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2-Furanylboronic Acid as an Effective Catalyst for the Direct Amidation of Carboxylic Acids at Room Temperature

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2-Furanylboronic acid has been identified as an inexpensive and effective catalyst for the dehydrative amide formation of carboxylic acids and amines. This transformation can be efficiently carried out at room temperature and is applicable to a wide range of carboxylic acids with primary and secondary amines to afford amides in good to excellent yields.

Introduction

Amides are abundant in nature and chemical products such as pharmaceuticals, fine chemicals and polymers. Consequently, amide bond formation is recognised as an important transformation in a variety of industries, especially in the pharmaceutical sector, wherein approximately 25% of drugs contain amide bonds (Figure 1).[1] Despite the crucial importance of amide formation, the most commonly used methods, that is, the use of acid derivatives and coupling reagents, are inefficient and unsustainable for the chemical industry. This is due to the use of hazardous chemicals and to the formation of large quantities of by-products that not only lead to difficulties in product isolation but also has an adverse environmental impact. Therefore, amide formation was identified by the industry as a top priority transformation for the development of more efficient and sustainable approaches.[2] This need has led to the development of a plethora of alternative, more efficient methods for amide formation.[3]

Despite the tremendous progress in the field, the coupling reaction between carboxylic acids and amines remains by far one of the most common approaches for amide synthesis in both research and the industry, primarily because of the wide availability of feedstock. However, because of the strong C–OH bond of the carboxylic acid, the reaction usually requires a stoichiometric coupling reagent to activate the carboxylic acid to drive the dehydration reaction (Figure 2).[3a,3b,3g,4] Given that most coupling reagents are

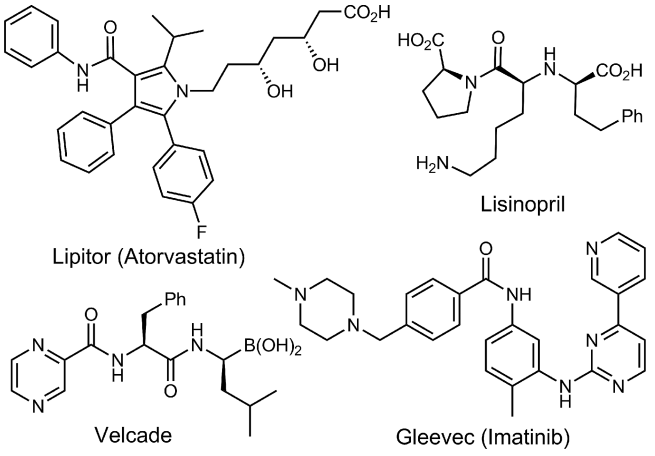

Figure 1. Examples of amide-containing drugs.

expensive and could have a molecular weight as high as that of the amide product, this approach suffers from cost ineffectiveness, poor atom efficiency, and tedious product isolation procedures.[5] Therefore, the development of more

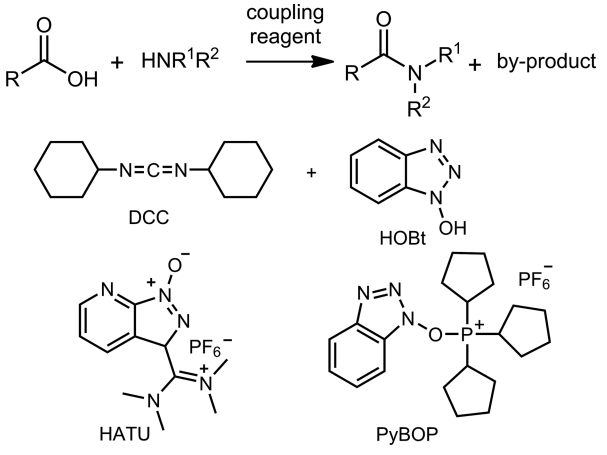

Figure 2. Amide formation using typical coupling reagents.

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efficient, catalytic approaches for the direct coupling of carboxylic acids and amines that enable sustainable amide formation represents a highly important yet challenging area of chemistry.

In this field, significant progress has been made recently, with several promising catalyst systems being reported.[6–9] Amongst these, the pioneering work by Yamamoto et al. on electron-deficient arylboronic acids as catalysts for the coupling of carboxylic acids and amines (referred to as direct amidation) represents one of the most important developments (Figure 3).[6] The best performing catalyst, (3,4,5-trifluorophenyl)boronic acid (**1a**), has been shown to effectively catalyse direct amidation in a refluxing solvent (> 120 °C) using 4 Å molecular sieves as a water scavenger. Subsequent improvements have been directed towards decreasing the reaction temperature for effective catalysis and convenient operation as well as avoiding racemisation of chiral substrates. For example, Whiting et al. have shown that bifunctional arylboronic acid **1b** enables the coupling reaction to be carried out in refluxing fluorobenzene at 85 °C.[7] More remarkably, Hall and co-workers have very recently reported that (*o*-haloaryl)boronic acids such as **1c** were able to mediate direct amidation at room temperature in the presence of molecular sieves as a dehydrating agent.[8] This represents significant progress toward catalytic direct amidation, although *o*-iodo arylboronic acid (**1c**) is not commercially available and requires the use of equimolar expensive silver(I) sulfate to introduce the iodide from its boronic acid precursor.[10]

