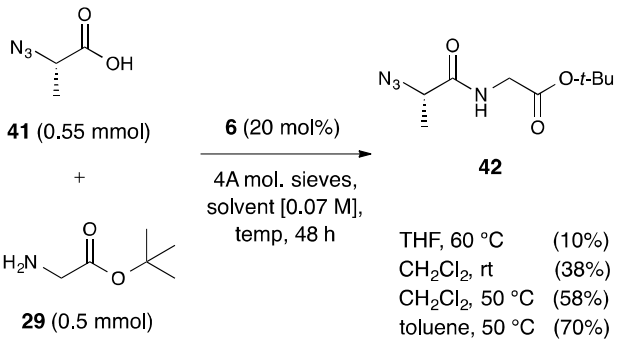


Figure 4. Direct amidations between doubly *N*-protected α-phthaloyl amino acids and *C*-protected α-amino acids (as free amines) catalyzed by boronic acid **6** at 50 °C.



Scheme 8. Solvent optimization for the coupling of α-azidoacids. Note. Indicated temperature is oil bath temperature (CH_2Cl_2 reflux temperature: 40 °C).

Along with the successful example of Scheme 8, the examples compiled in Figure 5 provide a promising glimpse of the potential of α-azido acids towards a direct boronic acid catalyzed synthesis of peptides. All amide products **42**–**46** were isolated in pure form and moderate yields after simple acid-base extractions. Although residues with functionalized side-chains were not tested as yet, the isolation of **46** demonstrates that α-substituted residues can be utilized.

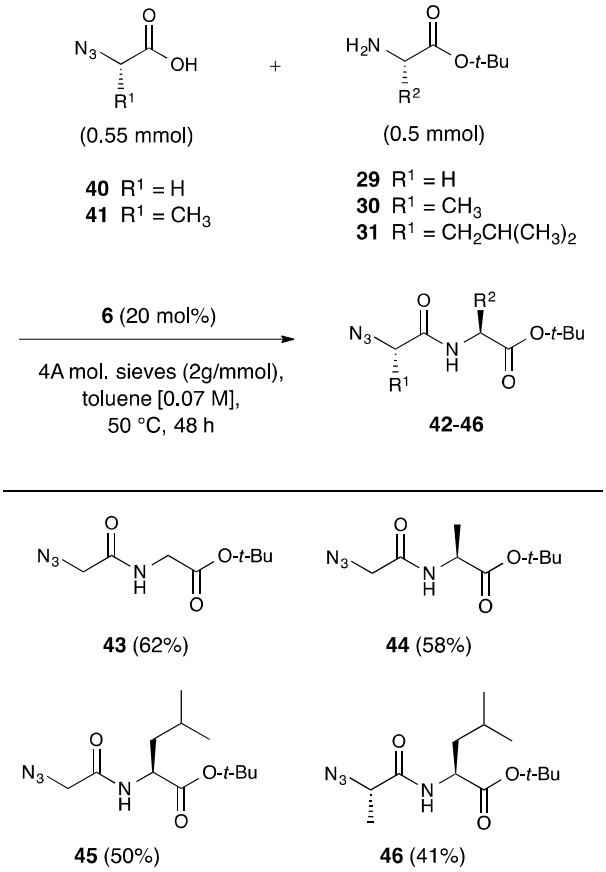
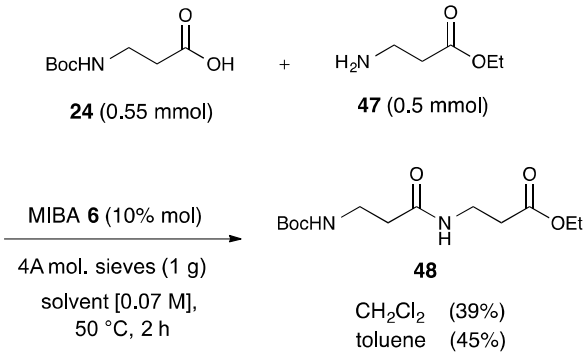


Figure 5. Direct amidations between α-azido acids and *C*-protected α-aminoesters (as free amines) catalyzed by boronic acid **6** at 50 °C.

Application to the synthesis of beta-dipeptides.

Evaluation of substrate scope.

As discussed above (cf., Scheme 4), β-aminoacids do not require double N-protection. A quick examination of solvents for the coupling of Boc-β-alanine with β-alanine ethyl ester, under a short reaction time of 2 hours at 50 °C, indicated that toluene is an appropriate solvent for the preparation of β-peptides (Scheme 9).



Scheme 9. Solvent optimization for the amidation of a monoprotected *N*-Boc β-amino acid. Note. Indicated temperature is oil bath temperature (CH_2Cl_2 reflux temperature: 40 °C).

As performed in the case of α-peptides, the steric tolerance of this direct amidation method was examined using a small panel of β-amino acids and β-aminoesters. The outcome, shown in Figure 6, is similar to the coupling of α-aminoacids. For the same reaction time, the yield of amide products decreases slightly with an increase of branching in the coupling partners.

