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Development of fluoros boronic acid catalysts integrated with sulfur for enhanced amidation efficiency†

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A thermally stable, fluoros sulfur-containing boronic acid catalyst has been developed and was shown to efficiently promote dehydrative condensation between carboxylic acids and amines under environmentally friendly conditions. The methodology can be applied to aliphatic, aromatic and heteroaromatic acids as well as primary and secondary amines. *N*-Boc protected amino acids were also successfully coupled in good yields with very little racemization. The catalyst could be reused four times with no significant loss of activity.

Introduction

The amide moiety is the most fundamental functional group in biology and chemistry. Besides being the key constituent of proteins, it is found in a wide variety of natural products, pharmaceuticals, fine chemicals and materials. Amides also serve as reaction intermediates for accessing other compound classes like heterocycles and complex amines.¹ Consequently the amide bond formation reaction is one of the most frequently performed reactions in organic chemistry research laboratories, and industrially it is commonplace in polymer, chemical, agrochemical and pharmaceutical production.² In view of its relevance, a plethora of strategies to generate the amide bond from alkene, alkynes, carbonyl compounds and other functional groups have been reported.³ Despite these developments, the direct condensation of carboxylic acids and amines in the presence of stoichiometric quantities of coupling reagents remains the most frequently employed approach to amide bond formation.⁴ However this process leads to the generation of large quantities of waste making it nonoptimal from the perspective of atom economy and cost effectiveness. To mitigate this issue, novel approaches to access amide containing molecules *via* transition metal or metal-free catalysis were developed.⁵ Among these approaches, the catalytic dehydrative condensation between carboxylic acids and amines is one of the most attractive methods because the only by-product of the reaction is water.

Using boronic acid as a catalyst for dehydrative condensation between carboxylic acids and amines have received much

attention since the seminal study by Yamamoto and coworkers in 1996.^{5m} Its popularity may be attributed to the catalyst's versatile reactivity, stability, low toxicity and its ultimate degradation to boric acid.⁶ Thus boronic acids are regarded as safe compounds and through the years, various arylboronic acid catalysts which promote the direct amidation reaction have been reported.⁷ However these reactions are almost universally carried out in toluene, *o*-xylene and chlorinated solvents which present safety and environmental issues and cost associated with their disposal. In addition, the water by-product is often scavenged by adding excess molecular sieves into the reaction mixture or by azeotropic reflux. The use of molecular sieves is common in the literature as it enables the catalytic amidation to occur at lower temperatures but they could possibly lead to increase solvent usage during the reaction and workup. Moreover molecular sieves are impractical in large-scale reactions due to the need to adequately dry them under high temperature and vacuum before use (large energy input).^{5b}

The move towards the adoption of sustainable chemistry has stimulated renewed interest in new methodologies for boronic acid-catalyzed amide bond formation. The most prevalent strategy involves the development of reusable boronic acid such as solid-phase,⁸ mesocellular siliceous foam (MCF)-supported,⁹ fluoros¹⁰ and phase-transfer boronic acid catalysts.^{8b} Despite the potential reusability of these boronic acids, the solvents employed in the amidation reactions remained unchanged. Since there is considerable merit in promoting the use of less harmful solvents¹¹ which would also help to increase sustainability within the industry, we sought to develop an operationally simple catalytic protocol for the formation of amide bonds. We herein present a new recyclable boronic acid catalyst which is able to promote amide/peptide bond formation reaction under neat or environmentally friendlier solvent conditions and without the need for any additives or dehydrating agents.

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Results and discussion

Inspired by earlier works on *o*-substituted phenylboronic acid¹¹ catalyzed reaction between carboxylic acids and amines which suggested that the *o*-substituent (X) is capable of engaging in O–H...X hydrogen bonding to stabilize the rate-determining transition-state and thus facilitate hemiaminal dehydration, we designed two sulfur-containing catalysts **1a–b** (Fig. 1) to appraise both the effects of the Lewis basicity of sulfur and the distance between the sulfur and boron on amide bond formation. A perfluoroalkyl chain (–C₈F₁₇) was tagged to each of the catalysts to enable easy purification and catalyst recovery. Catalysts **1a–b** are classified as “light fluororous” compounds (fluorine content <60%)¹² which have lower toxicity and persistence compared to “heavy fluororous” ones. They can be separated from the non-fluororous compounds using fluororous silica gel eluted with methanol and the fluororous silica gel can be reused multiple times after washing with acetone.¹³ Thus, compared to conventional column chromatography, this technique reduces the volume of solvent used and waste generated.