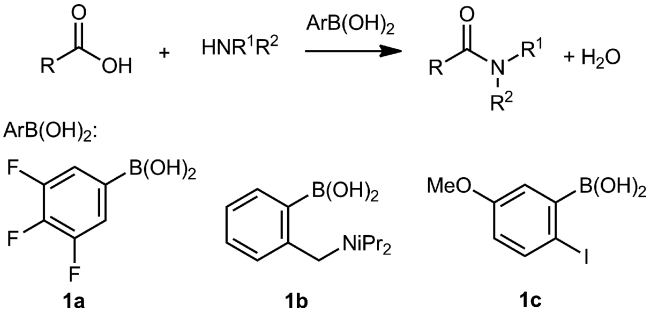


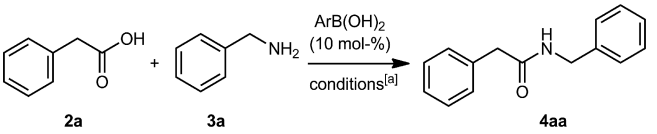
Figure 3. Representative arylboronic acids for the dehydrative coupling of carboxylic acids and amines.

In our continuing efforts to develop efficient and environmentally benign methods for amide formation,[11] our recent efforts were directed to the discovery of more cost-efficient, easily accessible arylboronic acids for direct catalytic amidation. In this context, we report herein the finding of 2-furanylboronic acid **1g** as an inexpensive and highly effective catalyst for direct amidation at ambient temperature.

Results and Discussion

Our investigation commenced with the screening of a broad range of commercially available arylboronic acids to identify active catalysts. This was based on the coupling reaction between phenylacetic acid (**2a**) and benzylamine (**3a**), benchmarking against the previously reported conditions.[8a] The screening was focused on *meta*-substituted benzeneboronic acids and heteroarylboronic acids, which have been much less explored. From the screening results (Table 1), five boronic acids (Figure 4), that is, (3-cyanophenyl)boronic acid (**1d**, entry 2), 3-(trifluoromethylphenyl)boronic acid (**1e**; entry 3), (3,5-difluorophenyl)-

Table 1. Screening of arylboronic acids for direct amidation.



Entry	Ar	Yield [%][b]
1	Ph	22
2	3-CNC_6H_4	95 (92)
3	3-$CF_3C_6H_4$	91 (92)
4	3-FC_6H_4	86
5	3-HOC_6H_4	0
6	3-$MeOC_6H_4$	78
7	3-*i*$PrOC_6H_4$	66
8	3-$BnOC_6H_4$	5
9	3-$F_2CHOC_6H_4$	52
10	3-$F_3COC_6H_4$	50
11	3-$MeSC_6H_4$	58
12	3-$Me_2NC_6H_4$	7
13	3-$MeNHSO_2C_6H_4$	0
14	3,4-$F_2C_6H_3$	78
15	3-F,4-BrC_6H_3	81
16	3-F,4-$MeOC_6H_3$	36
17	3,4-$Cl_2C_6H_3$	85
18	3-CF_3,4-ClC_6H_3	63
19	3,4-$(MeO)_2C_6H_3$	17
20	3,5-$F_2C_6H_3$	95 (93)
21	3,5-$Me_2C_6H_3$	34
22	4-ClC_6H_4	35
23	2-furanyl	99 (91)
24	3-furanyl	23
25	2-benzofuranyl	44
26	2-thiophenyl	92 (88)
27	5-Cl(2-thiophenyl)	55
28	5-CN(2-thiophenyl)	73
29	*N*-boc-1*H*-pyrrol-2-yl	84
30	1*H*-indol-5-yl	51
31	2-I,5-$MeOC_6H_3$[c]	99 (98)
32	no catalyst	0

[a] Reaction conditions: phenylacetic acid (**2a**; 0.275 mmol), benzylamine (**3a**; 0.25 mmol), boronic acid (10 mol-%), 4 Å MS (freshly activated, 0.5 g), CH_2Cl_2 (3.5 mL), room temp., 24 h. [b] Yields were determined by HPLC analysis. Yields given in parentheses were obtained in 3 h. [c] Hall's catalyst **1c**.

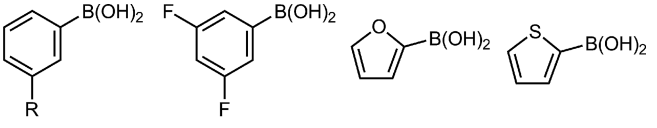
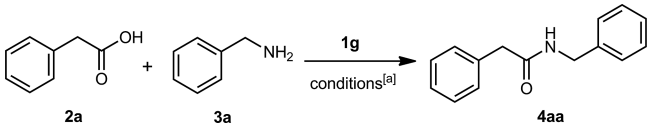


Figure 4. Best performing arylboronic acids identified from screening.

boronic acid (**1f**; entry 20), 2-furanylboronic acid (**1g**; entry 23) and (thiophen-2-yl)boronic acid (**1h**; entry 26) were found to perform excellently compared with the reported best catalyst **1c** (entry 31). These best performing catalysts were further evaluated for a shorter reaction time of 3 h and the yields (given in parentheses in Table 1) were only marginally lower than with **1c**. Based on these results, the easily accessible, inexpensive 2-furanylboronic acid (**1g**) was selected for further optimisation.

