

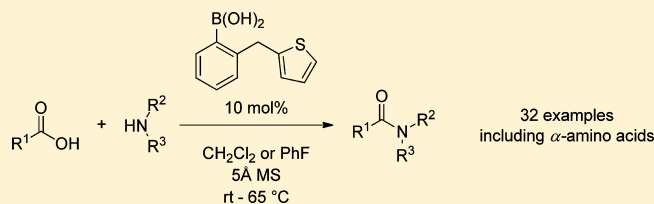
Catalytic Chemical Amide Synthesis at Room Temperature: One More Step Toward Peptide Synthesis

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S Supporting Information

ABSTRACT: An efficient method has been developed for direct amide bond synthesis between carboxylic acids and amines via (2-(thiophen-2-ylmethyl)phenyl)boronic acid as a highly active bench-stable catalyst. This catalyst was found to be very effective at room temperature for a large range of substrates with slightly higher temperatures required for challenging ones. This methodology can be applied to aliphatic, α -hydroxyl, aromatic, and heteroaromatic acids as well as primary, secondary, heterocyclic, and even functionalized amines. Notably, *N*-Boc-protected amino acids were successfully coupled in good yields with very little racemization. An example of catalytic dipeptide synthesis is reported.



INTRODUCTION

Among the fundamental chemical transformations of organic chemistry, amide synthesis is truly one of the most useful, encompassing a wide range of applications. From the synthesis of polymers, insecticides, and agrochemicals to pharmaceutical drugs, including peptides and lactams (antibiotics), the ubiquity of the amide bond has garnered the attention of the scientific community since the seminal reports of Schotten and Baumann 130 years ago.¹ In biological systems, the importance of the amide bond lies in sustaining life by linking amino acids together to form proteins. The most common amide synthesis involves the addition of an amine to an activated acyl compound derived from a carboxylic acid (anhydride, ester, or acyl chloride). Today, the long-sought activation of the carboxylic acid partner has come to a golden age using stoichiometric amounts of coupling reagents with the standard preparation of peptides longer than 50 amino acids.² However, this progress is tempered by the use of large amounts of toxic and expensive reagents and, as a result, poor overall atom economy and complications in the purification steps. According to recent reviews,³ anticipated developments in the catalysis of amide bond synthesis between amines and carboxylic acids would be widely adopted because of the considerable benefits when compared to the stoichiometric methods. Recently, this area of research has been notably rejuvenated with the introduction of catalysts. A catalyst able to achieve such transformation under mild conditions with the largest synthetic scope has been the focus of recent reports,⁴ which deal sparingly with metal salts⁵ and principally with boronic acid derivatives.⁶ The use of boron reagents to promote amide synthesis from carboxylic acids and amines has been known since 1970.⁷ However, the first efficient catalysis involving a boron derivative was reported in 1996 by Yamamoto using the 3,4,5-trifluoro-phenylboronic acid **1** in refluxing toluene (Figure

1).⁸ Consequently, other efficient boronic acids **2**,^{6d} **3**,^{6a} and **4** have been reported using high boiling temperature solvents.^{6c} Despite important progress achieved in this field of research, the only catalysts reported to promote amide synthesis at room temperature are boronic acids **5** and **6** developed by Hall.^{6f,g}

Another important feature of this catalysis is the racemization that is observed when chiral substrates, and especially α -amino acids, are involved, even under mild conditions.⁹ Indeed, α -amino acids were found to be much more challenging compared to simple amines and carboxylic acids in terms of reactivity and configurational stability. Accordingly, the combined challenge of reactivity and racemization calls for further developments.

In the context of our program directed toward the elaboration of new borylation of anilines¹⁰ and boron-based catalysts, we report a new catalyst (**7f**) able to efficiently promote amide synthesis at room temperature and avoid racemization when α -amino acids are involved.

