FULL PAPER

Direct amidation of amino acid derivatives catalyzed by arylboronic acids; applications in dipeptide synthesis.

Shouxin Liu, [a],[b]* **Yihua Yang,** [a] **Xinwei Liu,** [a] **Farhana K. Ferdousi,**[b] **Andrei S. Batsanov**[b] **and Andrew Whiting**[b]*

The direct amidation of amino acid derivatives catalyzed by arylboronic acids has been examined. The reaction was generally slow compared to simple amine-carboxylic acid combinations though proceeded at 65~68 °C generally avoiding racemization. 3,4,5-Trifluorophenylboronic and *o*-nitrophenylboronic acids were found to be the best catalysts, though for the slower dipeptide formations, high catalyst loadings were required and an interesting synergistic catalytic effect using two arylboronic acids was discovered.

[a] State Key Laboratory Breeding Base, Hebei Key Laboratory of Molecular Chemistry for Drug, College of Chemical and Pharmaceutical Engineering, Hebei University of Science & Technology, Shijiazhuang 050018, People's Republic of China.
E-mail: chlsx@hebust.edu.cn

[b] Centre for Sustainable Chemical Processes, Department of Chemistry, Durham University, Science Laboratories, South Road, Durham DH1 3LE, UK.
E-mail: andy.whiting@durham.ac.uk

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Introduction

The amide function is one of most important functional groups in organic chemistry, being present in a range of bioactive compounds, with about 25% of known pharmaceuticals containing at least one amide bond.[1] Although the formation of amide bonds is one of the most common reactions in organic synthesis,[2] the development of efficient amidation methods continues to be an important scientific pursuit. A lot of methods for the formation of amides have been reported, including: direct reaction of carboxylic acids with amines;[3] amination of acid halides or anhydrides;[4] and the reaction of carboxylic acids with amines in the presence of coupling reagents[5] and related approaches.[6] However, most of these synthetic methods are quite correctly considered to be poorly atom economic.[7] In spite of this, with the exception of direct amide formation, all of these methods have been studied widely and employed particularly heavily by industry. More recently, a number of papers have reported direct amidation using boronic acids and borate derivatives as catalysts,[8] and in order to get reaction temperatures down, arylboronic acids have found further application.[9] To date, however, the application of these methods to many carboxylic acid-amine combinations are still limited to relatively simple substrates and more reactive substrates. Direct amide formation using boronic acids have not been applied on amino acid derivatives, and in this paper, we report explorations in this area.

Peptides are important compounds, most being synthesized by the condensation of protected amino acid derivatives using coupling reagents of various types, such as carbodiimides, uronium/amonium and phosphonium salts, halo-uronium and halo-phosphonium salts.[10] These can be applied using both solid or solution phase synthetic strategies, which often requires the use of an excess of these expensive reagents to drive the condensation to completion. In addition, large amounts of solvent are required to wash the resin when using solid phase synthesis systems, in order to obtain clean products and separate excess reagent waste products. Hence, the development of new, cleaner synthetic methods for peptide synthesis is an important topic;[3c,11,12] there is still a need for novel approaches and thinking.[13] Herein, we describe studies into developing direct amide formation applied to amino acid derivatives and including its application on dipeptide formation using arylboronic acid catalysts particularly under conditions which cause minimal racemization.

Results and Discussion

Arylboronic acids such as *o-N,N*-di*iso*propylbenzylaminoboronic acid,[8b] *o*-iodophenylboronic acid[9] and 3,4,5-trifluorophenylboronic acid (TFPBA), have been successfully applied for catalyzing the direct amidation of a number of amine-carboxylic acid combinations.[3c] However, direct amidation of amino acids derivatives is limited despite its importance in drug synthesis. We, therefore, decided to examine the direct amidation of amino acids as both amine and carboxylic acid donor, reacting either with a simple carboxylic acid or amine partner in the first instance. If successful, the synthesis of dipeptides by direct amidation could be considered.

Direct amide formation on amino acid derivatives
N-Boc-proline was initially selected as carboxylic acid to react with benzylamine in order to synthesize the corresponding amide **3** (Eqn. 1). Boronic acids **4-10** were evaluated as catalysts at different temperatures, using different drying methods and solvents. The results are summarized in Table 1.
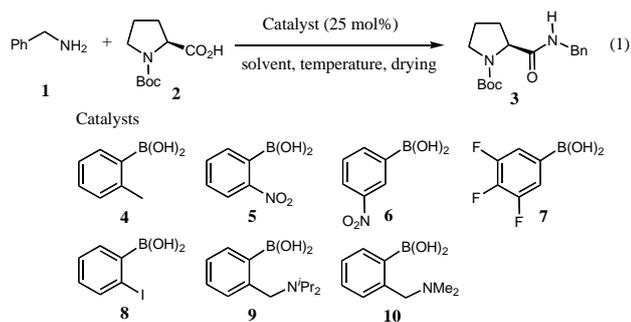
Catalysts

Table 1. The effect of different catalysts and conditions on Eqn. 1.