Optimisation of the conditions began with the screening of solvents (Table 2, entries 1–11). The best solvents for catalyst **1g** turned out to be similar to those reported for **1c**,[8b] with CH_2Cl_2 (entry 1) and toluene (entry 4) being the most suitable, and diethyl ether (entry 7) also performed well. Higher polarity solvents including tetrahydrofuran (THF), 2-Me-THF, acetonitrile, dioxane and ethanol gave much lower yields, whereas the use of *N*,*N*-dimethylformamide (DMF) led to transamidation, forming *N*-benzylformamide as a side-product.[12]

Table 2. Optimisation of reaction parameters for amidation.



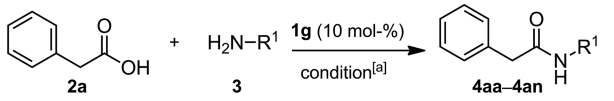
2a 3a 4aa

Entry	**1g** [mol-%]	Solvent	4 Å MS (g/mmol **3a**)	Concentration of **2a** [M]	Yield[b] [%]
1	10	CH_2Cl_2	2.0	0.079	99
2	10	THF	2.0	0.079	27
3	10	2-methyl-THF	2.0	0.079	8
4	10	toluene	2.0	0.079	98
5	10	DMF	2.0	0.079	23
6	10	CH_3CN	2.0	0.079	10
7	10	Et_2O	2.0	0.079	89
8	10	dioxane	2.0	0.079	54
9	10	EtOH	2.0	0.079	0
10	10	EtOAc	2.0	0.079	33
11	10	dimethyl carbonate	2.0	0.079	0
12	10	CH_2Cl_2	2.0	0.079	98
13	10	CH_2Cl_2	1.0	0.079	96
14	10	CH_2Cl_2	0.75	0.079	92
15	10	CH_2Cl_2	0.5	0.079	57
16	10	CH_2Cl_2	1.0	0.12	96
17	10	CH_2Cl_2	1.0	0.16	98
18	10	CH_2Cl_2	1.0	0.22	79
19	5	CH_2Cl_2	1.0	0.16	55

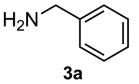
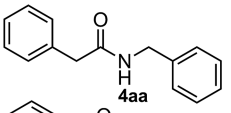
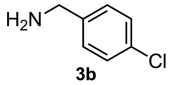
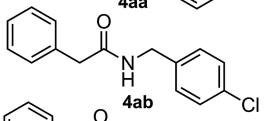
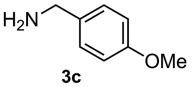
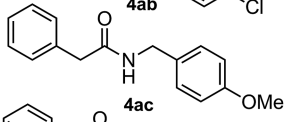
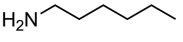
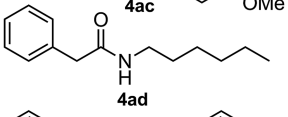
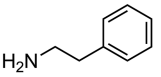
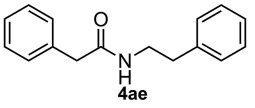
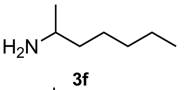
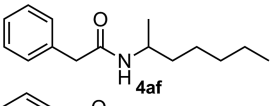
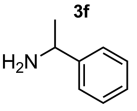
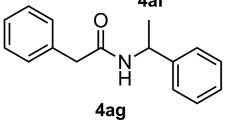
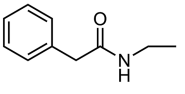
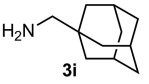
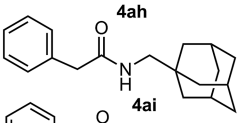
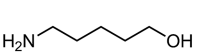
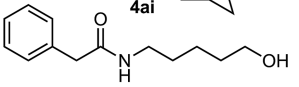
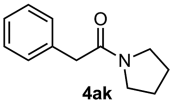
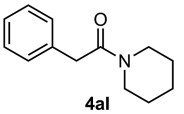
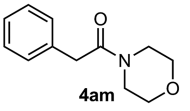
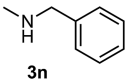
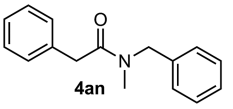
[a] Reaction conditions: phenylacetic acid (**2a**; 1.1 mmol), benzylamine **3a** (1.0 mmol), catalyst **1g** and 4 Å MS in the specified solvent at room temp. for 24 h. [b] Yields were determined by HPLC analysis.

Having identified the best solvent, we next turned our attention to other reaction parameters, including the amount of 4 Å molecular sieves used, substrate concentration and catalyst loadings (Table 2, entries 12–19). Optimal conditions were found to be 10 mol-% catalyst loading, 0.16 M carboxylic acid **2a** in CH_2Cl_2 and 1 g of 4 Å molecular sieves (MS) per millimole of amine **3a** (entry 17). Whereas increasing the concentration of **2a** beyond 0.2 M substantially reduced the yield (entry 18) (inefficient mixing observed), reducing the catalyst loading to 5 mol-% almost

Table 3. Direct amidation of carboxylic acid **2a** with various amines.[a]



2a 3 4aa–4an

Entry	Amine	Amide	Yield [%][b]
1	 **3a**	 **4aa**	98
2	 **3b**	 **4ab**	97
3	 **3c**	 **4ac**	77
4	 **3d**	 **4ad**	91
5	 **3e**	 **4ae**	99
6	 **3f**	 **4af**	60
7	 **3g**	 **4ag**	55
8	 **3h**	 **4ah**	50
9	 **3i**	 **4ai**	51
10	 **3j**	 **4aj**	0
11	 **3k**	 **4ak**	60
12	 **3l**	 **4al**	45
13	 **3m**	 **4am**	68
14	 **3n**	 **4an**	52