Inspired by Hall and Whiting results dealing with *o*-substituted arylboronic acids, we initiated our study by designing a series of catalyst candidates bearing a sulfur-containing moiety. The sulfur atom was anticipated to play a double role in the reaction by assisting in the formation of initial acyloxyboron intermediate **A** (Figure 2) and facilitating the collapse of tetrahedral intermediate **B**, which is the rate-determining step as shown in two independent DFT studies.¹¹

RESULTS AND DISCUSSION

Various boronic acids **7a–l** were envisaged to appraise both electronic and steric factors by exploring the effect of introducing a sulfur atom, the distance between the boron

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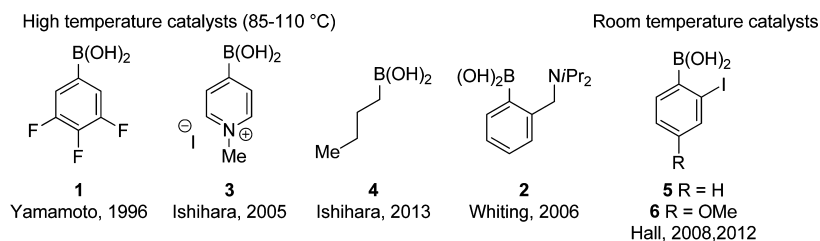


Figure 1. Previously reported active boronic acid catalysts.

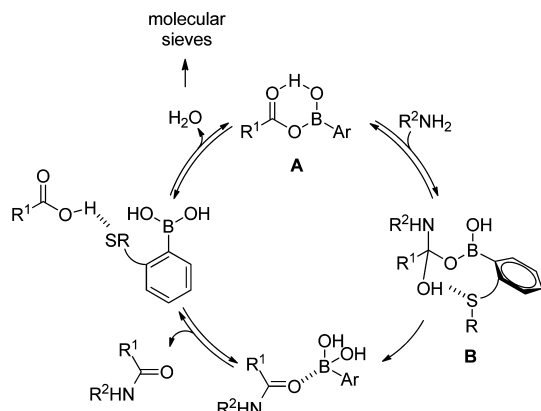
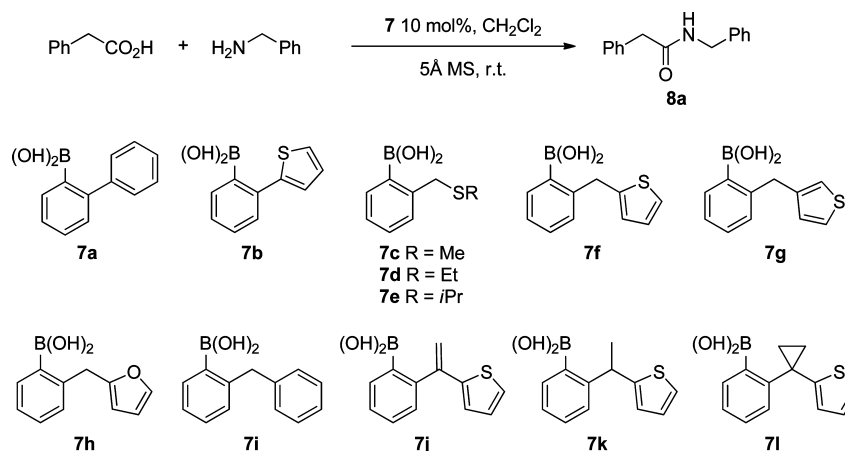


Figure 2. Working hypothesis.