Initial assessment of the catalytic efficiencies of **1a–b** (10 mol%) was conducted using phenylacetic acid **A** (1.1 equiv.) and benzylamine **B** (1 equiv.) in toluene under azeotropic reflux with removal of water *via* a Dean–Stark apparatus. The reaction was found to be completed after 17 h and provided *N*-benzyl-2-phenylacetamide **2a** in 73 and 99% yields respectively (Table 1, entry 1). Similarly, lactamization of 6-amino-hexanoic acid under the same reaction condition for 20 h with catalyst **1b** also gave ϵ -caprolactam in higher yield than with catalyst **1a** (Table 1, entry 2). In both reactions, the spent catalysts **1a–b** were readily recovered in quantitative yields. Since **1b** proved to be the more effective catalyst for this model reaction, it was used for subsequent reactions.

To optimize the reaction conditions, we first varied the solvent (Table 2, entries 2–4) and found that the reaction proceeded most efficiently under neat condition. Encouraged by the result, we investigated if the reaction could be carried out in a sealed tube under microwave irradiation. A neat reaction mixture was thus microwave irradiated at 130 °C and the reaction was followed by TLC every 15 min. The reaction was completed after 1 h and provided **2a** in 82% (Table 2, entry 5). Optimization of the reaction conditions by varying temperature, equivalence of **A** and **B**, and catalyst loading eventually gave **2a** in 99% yield when the reaction was performed under neat condition with **A** : **B** = 1 : 1.3 equivalence and 5 mol% of catalyst **1b** at 150 °C for 15 min (Table 2, entry 9). After the reaction, the excess base was removed by an aqueous acid wash and the product **2a** and catalyst **1b** were easily separated *via* fluororous solid-phase extraction (F-SPE) with fluororous silica and

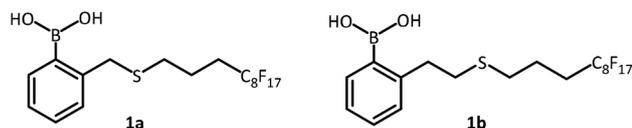


Fig. 1 Boronic acid catalysts.

Table 1 Comparing the effectiveness of catalysts **1a** and **1b** in amidation and lactamization reactions

Entry	Substrate	Yield (%)	
		1a	1b
1		73	99
2		70	90

methanol–water as eluent. This process significantly reduced the reaction time and solvent requirements as there was no need for chromatographic purification.

To explore the generality of this process, we prepared a selection of amides using various primary amines and structurally different carboxylic acids. The reaction proceeded cleanly to give the desired secondary amides **2a–2g** in excellent yields. Catalyst **1b** was also useful for reactions between secondary amines and carboxylic acids to give tertiary amides (**2k–2m**, Fig. 2) in very good yields.

To investigate if the methodology was applicable to peptide synthesis, we directed our efforts to the amidation of amino acids as they are important renewable raw materials for the synthesis of biological active targets. Initial assessment was conducted using the lactamization reaction of 5-aminovaleric acid. However under neat conditions, the isolated yield of the desired lactam was low with the side-products arising from intermolecular amidation reaction. To circumvent this problem, we diluted the reaction mixture with solvent such as anisole or benzotrifluoride¹⁴ and found that in the latter solvent, the side-product was absent and δ -valerolactam **2i** was obtained in 95% yield. Similarly, 4-aminobutyric acid and 6-aminocaproic acid gave γ -butyrolactam **2h** and ϵ -caprolactam **2j** respectively in excellent yields. Encouraged by these results, we proceeded to explore other coupling partners for this reaction.