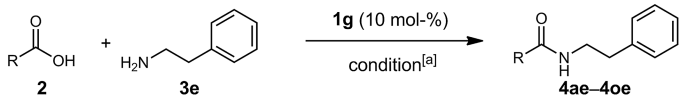
[a] Reaction conditions: phenylacetic acid (**2a**; 1.1 mmol), amine **3a**–**3n** (1.0 mmol), catalyst **1g** (10 mol-%), 4 Å MS (1.0 g), CH_2Cl_2 (7 mL), room temp., 24 h. [b] Isolated yield.

halved the yield (entry 19). Additionally, the order of addition of reagents and the stoichiometry of the carboxylic acid and the amine were crucial to this direct amidation. Premixing the carboxylic acid and the arylboronic acid in the presence of activated molecular sieves for several minutes prior to addition of the amine ensured the formation of an activated carboxylic acid intermediate to effectively couple with the amine. This was evident by a control reaction in which both substrates **2a** and **3a** were added concurrently with the catalyst, resulting in only 34% yield of amide product. Moreover, a slight excess of the carboxylic acid relative to the amine (1.1:1.0 mol ratio) was preferred, because an excess of amine (20 mol-%) significantly slowed the reaction. These observations are consistent with previously reported results.[8b]

With the optimised conditions in hand, the substrate scope of direct amidation catalysed by **1g** was investigated. First, the amidation between phenylacetic acid (**2a**) with a range of primary and secondary amines was studied (Table 3). In general, primary amines **3a**–**e** gave much better yields (generally >90%) than secondary amines. The isolation of the amide products was conveniently achieved by acid and base extraction without column chromatographic purification. However, substitution at both α- and β-positions of amines **3f**–**i** significantly reduced the yields, which is also reflected in cyclic and secondary amines **3k**–**n**. These results imply that the reaction is sensitive to steric hindrance around the amino group. The reaction is not compatible with a free hydroxyl group, as shown in **3j**, likely due to the formation of a borate ester,[13] which deactivates the boronic acid catalyst. As reported previously,[8b] less nucleophilic amines such as aniline does not undergo amidation (not shown).

The generality of this direct amidation was further demonstrated on a variety of carboxylic acids with amine **3e**. As shown in Table 4, the reaction works well with aliphatic acids **2a**–**g** without α-substitution, providing the corresponding amides in excellent yields. A variety of functional groups including ester and bromide were well tolerated. However, when substituents are present at the α-position of the carboxylic acids (**2h**–**k**), the yield of amide products decreases and the trend is aggravated as the steric bulk of the substituent increases (**2k**–**l**). These observations echo the limitation of steric effects observed in the case of amines

Table 4. Direct amidation of carboxylic acids with amine **3e**.[a]



Entry	Acid	Amide	Yield [%][b]	Entry	Acid	Amide	Yield [%][b]
1	**2a**	**4ae**	99	9	**2i**	**4ie**	60
2	**2b**	**4be**	87	10	**2j** R = Me	**4je** R = Me	77
3	**2c**	**4ce**	94	11	**2k** R = Ph	**4ke** R = Ph	17
4	**2d**	**4de**	73	12	**2l**	**4le**	0
5	**2e**	**4ee**	80	13	**2m**	**4me**	45
6	**2f**	**4fe**	98	14	**2n**	**4ne**	66
7	**2g**	**4ge**	90	15	**2o**	**4oe**	0
8	**2h**	**4he**	77				

[a] Reaction conditions: carboxylic acid (**2a**–**2o**; 1.1 mmol), amine **3e** (1.0 mmol), catalyst **1g** (10 mol-%), 4 Å MS (1.0 g), CH_2Cl_2 (7 mL), room temp., 24 h. [b] Isolated yields.

(see above). Carboxylic acids containing an amino group (**2m**) and *N*-heterocyclic motif (**2n**) gave only moderate yields of amide products, but benzoic acid (**2o**) essentially did not undergo amidation under the reaction conditions, which has been observed previously.[8]

Although it has been reported that 2-furanylboronic acid is prone to decomposition at ambient temperature or heating due to protodeboronation,[14] monitoring a solution of the compound in CD_2Cl_2 (equivalent to the reaction solvent CH_2Cl_2) at ambient temperature (ca. 25 °C) by ^1H NMR spectroscopic analysis for up to 30 h (reaction time 24 h) did not reveal any appreciable decomposition. Analysis of a bottle of 2-furanylboronic acid stored at 4 °C for 11 months did not show any decomposition either, and the result was well reproduced when it was tested on the amidation of **2a** with **3a**.