Entry	Cat.	Solvent	Temp. (°C)	Drying method	Time (h)	Yield[a] (%)
1-1	**4**	C_6H_5F	85	[b]	18	66
1-2	**4**	C_6H_5F	65	[b]	18	46[d]
1-3	**4**	C_6H_5F	41	[b]	18	35
1-4	**4**	Toluene	41	[b]	18	29
1-5	**4**	CH_2Cl_2	40	[b]	18	21
1-6	**4**	$CHCl_3$	41	[b]	18	21
1-7	**4**	CH_3CN	41	[b]	18	24
2-1	**5**	C_6H_5F	85	[b]	18	75
2-2	**5**	C_6H_5F	65	[b]	18	59[d]
2-3	**5**	C_6H_5F	41	[b]	18	37
2-4	**5**	Toluene	41	[b]	18	33
2-5	**5**	CH_2Cl_2	40	[b]	18	18
2-6	**5**	$CHCl_3$	41	[b]	18	21
2-7	**5**	CH_3CN	41	[b]	18	23
3-1	**6**	C_6H_5F	85	[b]	18	52(55)[d]
3-2	**6**	C_6H_5F	41	[b]	18	12
3-3	**6**	$CHCl_3$	41	[b]	18	14
3-4	**6**	CH_3CN	41	[b]	18	17
4-1	**7**	C_6H_5F	85	[b]	18	87(91)[d]
4-2	**7**	C_6H_5F	85	[c]	12	90(98)[d]
4-3	**7**	C_6H_5F	65	[b]	12	81(89)[d]
4-4	**7**	C_6H_5F	41	[b]	12	43
4-5	**7**	CH_2Cl_2	41	[b]	18	41
4-6	**7**	$CHCl_3$	41	[b]	18	26
4-7	**7**	CH_3CN	41	[b]	18	31
5-1	**8**	C_6H_5F	85	[b]	18	61
5-2	**8**	C_6H_5F	65	[b]	18	31
5-3	**8**	CH_3CN	41	[b]	18	22
6-1	**9**	C_6H_5F	85	[b]	18	56
6-2	**9**	C_6H_5F	65	[b]	18	30
6-3	**9**	CH_3CN	65	[b]	18	34
7-1	**10**	C_6H_5F	85	[b]	18	59
7-2	**10**	C_6H_5F	65	[b]	18	26
7-3	**10**	CH_3CN	65	[b]	18	28

[a]Isolated yield of pure amide. [b]Powdered 3 Å molecular sieves in the reaction. [c]Soxlet thimble containing powdered 3 Å molecular sieves. [d]Crude filter residue was washed with EtOAc (40 mL) (see ESI).

The preliminary studies shown in Table 1 demstontrate that TFPBA **7** and *o*-NPBA **5** had the highest catalytic activities under the same reaction conditions (*i.e.* in refluxing fluorobenzene at 85 °C). However, it was also found that the direct amidation of *N*-Boc-proline was considerably slower than that of many simpler carboxylic acid-amine combinations studied previously under the same conditions, which is why substantially higher catalyst loadings (25 *versus* 10 mol%) were required.[8b,c] The solvent

employed was also an important factor, and as expected from previous work,[14] non-polar solvents were preferable to polar solvents and not merely for azeotropic water removal. Five solvents, including polar and non-polar, and with higher and lower boiling points, were examined under the same catalytic and temperature conditions. Of these, fluorobenzene was the best solvent (see Entries 1-1, 2-1, 4-1, 4-2 and 4-3 in Table 1). In addition, temperature was found to be the third important factor controling the yield of the reaction. The isolated yield was highest at reflux temperature, especially while using Soxlet extraction. For example, with fluorobenzene and 3,4,5-trifluorophenylboronic acid (TFPBA) as catalyst, the yield of **3** was 90%, even at 65 °C, this reaction gave a yield of 81% (Entries 4-3 in Table 1). The advantage of the latter conditions are that reactions can be run with molecular sieves in the reaction mixture; potentially minimising any chance of racemization due to the lower reaction temperature. It is noteworthy that chiral HPLC analysis of the products from Entries 4-2 and 4-3 (Table 1) did not reveal any racemization (e.e.s were >99%, see ESI).

In order to confirm the scope of application of the best conditions determined from Table 1 and Eqn. 1, direct amidation of *N*-Boc-phenylalanine **11** was examined, as outlined in Eqn. 2. In this case, 3,4,5-trifluorophenylboronic acid **7** was not efficient enough for the amidation of the phenylalanine derivative **11**, rather *o*-nitrophenylboronic acid (*o*-NPBA) **5** was superior, providing the benzylamide **12** in 91-94% yield (Entry 1-1, Table 2) when using Soxlet extraction drying under reflux in fluorobenzene. In fact, even at 65 °C, 82-89% yields could be obtained over 24 h (Entry 1-2, Table 2). The superior activity of *o*-NPBA **5** is not necessarily surprising since Hall *et al.*[9] had reported its use and that it was not dissimilar to their preferred *o*-iodophenylboronic acid, however, since it is cheaper than TFPBA **7** and readily commercially available, its use is perhaps preferable to many other catalysts.

Single crystal X-ray analysis confirmed retention of the absolute stereochemistry of compound **12** and the structure of **3** (Figure 1). Chiral HPLC also confirmed the complete retention of the enantiopurity in both cases (see ESI).

Figure 1. X-ray structures of molecules **3** and **12**.
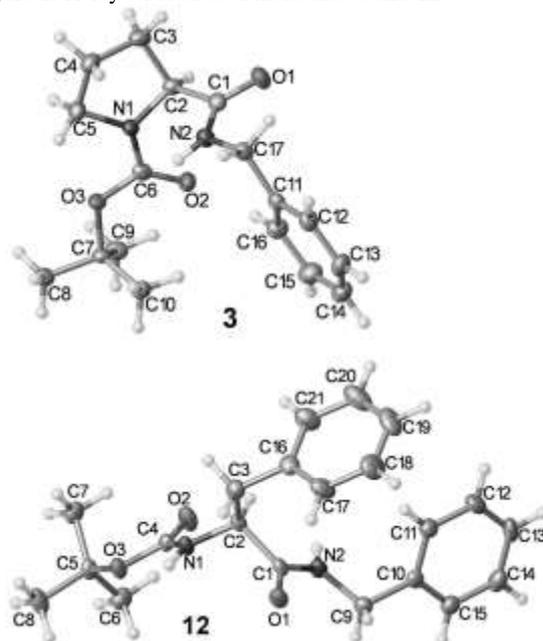
When benzylamine (Eqn. 2) was changed for (*R*)-(+)-α-methylbenzylamine **13** reacting with *N*-Boc-phenylalanine, the impact of the increased steric hindrance of the methyl group was quite obvious (Eqn. 3). The yield dropped from 82 (for **12**) to 56% (for **14**) at *ca.* 65 °C using *o*-NPBA **5** as catalyst. Importantly,

examination of the ^{1}H and ^{13}C NMR of the product **14** showed that it was obtained as a single diastereoisomer, again showing retention of the absolute stereochemistry during the amide formation reaction.