Table 2 Optimization of amidation reaction using a mixture of phenylacetic acid **A** and benzylamine **B** with catalyst **1b**

Entry	Solvent	Catalyst loading	A : B	Temp, time	Yield ^d (%)
1 ^a	Toluene	10 mol%	1.1 : 1	125 °C, 17 h	99
2 ^a	2-MeTHF	10 mol%	1.1 : 1	100 °C, 17 h	44
3 ^a	Anisole	10 mol%	1.1 : 1	130 °C, 17 h	71
4 ^b	Neat	10 mol%	1.1 : 1	130 °C, 17 h	82
5 ^c	Neat	10 mol%	1.1 : 1	130 °C, 1 h	82
6 ^c	Neat	10 mol%	1 : 1.1	130 °C, 1 h	87
7 ^c	Neat	10 mol%	1 : 1.3	130 °C, 1 h	91
8 ^c	Neat	10 mol%	1 : 1.3	150 °C, 15 min	94
9 ^c	Neat	5 mol%	1 : 1.3	150 °C, 15 min	99
10 ^c	Neat	1 mol%	1 : 1.3	150 °C, 15 min	93

^a Azeotropic reflux. ^b Conventional heating with water removal *via* a Dean–Stark apparatus. ^c MW. ^d Isolated yields.



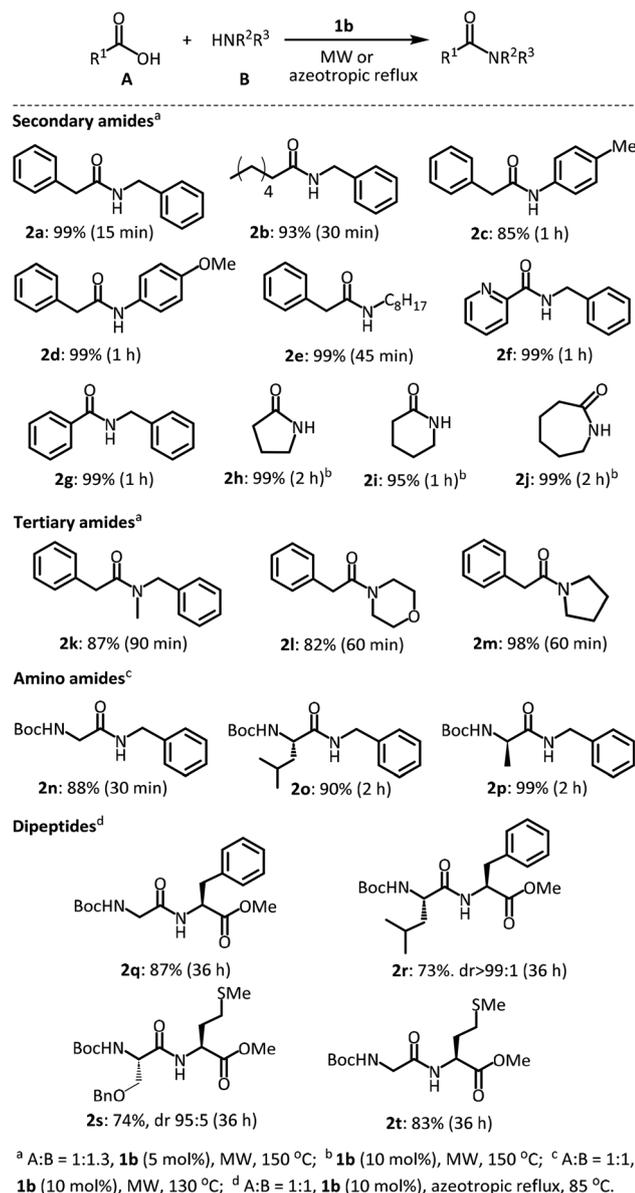


Fig. 2 Scope of **1b**-catalyzed amide bond formation.

Amidation of *N*-Boc-protected amino acids with benzylamine under neat condition and microwave irradiation at 130 °C gave the corresponding amino amides (**2n–2p**, Fig. 2) in good yields. However when the same reaction condition was applied to dipeptide synthesis using Boc-glycine and phenylalanine methyl ester, the reaction was sluggish and did not proceed to completion. This was attributed to the heterogenous reaction mixture and thus solvent was added to keep the reaction mixture liquid. We explored different solvents (entries 2–6, Table 3) and found that the reaction proceeded most efficiently in benzotrifluoride providing the desired dipeptide **2q** in 90% yield. However when the same reaction condition was applied to the dipeptide synthesis between Boc-leucine and phenylalanine, HPLC analysis of the product showed that the compound was a 60:40 mixture of two diastereomers. To address the

problem of racemization, the reaction was carried out *via* azeotrope water removal (reverse Dean–Stark conditions) in benzotrifluoride (azeotropic temperature for 90% benzotrifluoride^{14b} is 80 °C) at lower temperatures (entries 7–8, Table 3). Pleasingly, the reactions of phenylalanine with Boc-glycine and Boc-leucine both proceeded efficiently at 85 °C to provide compounds **2q** and **2r** in 87% and 73% yields respectively and there was also no detectable racemization in the reaction of Boc-leucine and phenylalanine. Amidation using other amino acids also gave the corresponding dipeptides in good yields.