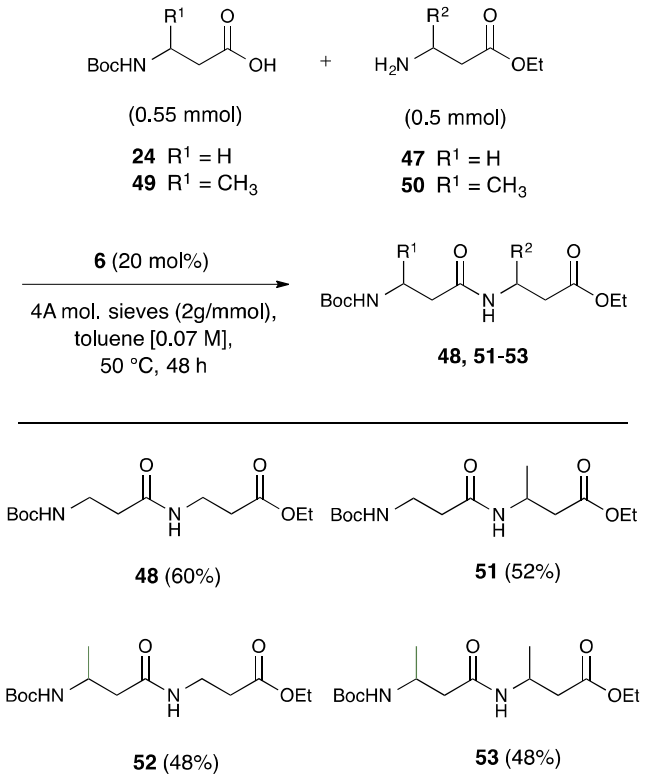
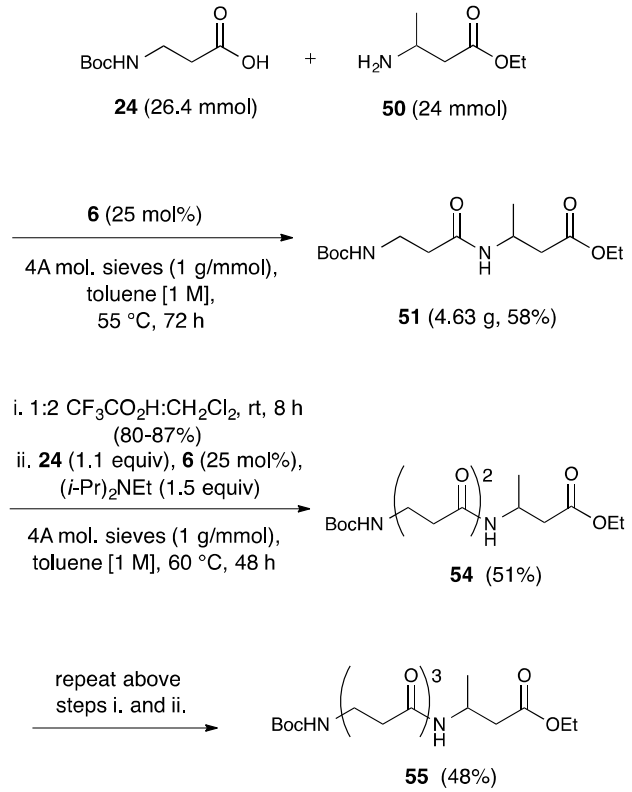


Figure 6. Direct amidations between *N*-Boc protected β-amino acid and *C*-protected β-amino acid (as free amines) catalyzed by boronic acid **6** at 50 °C.

Multigram preparation of a β–peptide.

The successful multigram scale results of Scheme 1 were obtained with unfunctionalized substrates. To demonstrate the suitability of our larger-scale procedure on functionalized substrates, we targeted the preparation of a **β**-dipeptide between N-Boc β-alanine **24** as the carboxylic acid partner, and β-amino ethyl ester **50** as the amine partner (Scheme 10). Although a slightly higher catalyst loading and a longer reaction

time was required at this scale, dipeptide **51** was obtained from 5 grams (26.4 mmol) of Boc-β-alanine (**24**) in a yield that is actually higher than the exploratory scale of Figure 6. This example, which was achieved with the optimal procedure featuring a decreased quantity of molecular sieves (1 vs 2 g/mmol) at a high concentration of 1 M in toluene, demonstrates the scalability of the direct amidation methodology catalyzed by MIBA (**6**). From β-dipeptide **51**, the possibility for preparing longer peptides was tested with a double-elongation affording tetra-β-peptide **55** in yields similar to that obtained for the first coupling of aminoester **50**.



Scheme 10. Scale up synthesis of β-dipeptide **51** using 5.0 g (26.4 mmol) of Boc-β-Ala-OH (**24**) by a direct amidation catalyzed by **6,** followed by elongation to β-tetrapeptide **55**.

Conclusions

This article described the identification of more economical, practical conditions for a direct amidation using 5-methoxy-2-iodophenylboronic acid (MIBA, **6**) as the catalyst. It is now possible to use half of the quantity of molecular sieves prescribed in the original procedure, at a higher concentration leading to a reduction of waste and a substantially improved E-factor. This mild and operationally simple procedure was successfully validated in the multigram scale preparation of prototypical amides using toluene as a relatively green solvent. The feasibility of the MIBA-catalyzed direct amidation was evaluated in the coupling of α- and β-aminoacids. Because of substrate inhibition of the catalyst with monoprotected α-aminoacids, the use of doubly-protected N-phthaloyl α-aminoacids or α-azidoacids is required in order to produce α-dipeptide products in moderate yields. β-Aminoacids do not suffer from this problem, and Boc-β-aminoacids could be coupled successfully. As observed previously, each substrate class often require a different optimal solvent (e.g., toluene or dicholoromethane) but toluene, an environmentally acceptable solvent, is usually the most suitable one. Of note, unlike other boronic acid catalysts, the remarkable ability of boronic acid **6** to act as a catalyst under ambient and low-heating conditions most likely played a key role in preventing any epimerization of α-aminoacid derivatives. Furthermore, this procedure generates only water as a by-product, and affords pure dipeptide products after a simple filtration and acid–base extractions to remove any unreacted substrates and recover the recyclable catalyst. In conclusion, although improved catalysts and an alternate water-removal strategy may be desirable in order to provide a general, practical, and higher-yielding methodology for the direct synthesis of α- and β-peptides, this study makes a significant step towards this important objective.

Experimental section

General information.