A mechanism for the 2-furanylboronic acid catalysed amidation is shown in Figure 5 based on the most recent experimental[8] and computational[15] studies. The catalytic cycle begins with the formation of an acyl intermediate **I** between boronic acid **1g** and the carboxylic acid **2**. This fast step[15] could be favoured by intramolecular hydrogen-bonding and by the coordination of the formed water molecule to the electron-deficient boron atom. The activated acyl group in **I** then reacts with amine **3**, leading to an orthoaminal transition state **II**, which rearranges to transition state **III**, favoured by a hydrogen-bonding network and minimised steric interactions with *cis*-aligned R^1 and R^2. In the final step, water is eliminated from **III** in the rate-determining step[15] with amide product **4** being released and catalyst **1g** enters a fresh cycle. Molecular sieves are used in the reaction as a dehydration agent to remove water formed in the reaction and possibly also functions as a water reservoir to hydrolyse bis- and tri-acyl borates that are inactive to the active mono-acyl borate **I**.[8]

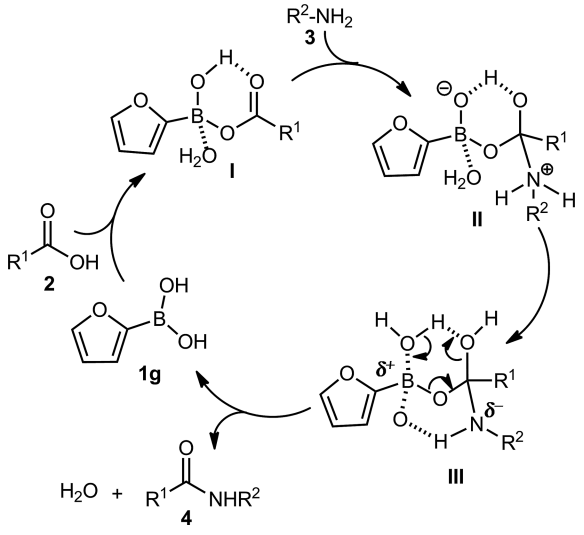


Figure 5. Proposed mechanism for direct amidation catalysed by 2-furanylboronic acid (**1g**).

Conclusions

Through extensive screening of commercially available arylboronic acids, we have identified 2-furanylboronic acid as a readily available, inexpensive and efficient catalyst for the direct amidation of carboxylic acids and amines at ambient temperature using 4 Å molecular sieves as a dehydrating agent. The reaction is applicable to the direct amidation of a wide range of aliphatic carboxylic acids with aliphatic primary and secondary amines, providing the amide compounds in good to excellent yields. The amide products can be easily isolated by acid and base extraction without column chromatographic purification. However, it has been observed that the reaction is limited to aliphatic substrates and that it is sensitive to steric hindrance at the α-position of both carboxylic acid and amine substrates. Another point to note is that although CH_2Cl_2 was found to be the most suitable solvent at this discovery stage, it is disfavoured from a sustainability point of view.[16] Hence, an alternative solvent should be sought when the reaction is carried out on larger scales. The findings of this study provide useful information for the understanding of arylboronic acid catalysed direct amidation and for the development of more effective, next-generation catalysts.

Experimental Section

General Information: All chemicals were obtained from commercial sources and were used as received. Dried solvents (acetonitrile, CH_2Cl_2, DMF, dioxane, THF, diethyl ether and toluene) were drawn from a Glass Contour solvent purification system. Anhydrous grade 2-methyltetrahydrofuran was purchased from a commercial source. All reactions requiring anhydrous conditions were carried out under argon atmosphere using oven-dried glassware. ^1H and ^{13}C NMR spectra were recorded with a Bruker 400 MHz instrument with a CryoProbe. Chemical shifts are reported in parts per million (ppm) using the undeuterated peak of $CDCl_3$ (7.26 for proton and 77.2 for carbon) as a reference. Mass spectra were run with the electrospray ionization time-of-flight (ESI-TOF) mode with an Agilent 6210 mass spectrometer. HPLC analysis was carried out with an Agilent 1260 infinity analytical system with a binary pump, using a Poroshell 120 EC-C18 column (Ø4.6 × 75 mm) with 1,3-dimethoxybenzene as an internal standard.

General Procedure for 2-Furanylboronic Acid (1g) Catalysed Amide Formation: A 10 mL glass tube was charged with carboxylic acid (1.1 mmol), 2-furanylboronic acid (**1g**; 11.2 mg, 10 mol-%), activated 4 Å molecular sieves (1.0 g), and anhydrous dichloromethane (7 mL). The mixture was stirred vigorously for 10 min before amine (1.0 mmol, 1.0 equiv.) was added. The resulting mixture was stirred at room temperature for 24 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was washed with 0.1 M HCl solution, followed by saturated sodium carbonate solution and brine. The organic phase was dried with anhydrous $MgSO_4$, filtered, and concentrated to provide pure amide products.

Compound Characterization Data

***N*-Benzyl-2-phenylacetamide (4aa):**[17] Yield 221 mg (98%); white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.24 (m, 8 H), 7.22–7.16 (m, 2 H), 6.00 (br. s, 1 H), 4.41 (d, J = 5.8 Hz, 2 H), 3.61 (s, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.1, 138.2, 134.9, 129.5, 129.1, 128.7, 127.6, 127.5, 127.4, 43.8, 43.7 ppm.

***N*-(4-Chlorobenzyl)-2-phenylacetamide (4ab):**[18] Yield 251 mg (97%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.32 (m, 2 H), 7.32–7.23 (m, 5 H), 7.14–7.06 (m, 2 H), 5.66 (br. s, 1 H), 4.37 (d, J = 6.0 Hz, 2 H), 3.63 (s, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.0, 136.9, 134.8, 133.4, 129.6, 129.3, 129.0, 128.9, 127.7, 44.1, 43.1 ppm.