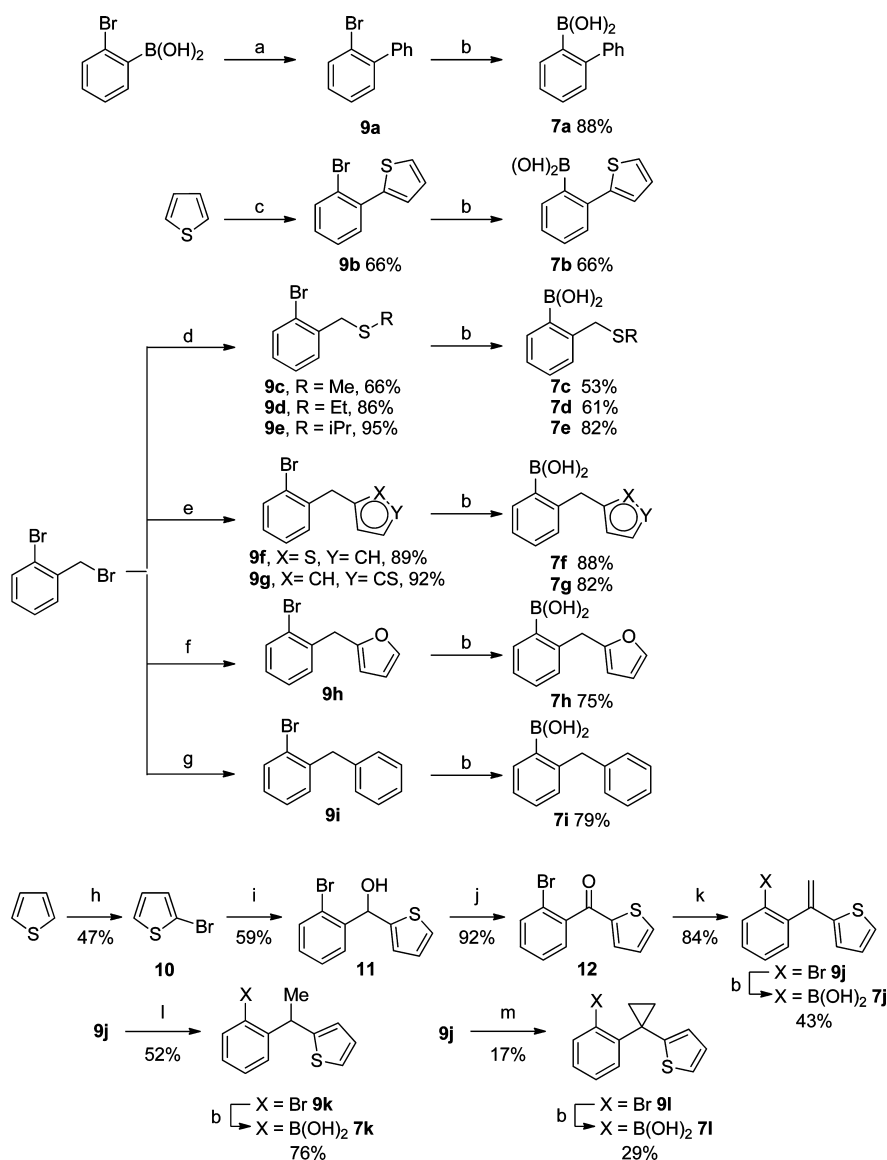
and sulfur atoms, and the steric hindrance of the neighboring substituents. Conveniently, a model reaction between phenylacetic acid and benzylamine using a substoichiometric amount of catalyst **7** was monitored by ^1H NMR using an internal reference (1,3,5-trimethoxybenzene). The results are disclosed in Table 1 (for optimization details, see Supporting Information).

Initially, the effectiveness of introducing a sulfur atom was evidenced by comparing the reactivity of biaryl-structured catalysts **7a** and **7b**. Substituting the phenyl ring in **7a** with 2-thiophene **7b** greatly increased the conversion from 34% to 88% after 8 h. Remarkably, a good conversion of 76% was observed only 30 min after the introduction of the amine partner. To improve the catalyst activity, we then used benzyl thioethers **7c–e**, where the sulfur atom is not involved in a thiophene heterocycle. Those boronic acids prove to be generally less efficient than **7b** with **7d** (R = Et) giving similar reactivity. The distance between the sulfur and boron atoms was then modified with catalysts **7f** and **7g**. Interestingly, clear improvement was obtained with **7f** with complete conversion being observed after 8 h. The difference in reactivity between **7f** and **7g** suggests an ideal conformation adopted by the catalyst in the transition state where the distance between the sulfur and the boron significantly affects the catalyst's efficiency. Accordingly, the replacement of thiophene with a furan or a phenyl ring led to the less efficient boronic acids **7h** and **7i**. Having recognized **7f** as the optimal catalyst, the steric hindrance at the benzylic position was altered by introducing various substituents. Catalysts **7j** and **7k** provided lower conversions of 58% and 81% of the desired amide, respectively, and suppression of activity was observed with **7l**. The various

Table 1. Comparative Amide **8a** Synthesis Catalyzed by Boronic Acids **7a–l** at Room Temperature^a

catalyst	NMR conversion (%)			catalyst	NMR conversion (%)		
	0.5 h	4 h	8 h		0.5 h	4 h	8 h
7a	30	34	34	7g	50	62	86
7b	76	82	88	7h	46	84	84
7c	29	40	50	7i	29	50	50
7d	66	82	84	7j	46	58	58
7e	58	75	84	7k	71	81	84
7f	77	90	>99	7l	0	0	0

^aReaction conditions: 0.50 mmol benzylamine, 0.55 mmol phenylacetic acid, 10 mol % **7**, 5 Å mol. sieves (1 g), dry CH_2Cl_2 , room temperature.