Next, we investigated the possibility of recycling and reusing catalyst **1b**. The amidation reactions were performed under the optimized reaction conditions and the recycling experiments were carried out over 4 cycles (Table 4). Gratifyingly, the fluoroboric acid catalyst **1b** recovered from reaction under microwave irradiation at 150 °C or prolonged reflux conditions was indistinguishable from the original catalyst and showed minimal decline in catalytic activity even after multiple recovery steps. Comparison of the yields after each cycle after a fixed reaction time also showed that the recovery of catalyst **1b** was very good.

Experimental

General

All chemicals purchased were used without further purification. Reactions were carried out under N₂ with commercially obtained anhydrous solvents. Analytical thin-layer chromatography (TLC) was carried out on pre-coated F254 silica plates and visualized with UV light. F-SPF was performed with Fluoro-Flash® silica gel (40 micron). ¹H and ¹³C NMR spectra were recorded at 298 K. Chemical shifts are expressed in terms of ppm relative to the internal standard tetramethylsilane (TMS). Mass spectra were performed under EI and ESI mode. Microwave reactions were performed on the Anton Paar Monowave 400 microwave synthesizer in quartz pressure tubes.

Synthesis of fluorous boronic acid **1b**

The synthesis of fluorous catalyst **1b** is outlined in Scheme 1.

4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-2-iodo-1-undecanol (**4**)

A mixture of C₈F₁₇I (12.3 mL, 46.6 mmol) and AIBN (0.197 g, 1.2 mmol) was stirred at 95 °C for 15 min under N₂. To the mixture, **3** (4.1 mL, 60.3 mmol) was added dropwise and the resulting solution was stirred for 20 h at 95 °C. After completion of reaction, the crude mixture was cooled to room temperature and the resulting solid dissolved in methanol. The crude mixture was evaporated under reduced pressure and recrystallized from hexane to give **4** as an off-white solid (13.9 g, 50%). ¹H NMR (400 MHz, CDCl₃): δ 4.47–4.41 (m, 1H), 3.86–3.77 (m, 2H), 3.09–2.94 (m, 1H), 2.85–2.69 (m, 1H), 1.81 (br s, 1H). ¹³C NMR (125 MHz, CDCl₃): δ 67.9, 37.5 (t, *J*(C, F) = 20 Hz), 21.8. ¹⁹F NMR (377 MHz, CDCl₃): δ –80.8 (t, *J* = 9.69 Hz, 3F), –112.2 to –114.5 (qt, *J* = 269.9, 13.8 Hz, 2F), –121.5 to –121.6 (m, 2F), –121.9 (m,



Table 3 Optimization of dipeptide synthesis using Boc-glycine and phenylalanine methyl ester with catalyst **1b** (10 mol%)

Entry	Solvent	Method, temp, time	Yield (%)
1	Neat	MW, 130 °C, 2 h	30
2	Diethyl carbonate	MW, 130 °C, 2 h	60
3	Ethylene carbonate	MW, 130 °C, 2 h	40
4	Propylene carbonate	MW, 130 °C, 2 h	45
5	Benzotrifluoride	MW, 130 °C, 2 h	90
6	Cyclopentyl methyl ether	MW, 130 °C, 2 h	55
7	Benzotrifluoride	Azeotropic reflux, 120 °C, 16 h	65
8	Benzotrifluoride	Azeotropic reflux, 85 °C, 36 h	87

Table 4 Recovery and reuse of catalyst **1b**

Cycle	1	2	3	4
Yield (%)	99	99	99	92
Recovered 1b (wt%)	99	99	99	97
Cycle	1	2	3	4
Yield (%)	87	85	85	85
Recovered 1b (wt%)	99	99	99	99