***N*-(4-Methoxybenzyl)-2-phenylacetamide (4ac):**[19] Yield 197 mg (77%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.31 (m, 2 H), 7.31–7.24 (m, 3 H), 7.11 (m, 2 H), 6.82 (m, 2 H), 5.61 (br. s, 1 H), 4.34 (d, J = 5.7 Hz, 2 H), 3.78 (s, 3 H), 3.61 (s, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.7, 159.2, 135.0, 130.4, 129.6, 129.2, 129.0, 127.5, 114.2, 55.4, 44.0, 43.3 ppm.

***N*-Hexyl-2-phenylacetamide (4ad):**[20] Yield 200 mg (91%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.32 (m, 2 H), 7.32–7.23 (m, 3 H), 5.34 (br. s, 1 H), 3.56 (s, 2 H), 3.29–3.01 (m, 2 H), 1.47–1.33 (m, 2 H), 1.33–1.13 (m, 6 H), 0.92–0.78 (m, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.0, 135.3, 129.6, 129.2, 127.5, 44.1, 39.8, 31.5, 29.6, 26.6, 22.6, 14.1 ppm.

***N*-Phenethyl-2-phenylacetamide (4ae):**[21] Yield 236 mg (99%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.08 (m, 8 H), 7.03–6.96 (m, 2 H), 5.70 (br. s, 1 H), 3.45 (s, 2 H), 3.40 (q, J = 6.9 Hz, 2 H), 2.68 (t, J = 6.9 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.9, 138.7, 135.0, 129.3, 128.9, 128.7, 128.5, 127.2, 126.4, 43.7, 40.7, 35.5 ppm.

(±)-*N*-(Heptan-2-yl)-2-phenylacetamide (4af):[22] Yield 140 mg (60%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.33 (m, 2 H), 7.32–7.20 (m, 3 H), 5.06 (br. s, 1 H), 4.01–3.89 (m, 1 H), 3.55 (s, 2 H), 1.38–1.14 (m, 8 H), 1.04 (d, J = 6.6 Hz, 3 H), 0.85 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.3, 135.4, 129.5, 129.1, 127.4, 45.5, 44.3, 36.8, 31.7, 25.6, 22.7, 21.0, 14.1 ppm.

(±)-2-Phenyl-*N*-(1-phenylethyl)acetamide (4ag):[23] Yield 132 mg (55%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.32 (m, 2 H), 7.32–7.22 (m, 6 H), 7.22–7.15 (m, 2 H), 5.62 (br. s, 1 H), 5.12 (quint, J = 7.1 Hz, 1 H), 3.58 (s, 2 H), 1.40 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.1, 143.2, 135.1, 129.5, 129.2, 128.8, 127.5, 127.4, 126.1, 48.9, 44.1, 21.9 ppm.

***N*-Cyclopropyl-2-phenylacetamide (4ah):** Yield 87 mg (50%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.19 (m, 5 H), 5.52 (br. s, 1 H), 3.54 (s, 2 H), 2.67 (tq, J = 7.1, 3.6 Hz, 1 H), 0.78–0.69 (m, 2 H), 0.44–0.37 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.7, 134.9, 129.5, 129.2, 127.5, 43.9, 22.9, 6.8 ppm. HRMS (ESI): m/z calcd. for $C_{11}H_{14}NO$ $[M + H]^+$ 176.1070; found 176.1068.

***N*-(Adamantan-1-ylmethyl)-2-phenylacetamide (4ai):**[18] Yield 144 mg (51%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.33 (m, 2 H), 7.32–7.24 (m, 3 H), 5.39 (br. s, 1 H), 3.59 (s, 2 H), 2.89 (d, J = 6.3 Hz, 2 H), 1.91 (br. s, 3 H), 1.71–1.64 (m, 3 H), 1.58–1.51 (m, 3 H), 1.33 (d, J = 2.4 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.3, 135.3, 129.6, 129.2, 127.6, 51.1, 44.2, 40.2, 37.0, 33.9, 28.3 ppm.

2-Phenyl-1-(pyrrolidin-1-yl)ethan-1-one (4ak):[24] Yield 113 mg (60%); colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.19 (m, 5 H), 3.66 (s, 2 H), 3.56–3.37 (m, 4 H), 1.98–1.78 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.7, 135.1, 129.1, 128.7, 126.8, 47.0, 46.1, 42.5, 26.3, 24.5 ppm.

2-Phenyl-1-(piperidin-1-yl)ethan-1-one (4al):[25] Yield 91 mg (45%); colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.19 (m, 5 H), 3.73 (s, 2 H), 3.61–3.53 (m, 2 H), 3.43–3.31 (m, 2 H), 1.66–1.43 (m, 4 H), 1.39–1.30 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.2, 135.4, 128.6, 128.5, 126.6, 47.2, 42.8, 41.1, 26.1, 25.5, 24.4 ppm.

1-Morpholino-2-phenylethan-1-one (4am):[12b] Yield 140 mg (68%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 2 H), 7.29–7.22 (m, 3 H), 3.74 (s, 2 H), 3.65 (s, 4 H), 3.54–3.40 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.7, 134.9, 128.9, 128.6, 127.0, 66.9, 66.6, 46.6, 42.3, 40.9 ppm.