Scheme 1. Synthesis of the Boronic Acids 7^a

^a(a) KMnO₄, benzene/AcOH, 100 °C; (b) (i) *n*-BuLi, THF, −78 °C, (ii) B(OMe)₃, −78 °C; (c) (i) *n*-BuLi, THF, −40 °C, (ii) dibromobenzene, −20 °C, (iii) H₂O; (d) Alkylthiol, NaH, reflux; (e) Two or 3-thienylboronic acid, Pd(PPh₃)₄ (5 mol %), Na₂CO₃, DME/EtOH/H₂O, 90 °C; (f) Furan, *n*-BuLi, Et₂O, reflux; (g) AlCl₃, benzene/nitrobenzene, reflux; h) HBr, H₂O₂, Et₂O, −20 °C; (i) (i) Mg/I₂, THF, rt, (ii) 2-bromobenzaldehyde, THF, 0 °C; (j) MnO₂, CH₂Cl₂, reflux; (k) (Ph₃PMe)I, *n*-BuLi, THF, 0 °C; (l) Pd/C, H₂, EtOH, rt; (m) Et₂Zn, CH₂I₂, TFA, CH₂Cl₂, 0 °C.

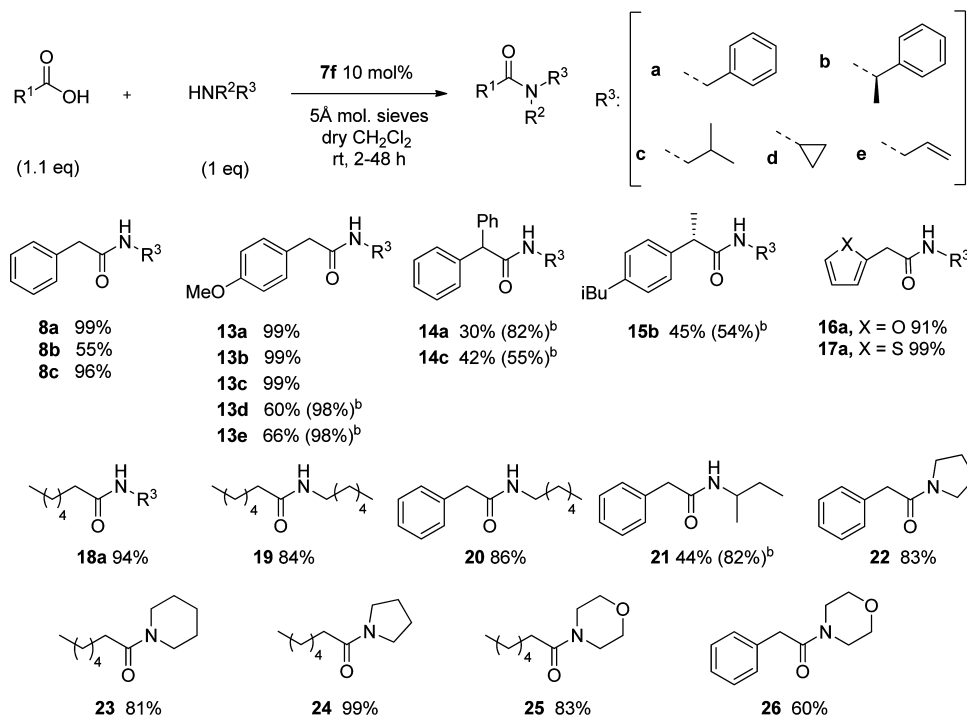
boronic acids 7 were prepared from the corresponding aryl bromides 9 using conventional bromine–lithium exchange followed by the trapping of the anion with trimethylborate (Scheme 1).

Having determined that boronic acid 7f is the optimal catalyst, we optimized the other reaction parameters, including catalyst loading, solvent, and dehydrating agent. After screening, optimal reaction conditions were found to be 10 mol % of 7f, CH₂Cl₂ as the solvent, and activated 5 Å powdered molecular sieves (see Supporting Information).