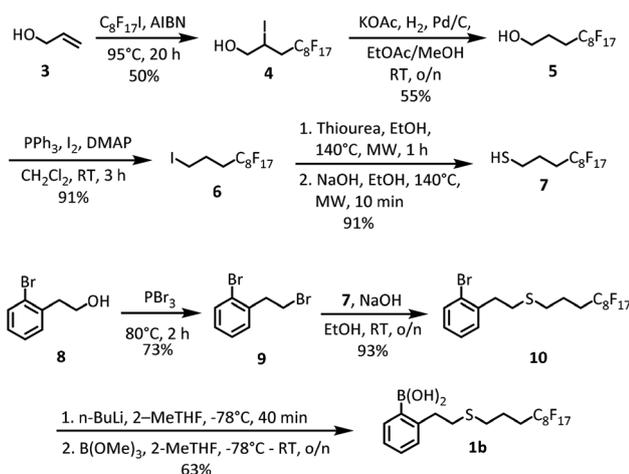
under reduced pressure. The residue was taken up in CH₂Cl₂ and washed successively with H₂O (3 × 50 mL) and brine (1 × 50 mL). The organic layer was dried over MgSO₄ and dry-loaded onto silica. The crude product was purified through column chromatography using a gradient eluent system of hexane : EA (16 : 1 to 4 : 1) to give **5** as a colourless oil, which solidifies at room temperature to a white crystalline solid (6.03 g, 55%). ¹H NMR (400 MHz, CDCl₃): δ 3.74 (t, *J* = 6.12 Hz, 2H), 2.28–2.15 (m, 2H), 1.90–1.83 (m, 2H), 1.78 (br s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 61.4, 27.6 (t, *J* = 22.1 Hz, C–F), 23.4. ¹⁹F NMR (377 MHz, CDCl₃): δ –80.9 (t, *J* = 10.63 Hz, 3F), –114.4 (t, *J* = 13.3 Hz, 2F), –121.8 to –122.0 (m, 6F), –122.8 (m, 2F), –123.5 (m, 2F), –126.2 (m, 2F). HRMS (+EI) calcd. for C₁₁H₆F₁₇O: 477.0142; found: 477.0146.

1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-Heptadecafluoro-11-iodoundecane (**6**)

A mixture of **5** (6.03 g, 12.6 mmol), triphenylphosphine (3.97 g, 15.1 mmol) and 4,4-dimethylaminopyridine (2.31 g, 18.9 mmol) in CH₂Cl₂ (50 mL) was stirred at room temperature for 15 min. Iodine (4.8 g, 18.9 mmol) was added and the reaction was stirred for 3 h at room temperature. After completion of reaction, the mixture was quenched using 5% Na₂S₂O₄ solution (15 mL) and washed successively with H₂O (3 × 50 mL) and brine (1 × 50 mL). The organic layer was dried over MgSO₄ and dry-loaded onto silica. The crude product was purified using column chromatography with pure hexane to give the desired product as a colourless oil, which solidifies at room temperature to a white, waxy solid (6.78 g, 91%). ¹H NMR (400 MHz, CDCl₃): δ 3.25 (t, *J* = 6.6 Hz, 2H), 2.29–2.10 (m, 4H). ¹³C NMR (100 MHz, CDCl₃): δ 31.9 (t, *J* = 22.2 Hz, C–F), 24.3, 3.9. ¹⁹F NMR (377 MHz, CDCl₃): δ –80.8 (t, *J* = 11.31 Hz, 3F), –113.7 (quint, *J* = 16.1 Hz, 2F), –121.7 to –121.9 (m, 6F), –122.7 (m, 2F), –123.4 (m, 2F), –126.1 to –126.2 (m, 2F). HRMS (+EI) calcd. for C₁₁H₆F₁₇I: 587.9237; found: 587.9241.

4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1-undecanethiol (**7**)

A solution of **6** (6.78 g, 11.5 mmol) and thiourea (1.05 g, 13.8 mmol) in deoxygenated EtOH (15 mL) was stirred at 140 °C under MW irradiation for 1 h. 4 M NaOH (3 mL) was then added into the clear solution and the mixture heated to 140 °C under MW irradiation for 10 min. The resulting light-yellow suspension was acidified using 4 M HCl (3 mL) and the cloudy

Scheme 1 Synthesis of catalyst **1b**.