From the above results, it appears that *N*-protected amino acids react quite efficiently with amines to form the corresponding amides using the electron deficient arylboronic acids as catalysts. We therefore examined the corresponding *C*-protected amino acids in the form of methyl ester HCl salts (conveniently neutralized *in situ* from the corresponding HCl salts using Hünig's base), where the amino group reacted with phenylacetic acid **16**. The reactions are outlined in Eqn. 4 and Table 3, employing phenylalanine and valine ammonium chloride derivatives **15**.

(2)
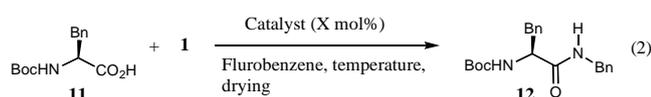
Table 2. The effect of different catalysts and conditions on Eqn. 2.

Entry	17	Cat.	Temp. (°C)	Drying method	Time (h)	Yield[a] (%)
1	**a**	**5**	85	[b]	14	67(92)[d]
2	**a**	**5**	65	[b]	14	86[d]
3	**a**	**7**	85	[b]	14	78(94)[d]
4	**a**	**7**	65	[c,b]	14	72(89)[d]
5	**b**	**5**	85	[b]	14	86[d]
6	**b**	**5**	65	[b]	14	78[d]
7	**b**	**7**	85	[b]	14	68(90)[d]
8	**b**	**7**	65	[c,b]	14	65(77)[d]

[a]Isolated yield of pure amide. [b]Soxlet thimble containing powdered 3 Å molecular sieves. [c]Powdered 3 Å molecular sieves in the reaction. [d]The crude filter residue was washed with EtOAc (40 mL) (see ESI).

(3)

56%

(4)

a; R = Bn
b; R = ^{i}Pr

a; R = Bn
b; R = ^{i}Pr
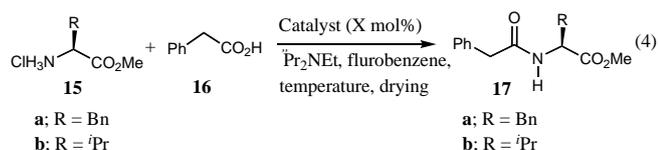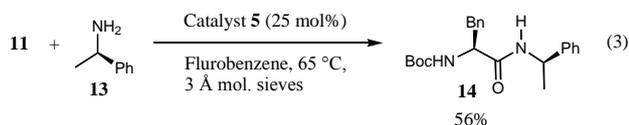
Table 3. Effect of different catalysts/conditions on Eqn. 4.

Entry	Cat.	Temp. (°C)	Drying method	Time (h)	Catalyst loading X (mol%)	Yield[a] (%)
1-1	**5**	85	[b]	18	25	91(94)
1-2	**5**	65	[c]	24	50	82(89)
2-1	**7**	85	[c]	18	25	37
2-2	**7**	85	[b]	18	25	40
2-3	**7**	65	[c]	18	50	54
2-4	**7**	65	[c]	18	25	trace

[a]Isolated yield of pure amide. [b]Soxlet thimble containing powdered 3 Å molecular sieves. [c]Powdered 3 Å molecular sieves in the reaction. [d]The crude filter residue was washed with EtOAc (40 mL) (see ESI).

This time, direct amide formation was reasonably efficient using either *o*-NPBA **5** or TFPBA **7** as catalysts, though TFPBA exhibited marginally higher activity, for example, 67% (or 92%) *versus* 78% (or 94%) yield respectively at 85 °C for the phenylalanine analogue **17a** (Entries 1 and 3, Table 3). However, even at 65 °C, the corresponding amides could be isolated in respectable yields of 72 (or 89%) and 65 (or 77%) yields for **17a** and **17b** respectively (Entries 4 and 8, Table 3). Single crystal X-ray structure analysis of both products showed the absolute stereochemistry to be still intact (Figure 2). However, chiral HPLC analysis gave a slightly different picture of the enantiopurity. Although the yields were quite high, some racemization had occurred during the amide formation of **17a**. It appears that neither temperature nor catalyst play the major role in causing loss of enantiopurity (*i.e.* the e.e.s are almost the same, see Table 4, Entries 6-8), rather the amino acid structure itself, such as the presence of a benzyl side-chain in **15a** (and hence **17a**), results in greater propensity for racemization under the reaction conditions. In contrast, the more highly enantiomerically pure amide products were generally derived from derivative **15b** using catalyst **7** at either 85 or 65 °C. However, the enantiopurity was diminished particularly when using catalyst **5** under the same reaction conditions for amides **3** and **17b**, causing some racemization (*e.g.* 79 and 71% e.e.s for Entries 1 and 9, Table 4, see ESI).

Table 4. Summary of effects of catalysts temperature on the racemization of amides derived from chiral aminoacids.

Entry	Amide	Catalyst	Temp. (°C)	e.e. (%)
1	**3**	**5**	85	79
2	**3**	**7**	85	>99
3	**3**	**7**	65	>99
4	**12**	**5**	85	>99
5	**12**	**5**	65	>99
6	**17a**	**5**	85	67
7	**17a**	**7**	85	64
8	**17a**	**7**	65	68
9	**17b**	**5**	85	71
10	**17b**	**7**	85	>99
11	**17b**	**7**	65	>99

Figure 2. X-ray structures of molecules **17a** (omitting the disorder) and **17b**.