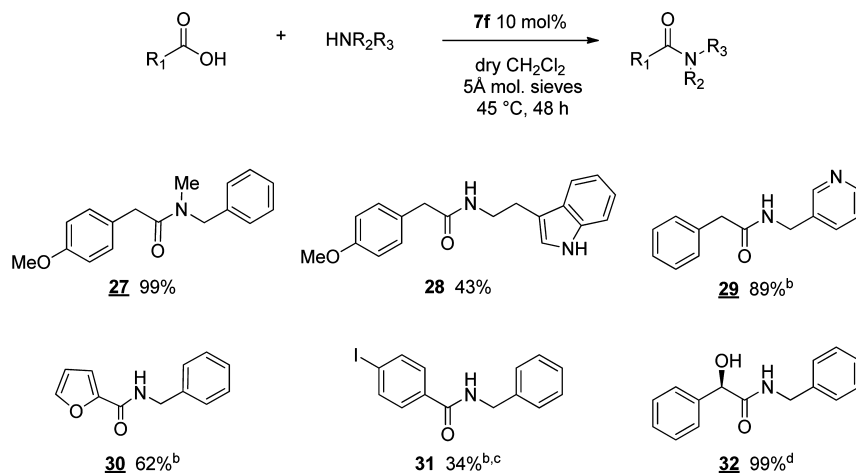
Scope of the Catalyzed Amide Synthesis. With the optimal conditions and the most active 2-(thiophen-2-ylmethyl)phenylboronic acid 7f in hands, the reaction was explored using various carboxylic acids and amines (Scheme 2). To explore the scope of the carboxylic acid partner, aliphatic, benzylic, benzoic, and heterocyclic carboxylic acids were

reacted with benzyl amine. *N*-Benzyl-2-arylacetamides 8a, 13a, furan derivative 16a, thiophene derivative 17a, and benzyl-2-alkylamide 18a were obtained in 91–99% yields at room temperature. Interestingly, the use of *p*-methoxy substituted phenyl acetic acid greatly enhances the reactivity, resulting in shorter reaction times (12a–c, see Supporting Information). More sterically hindered α -substituted arylacetic acids were poorly reactive at room temperature, but the corresponding amides 14a, 14c, and 15b were obtained in 54–82% yields when gently heated in dichloromethane under reflux. The optically active (*S*)-ibuprofen was successfully and mildly coupled with (*R*)- α -methylbenzylamine providing the corresponding amide 15b as a single diastereomer with no epimerization (see Supporting Information).

A variety of primary, secondary, aliphatic, and heterocyclic amines were then tested to further scrutinize the scope of the

Scheme 2. Substrate Scope of Room Temperature-Catalyzed Amide Synthesis^a

^aAll reactions were carried out with 0.55 mmol carboxylic acid, 10 mol % **7f**, 0.50 mmol amine, room temperature (unless otherwise stated), dry CH_2Cl_2 , powdered 5 Å mol. sieves (1 g). ^bReaction conducted at 45 °C.

Scheme 3. More Challenging Substrates in Amide Synthesis^a

^aAll reactions were carried out with 0.55 mmol carboxylic acid, 10 mol % **7f**, 0.50 mmol amine, 45 °C, dry CH_2Cl_2 , powdered 5 Å mol. sieves (1 g) unless otherwise stated. ^bWith **7f**, 20 mol %. ^cAt 50 °C in dry toluene. ^dAt 65 °C in dry 1,2-DCE.

reaction. Linear and α -substituted primary amines provided good to excellent yields at room temperature (see **8b–c**, **13b–c**, and **19–20**). Cyclopropylamine, *sec*-butylamine, and allylamine were found to be more challenging, requiring moderate heating at 45 °C to give **13d–e** and **21** in 82–98% yields. Cyclic secondary amines displayed useful reactivity at room temperature to furnish amides **22–26** in 60–99% yields, whereas a noncyclic secondary amine proved to be unreactive. However, gentle heating allowed the reaction to proceed with 99% yield (**27**, Scheme 3).