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. Dry toluene, THF and dichloromethane were obtained from a double cartridge solvent purification system. The indicated reaction temperature is that of the oil bath. Analytical thin layer chromatography was performed on Merck Silica Gel 60 F254 plates and was visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on 400, or 500 MHz instruments. The residual solvent protons (^1H) or the solvent carbon (^{13}C) were used as internal standards. ^1H-NMR data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant (*J*), integration). The following

abbreviations are used in reporting NMR data: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, m = multiplet, q = quartet, qd = quartet of doublets, qdt = quartet of doublet of triplets, qt = quartet of triplets, app = apparent, br. s = broad singlet. Estimated accuracy of *J*: (+/–) 0.5 Hz. High-resolution mass spectra (TOF analyzer) were recorded using either electron impact (EI) or electrospray ionization (ESI) techniques. Infrared spectra were obtained with frequencies expressed in cm^{-1}. Infrared spectra were obtained on a Nicolet Magna-IR 750 with frequencies expressed in cm^{-1}. The enantiomeric excesses for chiral compounds were determined using a HPLC Agilent instrument using Chiralcel-OD or Chiralpak-AS columns under UV detection (in comparison to racemic products). Powdered 4A molecular sieves (< 5 micron, Aldrich) were dried overnight in an oven (300 °C) for >12 h prior to use. All the different catalysts were stored in a fridge, under inert atmosphere.

General Procedure for Table 1 (Optimization of Amount of Molecular Sieves and Solvent) and Tables 2 (Optimization of Reaction Solvent and Temperature). Into a 25 ml round bottom flask equipped with a stir bar was added phenyl acetic acid (**7**) (75.0 mg, 0.55 mmol, 1.1 equiv), 5-methoxy-2-iodophenylboronic acid (**6**) (13.9 mg, 0.05 mmol, 10 mol%) and the indicated amount of activated 4A molecular sieves. Solvent (in the indicated concentration) was added and the mixture was stirred for 10 min. Then, pyrrolidine (**8**) (41 μL, 0.50 mmol, 1.0 equiv) was added. The resulting mixture was stirred for 18-48 h at room temperature. The reaction mixture was filtered through a pad of Celite® 545, which was rinsed with CH_2Cl_2 (15 ml). The filtrate was then washed with 1M aqueous acidic solution (15 ml), 1M aqueous basic solution (15 ml) and brine (15 ml). The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and evaporated to yield pure amide product **9**.

General Procedure for Table 2 (Optimization of the reaction solvent and temperature in a model amidation reaction catalyzed by 6). Into a 25 ml round bottom flask equipped with a stir bar was added phenyl acetic acid (**7**) (75.0 mg, 0.55 mmol, 1.1 equiv), 5-methoxy-2-iodophenylboronic acid (**6**) (13.9 mg, 0.05 mmol, 10 mol%) and 0.5 g of activated 4A molecular sieves. Solvent [1 M] was added and the mixture was stirred for 10 min. Then, pyrrolidine (8) (41 μL, 0.50 mmol, 1.0 equiv) was added. The resulting mixture was stirred for 18 h at room temperature or 50 °C. The reaction mixture was filtered through a pad of Celite® 545, which was rinsed with CH_2Cl_2 (15 ml). The filtrate was then washed with 1M aqueous acidic solution (15 ml), 1M aqueous basic solution (15 ml) and brine (15 ml). The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and evaporated to yield the pure amide product **9**.

General Procedure for Multigram Organocatalytic Direct Amidation (Scheme 1). Into a 250 mL round bottom flask equipped with a stir bar was added phenylacetic acid (**7**) (36 mmol, 1.1 equiv), 5-methoxy-2-iodophenylboronic acid (6) (3.3 mmol, 10 mol%) and 33 g (1 g per mmol of amine substrate) of activated 4A molecular sieves. Toluene was added to maintain a concentration at 1 M and the mixture was stirred. After 10 minutes, the amine (33 mmol, 1.0 equiv) was added. The resulting mixture was stirred for 18 h at 50 °C. The reaction mixture was filtered through a pad of Celite 545, which was rinsed with CH_2Cl_2 (50 ml). The filtrate was washed with a 1M aqueous acidic solution (4 x 50 ml), 1M aqueous basic solution (4 x 50 ml) and brine (50 ml). The combined aqueous solutions were back extracted with CH_2Cl_2 (4 x 50 mL), then the combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness to yield the title amide product.

Preparation and Characterization Data of Phenyl-1-pyrrolidin-1-yl-ethanone (9). The title compound was prepared using the general procedure for the multigram organocatalytic amidations, affording 2.893 g of product **9** in a 46% yield, 1.83 g in 29% yield, in toluene and CH_2Cl_2 respectively. Characterization data of the product matched that found in the literature.[21]

Preparation and Characterization Data of N-Benzyl-2-phenyl-acetamide (11). The title compound was prepared using the general procedure for the multigram organocatalytic amidations, affording 6.693 g of **11** and 89% yield, 5.415 g of **11** and 72% yield, in toluene and CH_2Cl_2 respectively. Characterization data of the product matched that found in the literature.[22]

General Procedure for Table 3: Comparison of product yields for catalysts 4-6 in a direct amidation reaction between

(Boc)-proline and benzylamine. Into a 25 ml round bottom flask equipped with a stir bar was added *N-tert*-butyloxycarbonyl(Boc)-proline (**12**) (108 mg, 0.50 mmol, 1.0 equiv), catalysts 4-6 (0.1 mmol, 20 mol%) and 1 g of activated 4A or 3A molecular sieves. Solvent [0.07 M] was added to the mixture and was stirred for 10 min. Then, benzylamine (**10**) (55 μL, 0.5 mmol, 1.0 equiv) was added. The resulting mixture was stirred for 18 h at 50 or 85 °C. The reaction mixture was filtered through a pad of Celite ® 545, which was rinsed with CH_2Cl_2 (50 ml). The filtrate was washed with a 1M aqueous acidic solution (15 ml), 1M aqueous basic solution (15 ml) and brine (15 ml). The organic layer collected, dried over anhydrous Na_2SO_4, filtered and evaporated to yield the title compound **13** as a pure product. Characterization data of the product matched that found in the literature.[16]