***N*-Benzyl-*N*-methyl-2-phenylacetamide (4an):**[20] Yield 124 mg (52%); colourless liquid; mixture of two rotamers (1.4:1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major rotamer) = 7.36–7.18 (m, 9 H), 7.14–7.05 (m, 1 H), 4.61 (s, 2 H), 3.79 (s, 2 H), 2.90 (s, 3 H) ppm; ^{1}H NMR (400 MHz, $CDCl_3$): δ (minor rotamer) = 7.36–7.18 (m, 9 H), 7.14–7.05 (m, 1 H), 4.53 (s, 2 H), 3.76 (s, 2 H), 2.96 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.6, 171.3, 137.5, 136.7, 135.3, 135.1, 129.1, 129.0, 128.9, 128.8, 128.7, 128.2, 127.8, 127.5, 127.0, 126.9, 126.6, 53.9, 51.2, 41.4, 41.0, 35.4, 34.2 ppm.

***N*-Phenethylhexanamide (4be):**[26] Yield 191 mg (87%); yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 2 H), 7.25–7.16 (m, 3 H), 5.44 (br. s, 1 H), 3.52 (q, J = 6.8 Hz, 2 H), 2.82 (t, J = 6.9 Hz, 2 H), 2.15–2.08 (m, 2 H), 1.59 (quint, J = 7.6 Hz, 2 H), 1.36–1.21 (m, 4 H), 0.88 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.3, 139.1, 128.9, 128.8, 126.6, 40.7, 36.9, 35.9, 31.6, 25.6, 22.5, 14.0 ppm.

***N*-Phenethylundec-10-enamide (4ce):** Yield 270 mg (94%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 2 H), 7.25–7.13 (m, 3 H), 5.81 (m, 1 H), 5.37 (br. s, 1 H), 4.99 (dq, J = 17.1, 1.6 Hz, 1 H), 4.93 (m, 1 H), 3.56–3.48 (m, 2 H), 2.82 (t, J = 6.9 Hz, 2 H), 2.15–2.08 (m, 2 H), 2.08–1.99 (m, 2 H), 1.63–1.56 (m, 2 H), 1.41–1.27 (m, 10 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.2, 139.3, 139.1, 128.9, 128.8, 126.6, 114.3, 40.6, 37.0, 35.9, 33.9, 29.4, 29.2, 29.1, 25.9 ppm. HRMS (ESI): m/z calcd. for $C_{19}H_{30}NO$ $[M + H]^+$ 288.2322; found 288.2323.

***N*-Phenethylhex-5-ynamide (4de):** Yield 157 mg (73%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.28 (m, 2 H), 7.25–7.16 (m, 3 H), 5.50 (br. s, 1 H), 3.53 (q, J = 6.9 Hz, 2 H), 2.82 (t, J = 6.9 Hz, 2 H), 2.30–2.18 (m, 4 H), 1.94 (t, J = 2.6 Hz, 1 H), 1.83 (quint, J = 7.0 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.0, 138.7, 128.6, 128.5, 126.4, 83.3, 68.9, 40.4, 35.5, 34.9, 24.0, 17.6 ppm. HRMS (ESI): m/z calcd. for $C_{14}H_{18}NO$ $[M + H]^+$ 216.1383; found 216.1378.

***(E)*-*N*-Phenethylhex-3-enamide (4ee):** Yield 174 mg (80%); yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (m, 2 H), 7.24–7.12 (m, 3 H), 5.81 (br. s, 1 H), 5.63–5.52 (m, 1 H), 5.48–5.36 (m, 1 H), 3.48 (q, J = 6.9 Hz, 2 H), 2.87 (d, J = 7.1 Hz, 2 H), 2.78 (t, J = 6.9 Hz, 2 H), 2.01 (q, J = 6.9 Hz, 2 H), 0.94 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.5, 138.9, 137.9, 128.8, 128.6, 126.5, 121.6, 40.6, 40.5, 35.6, 25.5, 13.4 ppm. HRMS (ESI): m/z calcd. for $C_{14}H_{20}NO$ $[M + H]^+$ 218.1539; found 218.1547.

Methyl 9-Oxo-9-(phenethylamino)nonanoate (4fe): Yield 300 mg (98%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.25 (m, 2 H), 7.23–7.14 (m, 3 H), 5.57 (br. s, 1 H), 3.64 (s, 3 H), 3.53–3.46 (m, 2 H), 2.81 (d, J = 7.0 Hz, 2 H), 2.28 (dt, J = 7.5, 2.3 Hz, 2 H), 2.12–2.06 (m, 2 H), 1.66–1.50 (m, 4 H), 1.32–1.22 (m, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.0, 173.2, 138.9, 128.5, 128.3, 126.2, 51.2, 40.5, 36.4, 35.6, 33.8, 28.9, 28.8, 28.7, 25.5, 24.7 ppm. HRMS (ESI): m/z calcd. for $C_{18}H_{28}NO_3$ $[M + H]^+$ 306.2064; found 306.2063.

7-Bromo-*N*-phenethylheptanamide (4ge): Yield 280 mg (90%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 2 H), 7.25–

7.17 (m, 3 H), 5.42 (br. s, 1 H), 3.56–3.49 (m, 2 H), 3.39 (t, J = 6.8 Hz, 2 H), 2.82 (t, J = 6.9 Hz, 2 H), 2.12 (t, J = 7.5 Hz, 2 H), 1.89–1.78 (m, 2 H), 1.61 (quint, J = 7.5 Hz, 2 H), 1.48–1.38 (m, 2 H), 1.38–1.22 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0, 139.0, 128.8, 128.7, 126.6, 40.6, 36.6, 35.8, 33.9, 32.6, 28.4, 27.9, 25.5 ppm. HRMS (ESI): m/z calcd. for $C_{15}H_{23}Br^{79}NO$ [M + H]$^+$ 312.0958; found 312.0957. HRMS (ESI): m/z calcd. for $C_{15}H_{23}Br^{81}NO$ [M + H]$^+$ 314.0938; found 314.0938.