The scope of the reaction was further investigated using synthetically relevant amines functionalized with heterocycles, including 3-indoles and 3-pyridine (Scheme 3). Corresponding

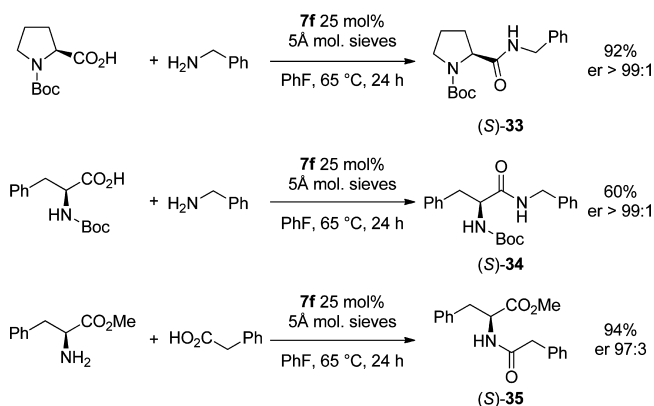
amides **28** and **29** were obtained in 43% and 89% yields, respectively. Aromatic carboxylic acids **30–31** were found to be reluctant, and additional catalyst loading was found to be effective in improving low initial conversions. Surprisingly, 4-iodobenzoic acid required a specific solvent switch to toluene to deliver **31** with a moderate 34% yield after optimization. Finally, α -hydroxyacid required a higher temperature and afforded **32** in 99% yield at 65 °C in dichloroethane.

Direct Coupling of α -Amino Acid Derivatives. Despite their significant importance in drug synthesis, α -amino acids derivatives being synthesized from catalytic amides is still difficult due to frequent racemization.¹² Only recently, high loading of 3,4,5-trifluorophenylboronic acid **1** or 2-nitro-

phenylboronic acid (typically 25–50 mol %) were found to promote amide synthesis involving a suitably protected α -amino acid.⁹ High temperatures associated with low performance catalysts resulted in extensive racemization with ee as low as 64% for amides derived from *N*-protected (*S*)-proline or (*S*)-phenylalanine. Under previous conditions, the peptide coupling of two α -amino acids required stoichiometric amounts of the catalysts (100 mol % of 2-methyl and 2-nitrophenylboronic acid) to provide moderate 46–62% yields of various protected pure dipeptides as single diastereomers (Pro-Phe, Phe-Val, Phe-Gly, or Phe-Phe).

Our attempts to address the issues related to α -amino acids began with the coupling of (*S*)-proline and (*S*)-phenylalanine to compare the relative efficiency of our catalyst **7f**. The optimization study pointed out the use of fluorobenzene as an optimal solvent among a variety of low polarity solvents (see Supporting Information). Accordingly, (*S*)-*N*-Boc-proline and (*S*)-*N*-Boc-phenylalanine were successfully coupled with benzyl amine, providing the corresponding amides **33** and **34** in 92% and 60% yields, respectively. HPLC analysis confirmed the absence of racemization (see Supporting Information). Finally, (*S*)-phenylalanine methyl ester was coupled with phenylacetic acid. Interestingly, amide **35** was previously reported for its propensity to racemize under boronic acid catalysis with substantial erosion of the enantiomeric excess being observed (ee of 68% with a 78% yield).⁹ Our result using catalyst **7f** compared favorably, because **35** was obtained with an excellent 94% yield and an enantiomeric ratio of 97:3.

Scheme 4. Direct Coupling of Protected Amino Acids^a



^aReaction conditions: 0.46 mmol Boc-Pro or Boc-Phe or phenyl acetic acid, 25 mol % **7f**, 0.46 mmol benzylamine or Phe-methyl ester, 5 Å mol. sieves (1 g), dry fluorobenzene, 65 °C, 24 h.

More importantly, **7f** was found to be effective for the synthesis of a dipeptide for which the use of a substoichiometric amount of reagents was unknown to date (Scheme 5).¹³

In our conditions, Boc-Phe-Val-OMe **36** was obtained with an encouraging 50% yield after 24 h. Careful examination of

NMR spectra showed no detectable amount of the (*R,S*) stereoisomer.