General Procedure for Study of Stereochemical Integrity (Table 4). Into a 25 ml round bottom flask equipped with a stir bar was added N-Boc proline (**13**) or phenylacetic acid (**14**) (0.55 mmol, 1.1 equiv), 5-methoxy-2-iodophenylboronic acid (**6**) (0.10 mmol, 20 mol%), and benzyl amine (**10**) or phenylalanine methyl ester hydrochloride (0.50 mmol, 1.0 equiv) pre-neutralized with *i*-Pr_2NEt (0.50 mmol, 1.0 equiv) were stirred at 50 °C for 18 h in dry CH_2Cl_2 containing 1 g of activated 4A molecular sieves. The reaction mixture was filtered through a pad of Celite ® 545, which was rinsed with CH_2Cl_2 (15 ml). The filtrate was washed with a 1M aqueous acidic solution (15 ml), 1M aqueous basic solution (15 ml) and brine (15 ml). The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and evaporated to yield the pure amide products **13** and **14**. Characterization data of the products matched that found in the literature.[16] HPLC analysis for **13**: Chiralcel IB, 50:50 H_2O/CH_3CN, 0.5 mL/minute, λ = 250 nm, T_{major} = 20.8 min, T_{minor} = 20.1 min, ee = 95%. HPLC analysis for **14**: Chiralcel IC, 50:50 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 17.9 min, T_{minor} = 9.2 min, ee = 100%.

General Procedure and Product Characterization for Scheme 3 (Coupling of Fmoc α-aminoacids with benzylamine catalyzed by 6). Into a 25 mL round-bottom flask equipped with a magnetic stir bar was added Fmoc-N-Me-L-Leu-OH (202 mg, 0.55 mmol, 1.1 equiv), 5-methoxy-2-iodophenylboronic acid **6** (14 mg, 0.05 mmol, 10 mol%) and 1 g of activated 4A molecular sieves. Dichloromethane (7 mL) was added, and the mixture was stirred vigorously for 10 min. Then, benzylamine (**10**) (55 μL, 0.50 mmol, 1.0 equiv) was added to the reaction mixture using a gastight 100-μL syringe. The resulting solution was stirred for 12 h at room temperature. The reaction mixture was filtered through a pad of Celite 545, which was rinsed with CH_2Cl_2 (15 ml). The filtrate was washed sequentially with a 1M aqueous acidic solution (15 ml), 1M aqueous basic solution (15 ml) and brine (15 ml). The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and evaporated to yield product **18** (0.196 g, 86% yield).

General Procedure and Product Characterization for Scheme 4 (Coupling of Boc-glycine and Boc-β-alanine with benzylamine catalyzed by 6). Into a 25 mL round-bottom flask equipped with a magnetic stir bar was added Boc-β-Alanine (104 mg, 0.55 mmol, 1.1 equiv), 5-methoxy-2-iodophenylboronic acid **6** (14 mg, 0.05 mmol, 10 mol%) and 1 g of activated 4A molecular sieves. Dichloromethane (7 mL) was added and the mixture was stirred vigorously for 10 min. Then, benzylamine (55 μL, 0.50 mmol, 1.0 equiv) was added to the reaction mixture using a Gastight® 100-μL syringe. The resulting solution was stirred for 2 h at room temperature. The reaction mixture was filtered through a pad of Celite 545, which was rinsed with CH_2Cl_2 (50 ml). The filtrate was washed sequentially with a 1M aqueous acidic solution (15 ml), 1M aqueous basic solution (15 ml) and brine (15 ml). The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and evaporated to yield pure product **25**. *t*-Butyl (3-(Benzylamino)-3-oxopropyl)carbamate **25**. This compound was prepared using the coupling of Boc-β-alanine with benzylamine catalyzed by **6**. Yield: 86%. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.32 (m, 5 H), 6.02 (br. s, 1 H), 5.21 (br. s, 1 H), 4.42 (d, J = 5.7 Hz, 2H), 3.42 (dt, J = 6.2, 6.0 Hz, 2H), 2.41 (t, J = 6.0 Hz, 2 H), 1.43 (s, 9H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 171.2, 156.1, 138.1, 128.8, 127.9, 127.6, 79.4, 43.6, 36.7, 36.3, 28.4 (3 C); **IR** (Microscope, cm^{-1}) 3289, 3087, 2949, 2921, 1776, 1728, 1660, 1561; **HRMS** (ESI) for $C_{15}H_{23}N_2O_3$ $(M+H)^+$: calcd. 279.1703; found, 279.1700.

General Procedure for Preparation of L-*N*-Phthaloyl Amino Acids 26-28 (Scheme 5). These substrates were prepared as described in reference 23. Characterization data of the product matched that found in the literature.[23]

General Procedure for Preparation of L-α-Azido Acids Acids 40 and 41 (Scheme 7). These substrates were prepared as described in reference 24. Characterization data of the product matched that found in the literature.[24] **CAUTION:** These low C+O/N ratio compounds are potentially explosive. They were prepared according to recommended safety precautions for preparing and handling small organic azides, in a small scale (< 1 g), and they were employed immediately after isolation.