4F), –122.7 (m, 2F), –123.5 (m, 2F), –126.1 (m, 2F). HRMS (+EI) calcd. for C₁₁H₆F₁₇OI: 603.9186; found: 603.9196.

4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1-undecanol (**5**)

To a solution of **4** (13.9 g, 23 mmol) in 2 : 1 EA : MeOH (90 mL), 10 wt% Pd/C (3 g) and KOAc (18.1 g, 0.184 mol) was added and stirred overnight under H₂. The reaction mixture was then filtered through a pad of Celite and the solvent was removed



suspension was extracted with diethyl ether (3 × 50 mL). The combined organic layer was washed with water (1 × 50 mL), brine (1 × 50 mL), dried over anhydrous MgSO₄ and evaporated under reduced pressure. The crude mixture was reconstituted in 30 mL hexane and filtered through a short silica column to yield the desired product as a yellowish oil (5.19 g, 91%). ¹H NMR (400 MHz, CDCl₃): δ 2.63 (dt, *J* = 8.0, 7.0 Hz, 2H), 2.29–2.16 (m, 2H), 1.97–1.80 (m, 2H), 1.38 (t, *J* = 8.2 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 29.5 (t, *J*(C, F) = 22.3 Hz), 24.6 (t, *J*(C, F) = 3.6 Hz), 23.9. ¹⁹F NMR (376 MHz, CDCl₃): –80.8 (t, *J* = 10.0 Hz, 3F), –113.9 to –114.03 (m, 2F), –121.7 to –121.9 (m, 6F), –122.7 (m, 2F), –123.5 (m, 2F), –126.1 to –126.2 (m, 2F).

1-Bromo-2(2-bromoethyl)benzene (9)

The procedure reported by Blanckaert *et al.* was used.¹⁵ 2-(2-Bromophenyl)ethanol (8) (1.48 g, 7.4 mmol) was added to a 25 mL vial, and the vial was cooled to 0 °C under N₂. Phosphorus tribromide (2.4 g, 0.83 mL, 8.9 mmol) was added dropwise. The reaction mixture was heated at 80 °C for 2 h. The mixture was poured onto crushed ice, saturated NaHCO₃ solution (20 mL) was added, and the mixture was stirred for 30 min. The mixture was extracted with chloroform (3 × 20 mL) and the combined extracts washed once with saturated NaHCO₃ solution (20 mL) and once with brine (20 mL). The solution was dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure. A clear oil was obtained, which was sufficiently pure and was used directly without further purification (1.42 g, 73%). ¹H NMR (400 MHz, CDCl₃): δ 7.60–7.56 (m, 1H), 7.31–7.27 (m, 2H), 7.18–7.14 (m, 1H), 3.62 (t, *J* = 7.4 Hz, 2H), 3.32 (t, *J* = 7.68 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 138.1, 133.0, 131.1, 128.7, 127.5, 124.3, 39.5, 30.9. MS (+ESI) calcd. for C₈H₉Br₂: 264.96; found: 264.79.

(2-Bromophenethyl)(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptafluoroundecyl)sulfane (10)

Compound 7 (5.19 g, 10.5 mmol) and NaOH (0.467 g, 11.7 mmol) were dissolved in degassed anhydrous EtOH (30 mL) and allowed to stir for 30 min at room temperature. A solution of 9 (3.06 g, 11.7 mmol) in 20 mL degassed anhydrous EtOH was added *via* syringe. The flask containing 9 was rinsed with 2 × 10 mL anhydrous EtOH and the combined reaction mixture was left to stir overnight at room temperature. Upon completion of the reaction, the colourless solution was evaporated to dryness before being redissolved in CH₂Cl₂ (50 mL), washed with water (25 mL), brine (1 × 25 mL) and dried over MgSO₄. The evaporated crude sample was purified by column chromatography (0–5% ethyl acetate in hexane) to afford the desired product as a yellowish liquid (6.65 g, 93%). ¹H NMR (400 MHz, CDCl₃): δ 7.55 (d, *J* = 7.84 Hz, 1H), 7.26–7.24 (dd, *J* = 4.88, 0.72 Hz, 1H), 7.12–7.07 (m, 1H), 3.04–2.99 (m, 2H), 2.79–2.76 (m, 2H), 2.64 (t, *J* = 7.04 Hz, 2H), 2.27–2.14 (m, 2H), 1.93 (quint, *J* = 7.08 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 139.5, 132.9, 130.8, 128.3, 127.6, 124.2, 36.8, 31.4, 31.2, 29.8, 20.2. ¹⁹F NMR (377 MHz, CDCl₃): δ –80.7 (t, *J* = 10.25 Hz, 3F), –114.0 (quint, *J* = 17.15 Hz, 2F), –121.7 to –121.9 (m, 7F), –122.7 (m, 2F), –123.4 (m, 2F),