Table 5. Dipeptide synthesis by direct amidation as in Eq. 5.

Entry	Carboxylic acid	Ammonium salt	Cat	Cat. loading X (mol%)	Temp. (°C)	Base	Yield[a,b] (%)	Product
1	**11**	**15a**	**7**	25	65[c]	Pr_2NEt	13	**20a**
2	**11**	**15a**	**7**	50	85[d]	Pr_2NEt	25	**20a**
3	**11**	**15a**	**7**	25	65[c]	K_2CO_3	16	**20a**
4	**11**	**15a**	**7**	100	65[c]	Pr_2NEt	31	**20a**
5	**11**	**15a**	**5**	100	65[c]	Pr_2NEt	58	**20a**
6	**11**	**15a**	**5**	100	65[c]	K_2CO_3	53	**20a**
7	**11**	**15b**	**5**	100	65[c]	Pr_2NEt	<2	**20b**
8	**18a**	**19**	**5**	100	65[c]	Pr_2NEt	47	**20c**
9	**18a**	**15a**	**5**	100	65[c]	Pr_2NEt	48	**20d**
10	**18a**	**15b**	**5**	100	65[c]	Pr_2NEt	20	**20e**
11	**18a**	**15b**	**5 + 4**	50 + 50	65[c]	Pr_2NEt	51	**20e**
12	**11**	**15b**	**5 + 4**	50 + 50	65[c]	Pr_2NEt	55	**20b**
13	**18b**	**15a**	**5 + 4**	50 + 50	65[c]	Pr_2NEt	62	**20f**
14	**2**	**15a**	**5 + 4**	50 + 50	65[c]	Pr_2NEt	46	**21**

[a]Isolated yield of pure amide. [b]All reactions were carried out for 32 h before work up and isolation. [c]Powdered 3 Å molecular sieves added to the reaction mixture to remove water. [d]Soxlet thimble containing powdered 3 Å molecular sieves used for removing water.

Direct amide formation to access dipeptide derivatives

Since the electron deficient arylboronic acids could be used to catalyze the direct amidation of either *N*- or *C*-protected amino acids, we considered whether it would be possible to couple N-terminal to C-terminal protected amino acids in fluorobenzene under conditions that would hopefully continue to avoid racemization (Eqn. 5) and derive the corresponding dipeptide derivatives. Initial studies showed that the different arylboronic acids exhibited considerably different activities, with *o*-NPBA and TFPBA (**5** and **7** respectively) showing considerably higher catalytic activity among all of the arylboronic acids (**4** to **10**) selected. The results of using these two catalysts to access dipeptides **20a-e** are shown in Table 5, Entries 1-10.

The reaction of phenylalanine methyl ester **15a** with *N*-Boc-phenylalanine **11** was studied under different conditions as a representative dipeptide and in order to optimize this direct amide formation reaction. The more active catalysts highlighted from the above studies were initially employed, *i.e.* TFPBA **7** and *o*-NPBA **5**, at different catalyst ratios and temperatures, and using different bases to neutralize the ammonium salt amine-donor. The results of these reactions are summarized in Entries 1-6 (Table 5). All these reactions were slow and hence, stoichiometric quantities of either boronic acid catalyst **5** or **7** was required in order to achieve even moderate yields of dipeptides **5**. However, the *o*-NPBA **5** was superior, especially when employed at 65 °C using Hünig's base to neutralize the ammonium salt, which resulted in a 58% isolated yield of amide **20a** (Entry 5, Table 5).

Employing these conditions on other amino acid derivatives was not entirely straightforward either, even after the initial optimization. Hence, comparing Entry 5 to Entries 7-10 (Table 5) demonstrates that: a) there is little effect upon changing an *N*-Boc

group to a less hindered *N*-Ac (compare Entries 5 with 9, Table 5) on the carboxylic acid donor; b) there is, however, a major impact upon changing the amino donor from being less to more hindered, *i.e.* comparing Entries 5 and 7 shows the effect of merely changing from phenylalanine methyl ester as the amine donor to the corresponding valine analogue, with the same phenylalanine carboxylic acid donor; the yield drops from 58% to zero. Indeed, the same trend is also shown by Entries 8 to 10 (Table 5) which show that for the same *N*-Ac phenylalanine carboxylic acid, reaction with a glycine *vs.* phenylalanine *vs.* valine amine donor results in yields of 47, 48 and 20%, respectively. The fact that the latter reaction was so inefficient (as with Entry 7, Table 5) highlights the need for further reaction improvements to tackle these less efficient direct amide couplings. After re-examining the seven arylboronic acids again for reactions involving a valine amine donor, none were found to be suitable for this reaction. However, upon examining mixed catalyst systems, a surprising synergetic, or cooperative, effect was discovered, involving the use of two catalysts, *i.e. o*-methylphenylboronic acid **4** and *o*-NPBA **5** employed in a 1:1 ratio with 50 mol% loadings of each being necessary to achieve good conversion. Hence, the synthesis of the dipeptide Boc-Phe-Val methyl ester **20b** was transformed from <2% yield (Entry 7, Table 5) to 55% yield (Entry 12, Table 5), and the corresponding *N*-Ac dipeptide **20e** could be isolated in 51% yield (Entry 11, Table 5) compared with 20% (Entry 10, Table 5) using the single catalyst. Although the mechanism by which this cooperative catalytic effect works is not clear at present, we found that it could be applied for the synthesis of further dipeptides with similar results. For example, Cbz-Phe-Phe **20f** and Boc-Pro-Phe **21** dipeptide methyl esters could also be accessed as shown in Entries 13 and 14 respectively (Table 5) giving yields of 62 and 46% yields. Hence, it appears that this method can be used generally to synthesize different dipeptides, including aryl-aryl, aryl-alkyl, and aryl-alicyclic systems. In addition and most importantly, the amino acid configurations were retained upon dipeptide formation, as demonstrated by both single crystal X-ray analysis of *N*-Ac-Phe-Phe methyl ester **20d** and ^{1}H NMR and chiral HPLC of all the dipeptides showed that single diasteoisomeric products were obtained (see ESI).