CONCLUSIONS

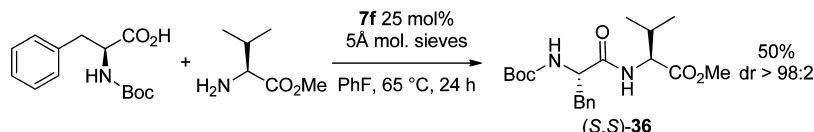
Although a number of catalytic protocols for amide synthesis involving carboxylic acids and amines have been developed, the use of protected amino acids is still a challenge. Driven by this goal, we were able to develop a mild, general, and efficient methodology using an original heterocyclic boronic acid as catalyst. Aliphatic, aromatic, and heterocyclic carboxylic acids as well as primary, secondary, aliphatic, and heterocyclic amines were successfully coupled at room temperature with good to excellent yields and reasonable reaction times. It is remarkable that almost no racemization was observed when chiral material was used. The operational simplicity, ease of catalyst synthesis, and absence of racemization make this an attractive approach compared to the use of stoichiometric activating reagents. However, it is obvious that there is still room for improvement, especially in the field of difficult peptide synthesis. This highlights the need for more effective and general catalysts. Further investigations concerning this topic are still ongoing in our laboratory.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all reactions were performed under an argon atmosphere using flame-dried glassware. Commercially available compounds were used without further purification. Solvents (THF, CH_2Cl_2 , MeCN, Et_2O , toluene) were dried and purified from a solvent purification system. 1,2-DCE, DMF, fluorobenzene, and chloroform were distilled from CaH_2 . MnO_2 was used without further treatment. NMR experiments were performed in deuterated solvents. ^1H NMR, ^{13}C NMR, and ^{11}B NMR spectra were recorded on 400 and 500 MHz spectrometers. Chemical shifts are reported in parts per million (ppm) relative to the residual solvent protons (^1H) or the solvent carbon (^{13}C) as internal standards. ^1H NMR data are presented as follows: chemical shift in ppm (δ) (multiplicity, coupling constant, integration, type of H). The following abbreviations were used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplet; td, triplet of doublet; ddd, doublet of doublet of doublet; m, multiplet; sept, septet; and quin, quintet. Because of their low intensity (resulting from quadruple coupling), ^{13}C signals arising from the quaternary carbon bearing the boronic acid group were not always observed and were therefore not always listed. Thin layer chromatography was performed on silica gel 60 F-524 plates (0.1 mm). Detection was accomplished by irradiation with a UV lamp or staining with KMnO_4 . Chromatographic separations were achieved on silica gel columns (Kieselgel 60, 40–63 μm). IR spectra were recorded on an FTIR spectrometer with frequencies expressed in cm^{-1} .

HSQCETGP (2D ^1H - ^{13}C correlation via double inept transfer phase sensitive using Echo/Antiecho-TPPI gradient selection with decoupling during acquisition using trim pulses in inept transfer), HMBGCPNDQF (2D ^1H - ^{13}C correlation via heteronuclear zero and double quantum coherence optimized on long-range couplings with low-pass J-filter to suppress one-bond correlations with no decoupling during acquisition using gradient pulses for selection), and DEPT135 (dept polarization transfer with 135 degree read pulse to give XH , XH_3 positive, and XH_2 negative with decoupling during

Scheme 5. Dipeptide Synthesis Catalyzed by **7f**



acquisition) were used to assign the NMR peaks. Mass spectra and high resolution mass spectra (HRMS) were obtained on a Q-TOF instrument and were recorded using either electron impact (EI) or electrospray ionization (ESI) techniques. Powdered molecular sieves and MgSO_4 were either dried for 3 h under high vacuum (<1 mbar) at 250 °C using a Kugelrohr instrument or using a microwave for 30 min.

Preparation of Aryl Bromides. General Procedure A. To a solution of alkylthiol (4.3 mmol) in 100 mL of THF at 0 °C was added sodium hydride (103 mg, 4.3 mmol). After the mixture was stirred at room temperature for 1 h, a solution of 2-bromobenzyl bromide (1g, 4 mmol) in THF (150 mL) was added, and the mixture was heated under reflux for 16 h. A saturated aqueous solution of NH_4Cl was added and extracted with Et_2O (3×50 mL). The organic phases were dried with MgSO_4 , filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using pentane/diethyl ether (80:20) as eluent to afford the desired product as an oil.

General Procedure B. To a sealed tube flushed with argon were introduced $\text{Pd}(\text{PPh}_3)_4$ (173 mg, 0.15 mmol, 5 mol %), 2-bromobenzyl bromide (750 mg, 3 mmol, 1.05 equiv), 2 or 3-thienylboronic acid (365 mg, 2.85 mmol), and Na_2CO_3 (1.58 g, 15 mmol). A mixture of degassed DME (16.2 mL), water (6.1 mL), and EtOH (1.22 mL) was added. The resulting suspension was stirred overnight at 90 °C. After being cooled to room temperature, the aqueous layer of the suspension was extracted with CH_2Cl_2 (2×40 mL). Drying of the organic phase over MgSO_4 and evaporation of the solvent gave the crude product, which was further purified by flash chromatography on silica gel using pentane (100%) to yield the desired product.