***N*-Phenethylcyclopentanecarboxamide (4he):** Yield 167 mg (77%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.27 (m, 2 H), 7.25–7.15 (m, 3 H), 5.54 (br. s, 1 H), 3.51 (dt, J = 6.9, 5.9 Hz, 2 H), 2.81 (t, J = 6.9 Hz, 2 H), 2.50–2.37 (m, 1 H), 1.86–1.65 (m, 6 H), 1.60–1.47 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.3, 139.2, 128.9, 128.7, 126.6, 46.0, 40.7, 35.9, 30.5, 26.0 ppm. HRMS (ESI): m/z calcd. for $C_{14}H_{20}NO$ [M + H]$^+$ 218.1539; found 218.1539.

(1*R*,4*R*)-4-Methyl-*N*-phenethylcyclohexane-1-carboxamide (4ie): Yield 146 mg (60%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 2 H), 7.25–7.16 (m, 3 H), 5.40 (br. s, 1 H), 3.55–3.47 (m, 2 H), 2.81 (t, J = 6.9 Hz, 2 H), 1.93 (m, 1 H), 1.87–1.69 (m, 4 H), 1.48–1.24 (m, 3 H), 0.95–0.83 (m, 5 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.2, 139.1, 128.9, 128.7, 126.5, 45.4, 40.5, 35.8, 34.6, 32.1, 29.7, 22.6 ppm. HRMS (ESI): m/z calcd. for $C_{16}H_{24}NO$ [M + H]$^+$ 246.1852; found 246.1853.

(±)-*N*-Phenethyl-2-phenylpropanamide (4je):[27] Yield 195 mg (77%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.14 (m, 8 H), 7.01–6.96 (m, 2 H), 5.31 (br. s, 1 H), 3.54–3.44 (m, 2 H), 3.42–3.33 (m, 1 H), 2.69 (dt, J = 6.8, 1.6 Hz, 2 H), 1.49 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.2, 141.4, 138.9, 129.0, 128.8, 128.7, 127.8, 127.4, 126.5, 47.3, 40.8, 35.7, 18.4 ppm.

***N*-Phenethyl-2,2-diphenylacetamide (4ke):**[28] Yield 53 mg (17%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.15 (m, 13 H), 7.06–7.02 (m, 2 H), 5.54 (br. s, 1 H), 4.87 (s, 1 H), 3.56 (q, J = 6.8 Hz, 2 H), 2.78 (t, J = 6.8 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.9, 139.6, 138.8, 129.1, 128.9, 128.8, 127.4, 126.6, 59.5, 41.0, 35.7 ppm.

2-(4-Aminophenyl)-*N*-benzylacetamide (4me): Yield 114 mg (45%); yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.16 (m, 3 H), 7.08–7.02 (m, 2 H), 6.96–6.90 (m, 2 H), 6.66–6.59 (m, 2 H), 5.40 (br. s, 1 H), 3.49–3.39 (m, 4 H), 2.72 (t, J = 6.9 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.8, 145.7, 138.9, 130.6, 128.8, 128.6, 126.5, 124.6, 115.7, 43.1, 40.8, 35.7 ppm. HRMS (ESI): m/z calcd. for $C_{16}H_{19}N_2O$ [M + H]$^+$ 255.1492; found 255.1488.

3-(1*H*-Indol-3-yl)-*N*-phenethylpropanamide (4ne):[29] Yield 192 mg (66%); white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (br. s, 1 H), 7.63 (d, J = 7.9 Hz, 1 H), 7.41 (d, J = 8.1 Hz, 1 H), 7.33–7.23 (m, 4 H), 7.18 (t, J = 7.4 Hz, 1 H), 7.09–7.02 (m, 2 H), 6.99 (s, 1 H), 5.49 (br. s, 1 H), 3.50 (q, J = 6.8 Hz, 2 H), 3.15 (t, J = 7.3 Hz, 2 H), 2.72 (t, J = 6.9 Hz, 2 H), 2.59 (t, J = 7.3 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.1, 138.9, 136.5, 128.8, 128.7, 127.2, 126.6, 122.2, 121.9, 119.5, 118.8, 114.9, 111.4, 40.7, 37.5, 35.7, 21.5 ppm.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra for all compounds.

Acknowledgments

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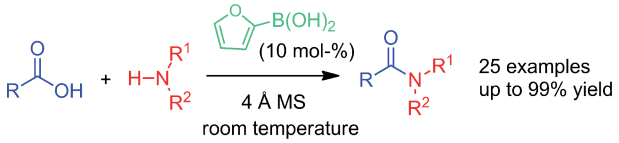
536 **Amides**



541 Commercially available, inexpensive 2-furanylboronic acid has been identified as an effective catalyst for the direct dehydrative amide formation of carboxylic acids and
546 amines. This transformation can be efficiently carried out *at room temperature* and is applicable to a wide range of carboxylic acids with primary and secondary amines to afford amides in good to excellent yields.

Keywords: Synthetic methods / Organocatalysis / Green chemistry / Amides / Amines / Carboxylic acids