Conclusions

We have shown that arylboronic acids can be used as catalysts for the direct amidation of amino acid analogues to form simple amide derivatives with reasonable efficiency and generally with retention

of the amino acid absolute configuration and enantio- or diastereo-purity in most, but not all, cases. o-NPBA, being commercially available and reasonably cheap, is perhaps the more attractive catalyst for this purpose, especially when used in fluorobenzene at around 65 °C. However, dipeptide formation is considerably more challenging and for that purpose it appears as though a binary arylboronic acid catalyst system is preferable, i.e. a 1:1 mixture of both o-tolyl- and o-nitrophenyl-boronic acids. This cooperative catalytic system is particularly effective with the least reactive amino acid combinations though the overall catalyst loading of course remains high. It is clear that there is still a way to go before developing highly efficient, general catalysts for all direct amide formations, however, the present work clearly indicates the applicability of boronic acid catalysis for accessing peptide analogues using direct amide formation approaches and avoiding the need for highly reactive intermediates and reagents. It also suggests that cooperative catalyst systems may prove beneficial in the future, and it is this aspect that we are examining at present. The fact that some racemization is observed, even under the milder conditions reported herein, show that further developments are required.
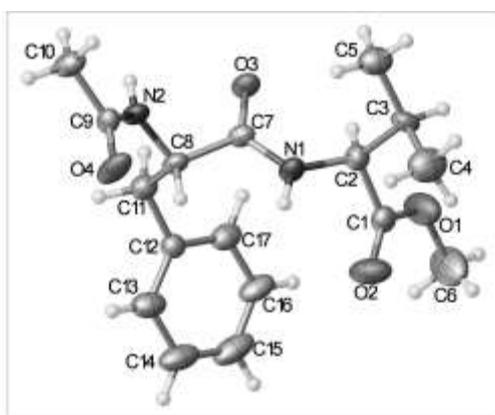
Figure 3. X-ray structure of molecule **20e** (omitting the disorder).

Experimental Section

General experimental

All ^{1}H and ^{13}C NMR were recorded with a Bruker Avance-400 or Varian Inova-500 spectrometer. Chemical shifts are expressed as parts per million (ppm) downfield from the internal standard TMS. Mass spectra were performed with a Micromass Autospec. All reagents were obtained from standard laboratory chemical suppliers. Molecular sieves were activated by heating to 220 °C.

General procedure for the direct amidation of an *N*-protected amino acids

To the catalyst (25~50 mol %), solvent (20 mL), the amine (1.4 mmol), *N*-protected amino acid (1.4 mmol) and activated 3 Å molecular sieves (if the reaction was carried out at reflux temperature or 65 °C, or if a Soxhlet apparatus was used, a thimble was loaded with the activated 3 Å molecular sieves; see Tables above) were added. The mixture was heated under Ar (time indicated in the Tables above). After the reaction finished, the solution was filtered and [in some cases (as indicated, see Tables 1-4) the filter residue was washed with of EtOAc (40 mL)] concentrated under reduced pressure, diluted with CHCl$_3$ (40 mL) and the solution was washed with sat. NaHCO$_3$ (3 x 10 mL), 1 M HCl (2 x 5 mL), H$_2$O (2 x10 mL) and brine (10 mL). After drying (MgSO$_4$), filtration and concentrated the crude product was re-crystallized from a mixture of acetone and petroleum ether to give pure product (see isolated yield in Tables above).

N-Boc-*proline benzylamide* **3** (CAS No: 92235-33-1): The compound was obtained by 3,4,5-trifluorophenylboronic acid as catalyst using Soxhlet apparatus loaded with 3 Å molecular sieves and C$_6$H$_5$F as solvent according to the general procedure in 90% yield. The single crystal was cultured in the mixture solvents of toluene and petroleum ether: ^{1}H NMR (DMSO, 80 °C, 500 MHz) δ 1.35 (s, 9H), 1.72-1.81 (m, 1H), 1.82-1.87 (m, 2H), 2.05-2.16 (m, 1H), 3.29-3.37 (m, 1H), 3.38-3.44 (m, 1H), 4.09-4.15 (m, 1H), 4.20-2.26 (m, 1H), 4.34 (dd, J = 15.1, 6.2 Hz, 1H), 7.18-7.33 (m, 5H), 8.05-8.08 (br, 1H); ^{13}C NMR (DMSO, 80 °C,125.6 MHz, CDCl$_3$) δ 24.1, 28.8, 30.9, 42.8, 47.3, 60.6, 79.2, 127.3, 127.8 (2C), 128.8 (2C), 140.3, 154.3, 173.0; MS (ES) m/z: 305.21 [M+H]$^+$.

N-Boc-*Phenylalanine benzylamide* **12** (CAS No: 84235-32-5): This compound was obtained using o-nitrophenylboronic acid using Soxhlex apparatus loaded with 3 Å molecular sieves and C$_6$H$_5$F as solvent according to the general procedure in 91% yield. The single crystal was grown from mixture of toluene and petroleum ether: ^{1}H NMR (DCCl$_3$, 400 MHz) δ 1.29 (s, 9H), 2.98 (d, J = 6.6 Hz, 2H), 4.24-4.30 (m, 2H), 5.16 (br, 1H), 6.31 (s, 1H), 7.00 (s, 2H), 7.05-7.21 (m, 8H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 28.3 (3C), 38.6, 43.4, 56.1, 80.2, 126.9, 127.4, 127.6 (2C), 128.6 (2C), 128.7 (2C), 129.4 (2C), 136.7, 137.7, 155.4, 171.1.