General Procedure for Dipeptide Synthesis Using Catalyst 6 (Figures 4-6). Into a 25 mL round-bottom flask equipped with a magnetic stir bar was added the L-α-azido/*N*-phthaloyl amino acid or β-*N*-Boc amino acid (0.55 mmol, 1.1 equiv), 2-iodo-5-methoxyphenylboronic acid **6** (0.10 mmol, 20 mol%) and 1 g of activated 4A molecular sieves. Dichloromethane or toluene (7 mL) was added (see the respective figures), and the mixture was stirred vigorously for 10 min. Then, *α* or *β*-amino alkyl ester (0.50 mmol, 1.0 equiv) was added to the reaction mixture using a gastight 100-μL syringe. The resulting solution was stirred for 48 h in a sealed flask at 50 °C temperature. The reaction mixture was filtered through a pad of Celite 545, which was rinsed with CH_2Cl_2 (50 ml). The filtrate was washed sequentially with a 1M aqueous acidic solution (2 x 15 ml), 1M aqueous basic solution (2 x 15 ml) and brine (2 x 15 ml). The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and evaporated to yield dipeptide products in a satisfactory level of purity.

t-Butyl (2-(1,3-Dioxoisoindolin-2-yl)acetyl)glycinate ***32.*** The title compound was prepared using the general procedure for dipeptide synthesis and CH_2Cl_2 as a solvent. Yield: 60%. M.p. 165-166 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.89 (m, 2 H), 7.78 (m, 2 H), 6.40 (br. s, 1 H), 4.40 (s, 2 H), 3.98 (d, J = 4.8 Hz, 2 H), 1.42 (s, 9 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 168.6, 167.8, 165.9, 134.2, 132.0, 123.6, 82.6, 42.4, 40.6, 28.0 (3 C); **IR** (Microscope, cm^{-1}) 3306, 3087, 2976, 2931, 1776, 1728, 1660, 1561; **HRMS** (ESI) for $C_{16}H_{19}N_2O_5$ $(M+H)^+$: calcd. 319.1288; found, 319.1290.

t-Butyl (2-(1,3-Dioxoisoindolin-2-yl)acetyl)-L-alaninate ***33.*** The title compound was prepared using the general procedure for dipeptide synthesis and CH_2Cl_2 as a solvent. Yield: 52%. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.89 (m, 2 H), 7.78 (m, 2 H), 6.60 (br. d, J = 6.9 Hz, 1 H), 4.48 (app pent, J = 7.0 Hz, 1 H), 4.38 (m, 2 H), 1.76 (s, 9 H), 1.42 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 169.0, 168.9, 167.8, 134.3, 131.9, 123.6, 82.5, 49.3, 42.4, 28.0 (3 C), 15.3; **IR** (Microscope, cm^{-1}) 3306, 3067, 2980, 2936, 1776, 1725, 1650, 1540; **HRMS** (ESI) for $C_{17}H_{21}N_2O_5$ $(M+H)^+$: calcd. 333.1445; found, 333.1445.

t-Butyl (2-(1,3-Dioxoisoindolin-2-yl)acetyl)-L-leucinate ***34.*** The title compound was prepared using the general procedure for dipeptide synthesis, **6** as a catalyst (25 mol%) and CH_2Cl_2 as a solvent. Yield: 34%. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.89 (m, 2 H), 7.78 (m, 2 H), 6.20 (br. d, J = 8.2 Hz 1 H), 4.54 (ddd, J = 8.2, 8.1, 5.7 Hz, 1 H), 4.40 (m, 2 H), 1.50-1.70 (m, 3 H), 1.42 (s, 9 H), 0.96 (d, J = 6.5 Hz, 6 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 171.9, 167.7, 165.4, 134.2, 132.1, 123.6, 82.3, 51.7, 42.2, 40.7, 28.0 (3 C), 24.9, 22.7, 22.3; **IR** (Microscope, cm^{-1}) 3333, 3067, 2959, 2871, 1776, 1725, 1543, 1468; **HRMS** (ESI) for $C_{20}H_{27}N_2O_5$ $(M+H)^+$: calcd. 375.1914; found, 375.1914.

t-Butyl (S)-(2-(1,3-Dioxoisoindolin-2-yl)propanoyl)glycinate ***35.*** The title compound was prepared using the general procedure for dipeptide synthesis and CH_2Cl_2 as a solvent. Yield: 52%. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.89 (m, 2 H), 7.78 (m, 2 H), 6.58 (br. s, 1 H), 5.00 (q, J = 7.2 Hz, 1 H), 3.90 (d, J = 4.8 Hz, 2 H), 1.80 (d, J = 7.3 Hz, 3 H), 1.42 (s, 9 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 169.0, 168.7, 167.8, 134.3, 131.9, 123.6, 82.6, 49.3, 42.4, 28.0 (3 C), 15.3; **IR** (Microscope, cm^{-1}) 2967, 1596, 1458, 1377, 1265, 1232, 998; **HRMS** (ESI) for $C_{17}H_{21}N_2O_5$ $(M+H)^+$: calcd. 333.1445; found, 333.1445.

t-Butyl ((S)-2-(1,3-Dioxoisoindolin-2-yl)propanoyl)-L-alaninate ***36.*** The title compound was prepared using the general procedure for dipeptide synthesis and CH_2Cl_2 as a solvent. Yield: 46%. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.89 (m, 2 H), 7.78 (m, 2 H), 6.62 (br. s, 1 H), 4.90 (q, J = 7.3 Hz, 1 H), 4.40 (m, 1 H), 1.78 (d, J = 7.3 Hz, 3 H), 1.42 (s, 9 H), 1.40 (d, J = 7.0 Hz, 3 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 172.0, 168.3, 167.8, 134.2, 131.9, 123.6, 82.2, 49.3, 49.0, 28.5 (3 C), 18.6, 15.3; **IR** (Microscope, cm^{-1}) 3347, 3063, 2980, 2936, 1715, 1682, 1531, 1457; **HRMS** (ESI) for $C_{18}H_{23}N_2O_5$ $(M+H)^+$: calcd. 347.1601; found, 347.1602.