–126.0 to –126.1 (m, 2F). HRMS (APCI) calcd. for C₁₉H₁₄F₁₇S: 597.0539; found: 597.0543.

(2-(2-((4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptafluoroundecyl)thio)ethyl)phenyl)boronic acid (1b)

The procedure by El Dine *et al.* was used.^{11c} To a solution of 10 (6.65 g, 9.8 mmol) in 10 mL dry 2-methyltetrahydrofuran at –78 °C under N₂ atmosphere was added dropwise *n*-BuLi solution (2 M in cyclohexane, 5.4 mL, 1.1 equiv.). The resulting mixture was stirred for 40 min, after which B(OMe)₃ (10.4 mL, 93.3 mmol, 9.5 equiv.) was added at –78 °C. The mixture was allowed to warm slowly to room temperature and stirred overnight. After the addition of 10 mL distilled water, the mixture was acidified with 1 M HCl to pH 1 and extracted with 30 mL EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated under vacuum. The resulting solid was recrystallized from hexane to give the desired product as a white solid (3.97 g, 63%). ¹H NMR (400 MHz, acetone-*d*₆): δ 7.62 (d, *J* = 7.32 Hz, 1H), 7.31–7.27 (td, *J* = 7.52, 1.52 Hz, 1H), 7.23–7.21 (m, 1H), 7.20 (s, 2H), 7.18–7.14 (td, *J* = 7.32, 1.36 Hz, 1H), 3.15–3.11 (m, 2H), 2.79–2.75 (m, 2H), 2.72 (t, *J* = 7.08 Hz, 2H), 2.44–2.31 (m, 2H), 1.96–1.89 (quint, *J* = 7.6 Hz, 2H). ¹³C NMR (125 MHz, acetone-*d*₆): δ 135.0, 130.7, 130.3, 130.2, 126.4, 126.2, 37.7, 34.7, 31.3, 31.2, 21.3. ¹⁹F NMR (377 MHz, acetone-*d*₆): δ –81.7 (t, *J* = 10.67 Hz, 3F), –114.4 (quint, *J* = 16.73 Hz, 2F), –122.3 to –122.5 (m, 6F), –123.3 (m, 2F), –123.9 (m, 2F), –126.7 to –126.8 (m, 2F). ¹¹B NMR (128 MHz, acetone-*d*₆): δ 30.2 (s, 1B). HRMS (+ESI) calcd. for C₁₉H₁₅[¹¹B]F₁₇O₂S: 641.0609; found: 641.0617.

General procedure for the synthesis of amides under azeotropic reflux

Into a two-neck round bottom flask equipped with a magnetic stirring bar was added the corresponding catalyst (0.05 mmol), phenylacetic acid (1 mmol), benzylamine (1.3 mmol), and solvent (5 mL). A Dean–Stark trap was fitted to the center neck, and a reflux condenser was fitted on top of the Dean–Stark trap. The reaction setup was wrapped with aluminium foil and heated in an oil bath for 17 h at the indicated temperature. The reaction mixture was then cooled down and transferred into a separatory funnel with ethyl acetate. The organic layer was washed with saturated Na₂CO₃ solution (3 mL), 5% citric acid solution (3 mL) and concentrated under reduced pressure. The resulting crude was reconstituted in 2-methyltetrahydrofuran (0.2 mL) and subjected to fluorous SPE. The non-fluorous and fluorous fractions were concentrated under reduced pressure to afford the amide and the recovered catalyst, respectively.