N-Boc-*Phenylalanine α-methylbenzylamide* **14** (CAS No: 174174-66-4)This compound was obtained using o-nitrophenylboronic acid as catalyst in C$_6$H$_5$F at 64-68 °C according to the general procedure in 56% yield: ^{1}H NMR (CDCl$_3$, 400 MHz) δ1.31 (d, *J* = 6.4 Hz, 3H), 1.43 (s, 9H), 2.97-3.03 (m, 1H), 3.13 (d, *J* = 6.2 Hz, 1H), 4.31-4.25 (br, 1H), 4.96-5.12 (br, 2H), 5.88 (d, *J* = 6.2 Hz, 1H), 7.15-7.38 (m, 10H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 21.7, 28.3 (3C), 38.7, 48.8, 56.1, 80.1, 126.1 (2C), 127.0, 127.3, 128.6 (2C), 128.7 (2C), 129.4 (2C), 155.4, 170.0.

General procedure for direct amidation of C-protected amino acids

To the catalyst (25 mol %), C$_6$H$_5$F (20 mL), phenylacetic aicd (1.4 mmol), amino acid methyl ester hydrochloride (1.4 mmol), di*iso*propylethylamine (1.4 mmol), and activated 3 Å molecular sieves (if the reaction was carried out at reflux temperature or 65 °C, or if a Soxhlet apparatus was used, a thimble was loaded with the activated 3 Å molecular sieves; see Tables above) were added. The mixture was heated under argon. After the reaction finished, the solution was filtered through Celite [in some cases (as indicated, see Tables 1-4) the filter residue was washed with of EtOAc (40 mL)], concentrated under reduced pressure. Then CHCl$_3$ (40 mL) was added to the residues and the solution was washed with sat. NaHCO$_3$ (3 x 10 mL), 1 M HCl (2 x 5 mL), H$_2$O (2 x10 mL) and brine (10 mL) respectively. The solution was dried over MgSO$_4$, filtered and concentrated to provide the product, which was re-crystallized from a mixed solvent of acetone and petroleum to give pure product.

N-*Phenylacetyl-phenylalanine methyl ester* **15a** (CAS No: 90966-33-9): Obtained by 3,4,5-trifluorophenyl-boronic acid catalysis according to the general procedure in 78% yield. The single crystal was grown in a mixed solvent of acetone and petroleum ether: ^{1}H NMR (CDCl$_3$, 400 MHz) δ2.95 (ddd, J = 31.3, 13.8, 5.8 Hz, 2H), 3.48 (s, 2H), 3.63 (s, 3H), 4.77 (dt, J = 7.8, 5.8 Hz, 1H), 5.79 (s, 1H), 6.75-6.85 (m, 2H), 7.06-7.17 (m, 4H), 7.21-7.28 (m, 4H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ$_{ppm}$ 37.64, 43.65, 52.26, 52.99, 127.02, 127.36, 128.52 (2 C), 128.97 (2 C), 129.13 (2 C), 129.39 (2 C), 134.45, 135.60, 170.38, 171.79.

N-*Phenylacetyl-valine methyl ester* **17b** (CAS No: 827619-23-8): Obtained by the catalysis of 3,4,5-trifluorophenylboronic acid according to the general procedure in 78% yield. The single crystal was grown from a mixture solvent of acetone and petroleum ether: ^{1}H NMR (DCCl$_3$, 400 MHz) δ 0.68 (d, J = 6.4 Hz, 3H), 0.77 (d, J = 6.4 Hz, 3H), 1.96-2.05 (m, 1H), 3.53 (s, 2H), 3.60 (s, 3H), 4.46 (dd, J = 8.8, 4.9 Hz, 1H), 5.97-6.05 (d, *J* = 8.2 Hz, 1H), 7.18-7.32 (m, 5H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ17.6, 17.9, 30.1, 42.6, 51.0, 56.1, 126.3, 127.9 (2C), 128.3 (2C), 133.8, 169.9, 171.3.

General procedure for dipeptide synthesis by direct amidation

The amino acid methyl ester hydrochloride (1.4 mmol) was neutralized using di*iso*propylethylamine (1.4 mmol, 246 μL) in fluorobenzene (5 mL). After 2 h, the catalyst (100 mol %), fluorobenzene (20 mL), *N*-protected amino acid (1.4 mmol) and activated 3 Å molecular sieves were added. The mixture was heated under argon at 65 °C for 32h with stirring. After the reaction finished, the mixture was filtered. The solution was concentrated and the crude solid was dissolved in CHCl$_3$ (40 mL). The solution was washed with 0.5 M K$_2$CO$_3$ (4 x10 mL), 1 M HCl (2 x 5 mL), H$_2$O (2 x10 mL) and brine (10 mL) respectively. The solution was dried over MgSO$_4$, filtered and concentrated to get the product which was re-crystallized from a mixture of acetone and petroleum to give pure product.

Table 6. Crystal data.