t-Butyl ((S)-2-(1,3-Dioxoisoindolin-2-yl)propanoyl)-L-leucinate ***37.*** The title compound was prepared using the general procedure for dipeptide synthesis, **6** as the catalyst (25 mol%) and CH_2Cl_2 as a

solvent. Yield: 31%. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.89 (m, 2 H), 7.78 (m, 2 H), 6.42 (br. S, 1 H), 4.96 (q, J = 7.5 Hz, 1 H), 4.45 (m, 1 H), 1.75 (d, J = 7.3 Hz, 3 H), 1.43-1.68 (m, 3 H), 1.42 (s, 9 H), 0.94 (d, J = 6.3 Hz, 6 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 171.8, 168.6, 167.7, 134.2, 131.9, 123.5, 82.0, 53.8, 51.7, 42.0, 28.0 (3 C), 24.9, 22.7, 22.3, 15.3; **IR** (Microscope, cm^{-1}) 3356, 3066, 2960, 2872, 1780, 1718, 1684, 1531, 1469; **HRMS** (ESI) for $C_{21}H_{29}N_2O_5$ $(M+H)^+$: calcd. 389.2071; found, 389.2064.

t-Butyl (S)-(2-(1,3-Dioxoisoindolin-2-yl)-4-methylpentanoyl)glycinate ***38.*** The title compound was prepared using the general procedure for dipeptide synthesis and CH_2Cl_2 as a solvent. Yield: 44%. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.89 (m, 2 H), 7.78 (m, 2 H), 6.65 (br. s, 1 H), 4.49 (dd, J = 11.4, 4.8 Hz, 1 H), 3.90 (d, J = 4.8 Hz, 2 H), 2.42 (ddd, J = 13.9, 11.4, 4.4 Hz, 1 H), 1.83 (ddd, J = 14.0, 9.6, 4.8 Hz, 1 H), 1.44-1.49 (m, 1 H), 1.42 (s, 9 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.94 (d, J = 6.6 Hz, 3 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 169.2, 168.7, 168.2, 134.2, 131.7, 123.6, 82.4, 53.0, 42.3, 37.4, 28.0 (3 C), 25.3, 23.1, 21.2; **IR** (Microscope, cm^{-1}) 3342, 3067, 2962, 2873, 1716, 1681, 1537, 1469; **HRMS** (ESI) for $C_{20}H_{27}N_2O_5$ $(M+H)^+$: calcd. 375.1914; found, 375.1916.

t-Butyl ((S)-2-(1,3-Dioxoisoindolin-2-yl)-4-methylpentanoyl)-L-leucinate ***39.*** The title compound was prepared using the general procedure for dipeptide synthesis, **6** as the catalyst (25 mol%) and CH_2Cl_2 as solvent. Yield: 28%. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.89 (m, 2 H), 7.78 (m, 2 H), 6.60 (br. d, J = 8.0 Hz, 1 H), 4.94 (dd, J = 11.3, 5.0 Hz, 1 H), 4.50 (ddd, J = 13.5, 7.5, 5.3 Hz, 1 H), 1.43-1.70 (m, 6 H), 1.42 (s, 9 H), 0.94 (m, 12 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 171.3, 168.3, 167.7, 133.8, 131.2, 123.1, 81.5, 52.7, 51.2, 41.5, 37.0, 27.5 (3 C), 24.8, 24.5, 22.6, 22.4, 21.7, 20.8; **IR** (Microscope, cm^{-1}) 3348, 3062, 2959, 2872, 1717, 1683, 1529, 1469; **HRMS** (ESI) for $C_{24}H_{35}N_2O_5$ $(M+H)^+$: calcd. 431.2540; found, 431.2539.

t-Butyl (S)-(2-Azidopropanoyl)glycinate ***42.*** The title compound was prepared using the general procedure for dipeptide synthesis and toluene as the solvent. Yield: 70%. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.80 (br. s, 1 H), 4.15 (q, J = 7.0 Hz, 1 H), 3.95 (d, J = 5.1 Hz, 1 H), 3.94 (d, J = 5.2 Hz, 1 H), 1.58 (d, J = 7.0 Hz, 3 H), 1.45 (s, 9 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 169.9, 168.5, 82.6, 59.0, 41.9, 28.0 (3 C), 17.0; **IR** (Microscope, cm^{-1}) 3306, 3094, 2981, 2935, 2110, 1743, 1665, 1540, 1478; **HRMS** (ESI) for $C_9H_{16}N_4NaO_3$ $(M+Na)^+$: calcd. 251.1115; found, 251.1117.

t-Butyl (2-Azidoacetyl)glycinate ***43.*** The title compound was prepared using the general procedure for dipeptide synthesis and toluene as the solvent. Yield: 62%. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.80 (br. s, 1 H), 4.00 (s, 2 H), 3.98 (d, J = 5.3 Hz, 2 H), 1.51 (s, 9 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 168.0, 166.2, 82.2, 52.1, 41.3, 27.6 (3 C); **IR** (Microscope, cm^{-1}) 3323, 3082, 2979, 2935, 1735, 1716, 1653, 1527, 1449; **HRMS** (ESI) for $C_8H_{14}N_4NaO_3$ $(M+Na)^+$: calcd. 237.0958; found, 237.0956.

t-Butyl (2-Azidoacetyl)-L-alaninate ***44.*** The title compound was prepared using the general procedure for dipeptide synthesis and toluene as the solvent. Yield: 58%. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.90 (br. s, 1 H), 4.51 (app. pent, J = 7.2, 1 H), 4.00 (s, 2 H), 1.51 (s, 9 H), 1.41 (d, J = 7.2 Hz, 3 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 171.7, 166.0, 82.4, 52.6, 48.6, 28.0 (3 C), 18.6; **IR** (Microscope, cm^{-1}) 3311, 3072, 2981, 2934, 2108, 1735, 1664, 1535, 1479; **HRMS** (ESI) for $C_9H_{16}N_4NaO_3$ $(M+Na)^+$: calcd. 251.1115; found, 251.1113.