General procedure for synthesis of amides under neat condition and microwave irradiation

Into a G10 Anton Paar microwave vial equipped with a magnetic stirring bar was added the corresponding catalyst (0.05 eq., 5 mol%), acid (1 eq.), and amine (1.3 eq.). The vial was capped and subjected to microwave irradiation for the indicated reaction time at 150 °C, maximum power. Upon complete consumption of acid as confirmed by TLC, the reaction mixture



was reconstituted in 5 mL ethyl acetate. The organic layer was washed with saturated Na₂CO₃ solution (3 mL), 5% citric acid solution (3 mL) then concentrated under reduced pressure. The resulting crude was then reconstituted in 2-methyltetrahydrofuran (0.2 mL) and subjected to fluoros SPE. The non-fluorous and fluoros fractions were concentrated under reduced pressure to afford the amide and the recovered catalyst, respectively.

General procedure for fluoros SPE

2 g of FluoroFlash silica was added into a 10 mL cartridge. The fluoros silica was conditioned with 80 : 20 MeOH/H₂O (5 mL). The crude mixture was dissolved in 2-methyltetrahydrofuran (0.2 mL) and loaded onto the column using positive pressure, ensuring that all the solution is properly loaded. The flask containing the crude mixture was further rinsed with 3 × 1 mL 80 : 20 MeOH/H₂O to transfer the remaining crude product. The column was then flushed with 20% H₂O in MeOH (10 mL) to elute the non-fluorous fraction, and subsequently with MeOH (12 mL) to elute the fluoros fraction. Upon completion, the column was washed with acetone (5 mL). Prior to reuse, the column was reconditioned with 80 : 20 MeOH/H₂O (5 mL).

General procedure for the synthesis of dipeptides under azeotropic reflux

Into a two-neck round bottom flask equipped with a magnetic stirring bar was added the corresponding catalyst (0.1 mmol), Boc-protected amino acid (1 mmol), amino acid methyl ester (1 mmol), and benzotrifluoride (5 mL). A reverse Dean–Stark trap was fitted to the center neck, and a reflux condenser was fitted on top of the reverse Dean–Stark trap. The reaction setup was wrapped with aluminium foil and heated in an oil bath for 18–36 h at 85 °C. The reaction mixture was then cooled down and transferred into a separatory funnel with ethyl acetate. The organic layer was washed with saturated Na₂CO₃ solution (3 mL), 5% citric acid solution (3 mL) and concentrated under reduced pressure. The resulting crude was reconstituted in 2-methyltetrahydrofuran (0.2 mL) and subjected to fluoros SPE. The non-fluorous and fluoros fractions were concentrated under reduced pressure to afford the amide and the recovered catalyst, respectively. In cases where the resulting dipeptide contained impurities, the dipeptide was further purified through a short pad of silica using ethyl acetate as eluent.

Determination of diastereomeric purity through chiral HPLC

Diastereomeric purity was determined on an Agilent LC 1200 DAD HPLC system (Agilent Tech. Inc., Loveland, CO). Separation was carried out on a DAICEL Chiralpak ID (4.6 × 250 mm, 5 μm; Daicel Corporation, Japan), using an isocratic elution method (80% hexane/20% isopropanol, flow rate 1 mL min⁻¹, detector channel 210 nm). The chromatogram was monitored for 20 min for the detection of the major peak of test compound, which was expressed as a percentage of total peaks detected during the run.

Conclusions

Two versions of sulfur-containing fluoros boronic acid catalysts (**1a** and **1b**) were developed. Catalyst **1b** was shown to promote efficient dehydrative condensation between carboxylic acids and amines under environmentally friendly conditions. The methodology could be applied to the synthesis of secondary and tertiary amides, amino amides and dipeptides. Catalyst **1b** could also be recovered and reused four times with minimal loss of catalytic activity.

Author contributions

L.-C. L. and Y. L. conceptualized this work. Investigation was carried out by K. T. F. and Y.-P. W. and K. T. F., L.-C. L. and Y. L. contributed to the writing of the manuscript. Review and editing were performed by all authors. L.-C. L. and Y. L. contributed to funding acquisition. Supervision was performed by L.-C. L. and Y. L. Corresponding authors L.-C. L. and Y. L. contributed equally to this work.

Conflicts of interest

There are no conflicts to declare.

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