Compound	3	12	17a	17b	20e
CCDC dep. no.	890395	890396	890397	890398	890399
Formula	$C_{17}H_{24}N_2O_3$	$C_{21}H_{26}N_2O_3$	$C_{18}H_{19}NO_3$	$C_{14}H_{19}NO_3$	$C_{17}H_{24}N_2O_4$
Formula mass	304.38	354.44	297.34	249.30	320.38
Crystal system	orthorhombic	monoclinic	monoclinic	orthorhombic	orthorhombic
a/Å	9.5067(4)	20.9067(5)	9.7679(2)	6.5750(4)	4.8816(2)
b/Å	9.5926(4)	15.1539(3)	15.7664(3)	9.5472(6)	16.4990(6)
c/Å	17.8503(8)	18.2138(4)	10.1211(2)	21.6484(14)	21.3710(9)
β/°	90	95.960(7)	99.732(4)	90	90
V/Å^3	1627.84(12)	5739.3(2)	1536.27(5)	1358.93(14)	1721.25(12)
Temperature/K	120(2)	100(3)	100(3)	100(3)	120(2)
Space group (no.)	$P2_12_12_1$ (#19)	$C2$ (#5)	$P2_1$ (#4)	$P2_12_12_1$ (#19)	$P2_12_12_1$ (#19)
Z	4	12	4	4	4
λ/ Å	0.71073	1.54188	1.54188	1.54184	1.54184
μ/mm^{-1}	0.085	0.66	0.71	0.69	0.72
No. of refls total	17204	34685	11853	16530	15929
No. of refls unique	2866	8828	4581	2032	2591
excluding Friedels	1662	4786	2621	1212	1552
R_{int}	0.095	0.040	0.028	0.029	0.031
R_1 ($I > 2\sigma(I)$)	0.034	0.036	0.029	0.021	0.034
$wR(F^2)$ (all data)	0.065	0.110	0.078	0.056	0.088
Flack parameter, x	-	-0.04(19)	-0.04(16)	-0.05(21)	0.1(3)
Parsons' method, x	-	0.03(7)	0.05(5)	0.00(5)	-0.02(8)
Hooft parameter, y	-	0.08(6)	0.05(4)	0.01(5)	0.01(7)

N-*Boc-Phe-Phe methyl ester* **20a** *(CAS No: 13122-89-9):* This compound was obtained by *o*-nitrophenylboronic acid catalysis according to the general procedure in 58% yield: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.33 (s, 9H), 2.91-3.03 (m, 4H), 3.59 (s, 3H), 4.26 (br, 1H), 4.71 (br, 1H), 4.86 (br, 1H), 6.19 (d, J = 6.6 Hz, 1H), 6.91 (dd, J = 7.2, 2.1 Hz, 2H), 7.10-7.23 (m, 8H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 28.2 (3C), 38.0, 38.3, 52.3, 53.3, 55.7, 80.21, 127.0, 127.1, 128.6 (2C), 128.7 (2C), 129.2 (2C), 129.4 (2C), 135.6, 136.5, 155.2, 170.8, 171.4.

N-*Boc-Phe-Val methyl ester* **20b** *(CAS No: 2754-02-1):* This compound was obtained by the catalysis of 50% *o*-nitrophenylboronic acid and 50% *o*-methylphenylboronic acid according to the general procedure in 55% yield: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.77 (d, J = 6.9 Hz, 3H), 0.80 (d, J = 6.9 Hz, 3H), 1.35 (s, 9H), 2.03 (dd, J = 6.9 Hz, 1H), 3.00 (d, J = 6.9 Hz, 2H), 3.62 (s, 3H), 4.28 (br, 1H), 4.39 (dd, J = 8.6, 5.1 Hz, 1H), 4.96 (br, 1H), 6.31 (d, J = 8.5 Hz, 1H), 7.11-7.24 (m, 5H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 17.8, 18.8, 28.3 (3C), 31.3, 38.0, 52.1, 55.9, 57.2, 80.2, 126.9, 128.7 (2C), 129.3 (2C), 136.6, 155.4, 171.1, 171.8.

N-*Ac-Phe-Gly ethyl ester* **20c** *(CAS No: 52134-81-3):* This compound was obtained by *o*-nitrophenylboronic acid catalysis according to the general procedure in 42% yield: ^{1}H NMR (DCCl$_3$, 400 MHz) δ 1.27 (t, J = 7.1 Hz, 3H), 1.98 (s, 3H), 3.09 (d, J = 7.1 Hz, 2H), 3.96 (ABq, J = 18.2, 5.3 Hz, sep. 40.9 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 4.75 (q, J = 7.2 Hz, 1H), 6.31 (br, 1H), 6.55 (br, 1H), 7.19-7.31 (m, 5H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 14.1, 23.1, 38.2, 41.3, 54.3, 61.5, 127.0, 128.7 (2C), 129.2 (2C), 136.5, 169.3, 170.2, 171.2.

N-*Ac-Phe-Phe methyl ester* **20d** *(CAS No: 2562-48-3):* This compound was obtained by *o*-nitrophenylboronic acid catalysis according to the general procedure in 48% yield. A single crystal grown in the mixture solvents of acetone and petroleum ether: ^{1}H NMR (DCCl$_3$, 400 MHz) δ 1.87 (s, 3H), 2.86-3.03 (m, 4H), 3.60 (s, 3H), 4.54 (dd, J = 10.8, 4.3 Hz, 1H), 4.65-4.70 (m, 1H), 5.91 (d, J = 7.2 Hz, 1H), 6.05 (d, J = 7.5 HZ, 1H), 6.94 (dd, J = 4.5, 2.6 Hz, 2H), 7.09-7.22 (m, 8H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 23.1, 37.9, 38.1, 52.3, 53.4, 54.3, 127.0, 127.1, 128.6 (2C), 128.7 (2C), 129.2 (2C), 129.3 (2C), 135.6, 136.4, 169.83, 170.4, 171.2.

N-*Boc-Phe-Val methyl ester* **20e** *(CAS No: 53842-46-9):* This compound was obtained by the catalysis of 50 mol% *o*-nitrophenylboronic acid and 50 mol% *o*-methylphenylboronic acid according to the general procedure in 51% yield: ^{1}H NMR (DCCl$_3$, 400 MHz) δ 0.77 (d, J = 6.9 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H), 1.92 (s, 3H), 1.97-2.03 (m, 1H), 2.95-3.03 (m, 2H), 3.61 (s, 3H), 4.34 (dd, J = 8.5, 5.0 Hz, 1 H), 4.64-4.56 (m, 1H), 6.00 (d, J = 17.2 Hz, 1H), 6.07 (d, J = 17.2 Hz, 1H), 7.11-7.23 (m, 5H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 17.7, 18.8, 23.2, 31.1, 38.2, 52.1, 54.6, 57.4, 127.0, 128.7 (2C), 129.3 (2C), 136.3, 170.0, 170.7, 171.6.