t-Butyl (2-Azidoacetyl)-L-leucinate ***45.*** The title compound was prepared using the general procedure for dipeptide synthesis and toluene as the solvent. Yield: 50%. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.70 (br. d, J = 8.4 Hz, 1 H), 4.50 (ddd, J = 8.5, 8.5, 5.2 Hz, 1H), 4.00 (s, 2 H), 1.51-1.72 (m, 3 H), 1.46 (s, 9 H), 0.95 (d, J = 6.0 Hz, 3 H), 0.94 (d, J = 6.2 Hz, 3 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 171.7, 166.2, 82.2, 52.5, 52.1, 41.7, 27.6 (3 C), 24.9, 22.8, 22.0; **IR** (Microscope, cm^{-1}) 3317, 3070, 2961, 2935, 2107, 1736, 1665, 1537, 1471; **HRMS** (ESI) for $C_{12}H_{22}N_4NaO_3$ $(M+Na)^+$: calcd. 293.1584; found, 293.1585.

t-Butyl ((S)-2-Azidopropanoyl)-L-leucinate ***46.*** The title compound was prepared using the general procedure for dipeptide synthesis and toluene as the solvent. Yield: 41%. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.70 (br. s, 1 H), 4.47 (ddd, J = 8.4, 8.4, 5.3 Hz, 1 H), 4.08 (q, J = 7.0 Hz, 1 H), 1.60-1.70 (m, 3 H), 1.54 (d, J = 7.0 Hz, 3 H), 1.46 (s, 9 H), 0.95 (d, J = 6.5 Hz, 3 H), 0.94 (d, J = 6.0 Hz, 3 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 171.7, 169.4, 82.2, 59.2, 51.3, 41.7, 28.0 (3 C), 25.0, 22.7, 22.1, 17.1; **IR** (Microscope, cm^{-1}) 3311, 3082, 2960, 2873, 2115, 1737, 1660, 1536, 1470; **HRMS** (ESI) for $C_{13}H_{24}N_4NaO_3$ $(M+Na)^+$: calcd. 307.1741; found, 307.1741.

Ethyl 3-(3-((t-Butoxycarbonyl)amino)propanamido)propanoate ***48.*** The title compound was prepared using the general procedure for dipeptide synthesis and toluene as the solvent. Yield: 60%. M.p. 59-61 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.40 (br. s, 1 H), 5.20 (br. s, 1 H), 4.14 (q, J = 7.2 Hz, 2 H), 3.50 (td, J = 6.2, 6.2 Hz, 2 H), 3.36 (td, J = 6.2, 6.2 Hz, 2 H), 2.52 (t, J = 6.2 Hz, 2 H), 2.36 (t, J = 6.2 Hz, 2 H), 1.42 (s, 9 H), 1.22 (t, 7.2 Hz, 3 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 172.5, 171.4, 156.1, 79.2, 60.7, 36.7, 36.2, 34.8, 34.0, 28.4 (3 C), 14.1; **IR** (Microscope, cm^{-1}) 3323, 3082, 2979, 2935, 1735, 1716, 1653, 1527, 1449; **HRMS** (ESI) for $C_{13}H_{25}N_2O_5$ $(M+H)^+$: calcd. 289.1758; found, 289.1760.

Ethyl 3-(3-((t-Butoxycarbonyl)amino)propanamido)butanoate ***51.*** The title compound was prepared using the general procedure for dipeptide synthesis and toluene as the solvent. Yield: 52%. M.p. 64-66 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.20 (br. s, 1 H), 5.20 (br. s, 1 H), 4.38 (m, 1 H), 4.22 (q, J = 6.1 Hz, 2 H), 3.38 (dt, J = 6.2, 6.2 Hz, 2 H), 2.44 (d, J = 5.4 Hz, 2 H), 2.31 (t, J = 6.2 Hz, 2 H), 1.40 (s, 9 H), 1.25 (t, J = 6.6 Hz, 3 H), 1.20 (d, J = 6.7 Hz, 3 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 171.5, 170.4, 155.6, 78.7, 60.1, 41.5, 40.0, 36.1, 35.8, 27.9 (3C), 19.5, 13.6; **IR** (Microscope, cm^{-1}) 3311, 3078, 2979, 2935, 1736, 1716, 1648, 1529, 1454; **HRMS** (ESI) for $C_{14}H_{27}N_2O_5$ $(M+H)^+$: calcd. 303.1914; found, 303.1915.

Ethyl 3-(3-((t-Butoxycarbonyl)amino)butanamido)propanoate ***52.*** The title compound was prepared using the general procedure for dipeptide synthesis and toluene as the solvent. Yield: 48%. M.p. 65-67 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.40 (br. s, 1 H), 5.30 (br. s, 1 H), 4.25 (q, J = 7.3 Hz, 2 H), 3.94 (m, 1 H), 3.50 (td, J = 6.2, 6.2 Hz, 2 H), 2.54 (t, J = 6.2 Hz, 2 H), 2.38 (d, J = 5.7 Hz, 2 H), 1.40 (s, 9 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.20 (d, J = 6.8 Hz, 3 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 172.5, 170.9, 155.4, 79.2, 60.7, 44.1, 42.6, 34.8, 34.0, 28.4 (3 C), 20.5, 14.2; **IR** (Microscope, cm^{-1}) 3317, 3084, 2979, 2934, 1737, 1714, 1690, 1649, 1526, 1453; **HRMS** (ESI) for $C_{14}H_{27}N_2O_5$ $(M+H)^+$: calcd. 303.1914; found, 303.1912.

Ethyl 3-(3-((t-Butoxycarbonyl)amino)butanamido)butanoate ***53.*** The title compound was prepared using the general procedure for dipeptide synthesis and toluene as the solvent. Yield: 48%. M.p. 69-71 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.40 (br. s, 1 H), 5.30 (br. s, 1 H), 4.18 (m, 1 H), 4.11 (q, J = 7.2 Hz, 2 H), 3.96 (m, 1 H), 2.58 (m, 2 H), 2.38 (m, 2 H), 1.40 (s, 9 H), 1.22 (t, J = 7.1 Hz, 3 H), 1.15-1.20 (m, 6 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 171.6, 169.5, 154.9, 78.7, 60.6, 43.6, 42.3, 41.5, 39.5, 27.9 (3 C), 20.5, 19.5, 13.7; **IR** (Microscope, cm^{-1}) 3305, 3071, 2978, 2934, 1737, 1715, 1689, 1649, 1525, 1454; **HRMS** (ESI) for $C_{15}H_{29}N_2O_5$ $(M+H)^+$: calcd. 317.2071; found, 317.2070.

Multigram Scale Preparation and Characterization Data of Dipeptide 51 (Scheme 10). The title compound was prepared using catalyst **6** (25 mol%) and the general procedure for the multigram organocatalytic amidations, 5.0 g (26.4 mmol) of Boc-β-Ala-OH (**24**) and 3.25 mL (24.0 mmol) of 3-aminobutanoic acid ethyl ester (**50**), in toluene at 55 °C, affording 4.629 g of **51** in high purity and 58% yield.

General Procedure for the Boc-Deprotection of Scheme 10, step i. To the Boc-protected compounds **51** or **54** (3.00 mmol) at 0 °C was added a TFA:DCM solution (1:2 ratio, 0.3 M) and the mixture was stirred for 8 hours. The reaction mixture was concentrated under reduced pressure; affording products in 80%-87% yield.[25]

General Procedure and Product Characterization for the Synthesis of tri- and tetrapeptides 54 and 55 (Scheme 10, step ii). Into a 25 mL round-bottom flask equipped with a magnetic stirbar was added the β-*N*-Boc amino acid **24** (0.55 mmol, 1.1 equiv), 2-iodo-5-methoxyphenylboronic acid **6** (0.25 mmol) and 1 g of activated 4A molecular sieves. Toluene (7 mL) was added and the mixture was stirred vigorously for 1 hour. Then, the substrate from step i (0.50 mmol, 1.0 equiv) neutralized with DIPEA (1.50 mmol, 1.5 equiv), was cannulated to the reaction mixture. The resulting solution was stirred for 48 h in a sealed flask at 60 °C. The reaction mixture was allowed to cool down to room temperature and it was filtered through a pad of Celite 545, which was rinsed with CH_2Cl_2 (50 ml). The filtrate was washed sequentially with a 1M aqueous acidic solution (2 x 15 ml), 1M aqueous basic solution (2 x 15 ml) and brine (2 x 15 ml). The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and evaporated to yield dipeptide products in a satisfactory level of purity.

Ethyl 2,2,14-trimethyl-4,8,12-trioxo-3-oxa-5,9,13-triazahexadecan-16-oate ***54.*** The title compound was prepared using the

above general procedure for tripeptide synthesis. Yield: 51%. M.p. 86-88 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.70 (br. s, 1 H), 6.50 (br. s, 1 H), 5.20 (br. s, 1 H), 4.30 (m, 1 H), 4.22 (q, J = 7.2 Hz, 2 H), 3.30-3.60 (m, 4 H), 2.40-2.50 (m, 6 H), 1.40 (s, 9 H), 1.22 (t, J = 7.2 Hz, 3 H), 1.21 (d, J = 6.8 Hz, 3 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 171.4, 171.0, 170.3, 155.6, 78.8, 60.3, 41.8, 39.9, 36.4, 35.9, 35.5, 35.1, 27.9 (3C), 19.7, 13.6; **IR** (Microscope, cm^{-1}) 3323, 3275, 3075, 2978, 2931, 1737, 1691, 1642, 1549, 1451; **HRMS** (ESI) for $C_{17}H_{32}N_3O_6$ $(M+H)^+$: calcd. 374.2286; found, 374.2286.

Ethyl 2,2,18-trimethyl-4,8,12,16-tetraoxo-3-oxa-5,9,13,17-tetraazaicosan-20-oate ***55.*** The title compound was prepared using the above general procedure for tetrapeptide synthesis. Yield: 48%. M.p. 135-137 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 6.76 (br. s, 1 H), 6.58 (br. s, 1 H), 6.42 (br. s, 1 H), 5.38 (br. s, 1 H), 4.38 (m, 1 H), 4.05 (q, J = 7.2 Hz, 2 H), 3.30-3.60 (m, 6 H), 2.40-2.50 (m, 8 H), 1.40 (s, 9 H), 1.22 (t, J = 7.2 Hz, 3 H), 1.20 (d, J = 6.8 Hz, 3 H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 172.1, 171.6, 170.9, 156.1, 79.2, 60.8, 42.4, 40.4, 36.9, 36.4, 36.1, 36.0, 35.8, 29.7, 28.4 (3C), 20.2, 14.2, 14.1; **IR** (Microscope, cm^{-1}) 3293, 3076, 2925, 2854, 1715, 1687, 1638, 1544, 1454; **HRMS** (ESI) for $C_{20}H_{37}N_4O_7$ $(M+H)^+$: calcd. 445.2657; found, 445.2658.

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Notes and references

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: NMR spectral reproductions for new compounds and chiral HPLC chromatograms for **13** and **14**. See DOI: 10.1039/b000000x/

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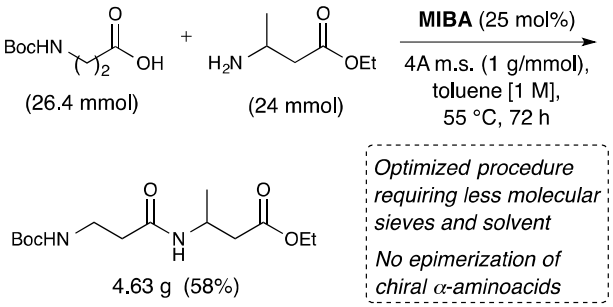

More economical conditions for direct amidation between amines and carboxylic acids, including α- and β-amino acids, have been optimized using the MIBA catalyst (5-methoxy-2-iodophenylboronic acid, **6**).