N-*Boc-Pro-Phe methyl ester* **21** *(CAS No: 52071-64-4):* This compound was obtained by the catalysis of 50 mol% *o*-nitrophenylboronic acid and 50 mol% *o*-methylphenylboronic acid according to the general procedure in 46% yield: ^{1}H NMR (DMSO, 80 °C, 500 MHz) δ 1.34 (s, 9H), 1.76 (m, 3H), 2.00 (m, 1H), 2.97-3.14 (m, 2H), 3.22-3.29 (m, 1H), 3.30-3.37 (m, 1H), 3.61 (s, 3H), 4.11-4.14 (m, 1H), 4.52-4.56 (m, 1H), 7.20-7.31 (m, 5H), 7.84-7.88 (m, 1H); ^{13}C NMR (DMSO, 80 °C, 125.6 MHz, CDCl$_3$) δ 23.8, 28.8 (3C), 36.9, 47.1, 52.2, 54.3, 60.3, 79.3, 127.1, 128.8 (2C), 129.6 (2C), 137.9, 154.3, 172.4, 173.0.

X-ray crystallography

Single-crystal diffraction experiments were carried out for **3** on a Bruker 3-circle diffractometer with SMART 6000 CCD area detector, using graphite-monochromated sealed-tube Mo-*K*a radiation; for **17b** and **20e** on a Gemini S Ultra (Oxford Diffraction) κ-diffractometer with a Sapphire3 CCD detector, using Cu-*K*α radiation from a sealed tube with Enhance Ultra X-ray optics. Due to the comparatively small crystal size, data for **12** and **17a** had to be collected on a Bruker 3-circle diffractometer with Platinum135 CCD detector, using Cu-*K*α radiation from a Microstar rotating anode source with cross-coupled Göbel mirrors.[15]

Crystals were cooled using Oxford Cryosystems open-flow cryostats Cryostream 700 (liquid N$_2$) for **3, 17b** and **20e** or Cobra (non-liquid N$_2$) for **12** and **17a**. Reflection intensities were integrated using SAINT 7.46A (**3**), SAINT 7.60A (**12**, **17a**) and CrysAlisPro (**17b**, **20e**) software. The structures were solved by direct methods and refined by full-matrix least squares against F^2 of all reflections, using SHELXTL or SHELX-2013/2[16] and OLEX2[17] software. Crystal data and other experimental details are listed in Table 6.

The crystal of **12** was a non-merohedral twins with the components related by a 180° rotation around the reciprocal axis (0.575 0 1) or the real axis (0.5 0 1). The diffraction pattern was deconvoluted by CELL_NOW program[18] and F^2 were calculated by TWINABS program,[19] using well-separated reflections of both components, as well as the overlapping reflections.

Structure **12** has a (*a*, *b*/3, *c*) subcell; the asymmetric unit comprises three independent molecules related via approximate *b*/3 translations. The reflections with $k=3n$ have the mean intensity 26 times higher than those with $k{\neq}3n$. Structure **17a** has a (**a**, **b**, **c**/2) subcell: the asymmetric unit comprises two independent molecules related via an approximate *c*/2 translation. The reflections with even *l* indices have the mean intensity 4.8 times higher than those with even *l*. In one independent molecule, the C(1)=O(2) group is disordered (in a 9:1 ratio) between two orientations differing by 26°; the *minor* orientation is identical with that realized in the other (ordered) independent molecule. In structure **20e,** which has a low

packing coefficient (0.61), the phenyl and isopropyl groups are disordered between two orientations each (see ESI), with practically equal probability. On cooling below 120 K, **20e** converted into a modulated phase with a (7**a**, **b**, **c**) supercell.

The absolute configuration of **3** was assigned *S*, those of four other compounds were determined from anomalous scattering, by calculating the Flack[20] (*x*) and Hooft[21] (*y*) parameters which should equal 0 for the correct absolute structure and 1 for the inverted model; *x* was calculated both by the conventional 'hole-in-one' fit to all intensities and by Parsons' method based on selected quotients.[21] In each case, both *x* and *y* equaled 0 within the standard uncertainty (s.u.), but for the conventional *x* the s.u.'s were too large to regard the absolute structures as unequivocal (see discussion[23]), whereas Hooft method (using either Gaussian or Student's *t*-distribution[24]) and Flack-Parsons method gave statistically reliable discrimination.

Supporting Information (see footnote on the first page of this article): X-ray crystallographic data, ^{1}H NMR and ^{13}C NMR spectra for all key intermediates and final products are provided and HPLC data for single chiral centre products.

Acknowledgments

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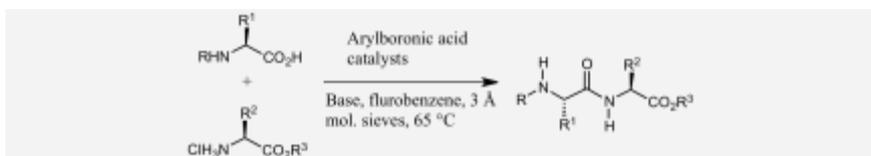
Arylboronic acids can be used to catalyze the direct amide formation of protected amino acid derivatives. For less reactive amino acids, cooperative catalysis can be used involving two arylboronic acids, one electron rich, one electron deficient and at high catalyst loadings to give good conversions at moderate temperatures.