2-(2'-Bromophenyl)thiophene (9b). To a solution of thiophene (1.513 g, 18 mmol) in 14 mL of dry THF at -40 °C was *n*-BuLi (11.25 mL, 18 mmol, 1.6 M in hexane) added dropwise. After the mixture was stirred for 1 h at this temperature and further warmed slowly to -20 °C, 1,2-dibromobenzene (0.724 mL, 6 mmol) was added dropwise. The solution was warmed to room temperature overnight, then H_2O (20 mL) was added, and the resulting mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with Et_2O (60 mL), washed with brine, dried over MgSO_4 , filtered, and concentrated under vacuum. Purification of the crude mixture by flash column chromatography on silica gel (eluent: cyclohexane) afforded desired product **9b** as a colorless oil (946 mg, 3.96 mmol, 66%). The ^1H and ^{13}C data were consistent with those reported in the literature.¹⁴ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.68 (dd, $J = 8, 1.2$ Hz, 1H_{Ar}), 7.49 (dd, $J = 7.6, 1.6$ Hz, 1H_{Ar}), 7.40 (dd, $J = 5.2, 1.0$ Hz, 1H_{Ar}), 7.34 (td, $J = 7.6, 1.6$ Hz, 1H_{Ar}), 7.31 (dd, $J = 3.6, 0.8$ Hz, 1H_{Ar}), 7.18 (td, $J = 8.0, 1.6$ Hz, 1H_{Ar}), 7.12 (dd, $J = 5.2, 3.6$ Hz, 1H_{Ar}). ^{13}C NMR (400.0 MHz; CDCl_3) δ_{C} : 141.9 (C_{qAr}), 135.4 (C_{qAr}), 133.8 (CH_{Ar}), 132.1 (CH_{Ar}), 129.1 (CH_{Ar}), 127.9 (CH_{Ar}), 127.5 (CH_{Ar}), 127.1 (CH_{Ar}), 126.2 (CH_{Ar}), 123.0 (C_{qAr}).

2-Bromobenzyl(methyl)sulfide (9c). Following general procedure A, **9c** was obtained from methanethiol (0.24 mL, 4.3 mmol) as a colorless oil (799 mg, 3.68 mmol, 86%). The ^1H and ^{13}C data were consistent with those reported in the literature.¹⁵ ^1H NMR (400 MHz; CDCl_3) δ_{H} : 7.57 (d, $J = 8.0$ Hz, 1H_{Ar}), 7.44 (dd, $J = 7.8, 1.6$ Hz, 1H_{Ar}), 7.32–7.24 (m, 1H_{Ar}), 7.12–7.08 (m, 1H_{Ar}), 3.80 (s, 2H), 2.05 (s, 3H). ^{13}C NMR (400.0 MHz; CDCl_3) δ_{C} : 137.7 (C_{qAr}), 133.3 (CH_{Ar}), 130.9 (CH_{Ar}), 128.7 (CH_{Ar}), 127.5 (CH_{Ar}), 124.7 (C_{qAr}), 38.6 (CH_2), 15.3 (CH_3).

2-Bromobenzyl(ethyl)sulfide (9d). Following general procedure A, **9d** was obtained from ethanethiol (0.32 mL, 4.3 mmol) as a colorless oil (940 mg, 4.07 mmol, 95%). The ^1H and ^{13}C data were consistent with those reported in the literature.¹⁶ ^1H NMR (400.0 MHz; CDCl_3) δ : 7.56 (d, $J = 7.7$ Hz, 1H_{Ar}), 7.54 (d, $J = 7.7$ Hz, 1H_{Ar}), 7.38–7.24 (m, 1H_{Ar}), 7.11–7.07 (m, 1H_{Ar}), 3.85 (s, 2H), 2.52 (q, $J = 7.6$ Hz, 2H), 1.27 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 138.1 (C_{qAr}), 133.1 (CH_{Ar}), 130.7 (CH_{Ar}), 128.5 (CH_{Ar}), 127.4 (CH_{Ar}), 124.5 (C_{qAr}), 36.2 (CH_2), 25.7 (CH_2), 14.6 (CH_3).

2-Bromobenzyl(isopropyl)sulfide (9e). Following the general procedure A, **9e** was obtained from propane-2-thiol (0.40 mL, 4.3 mmol) as a colorless oil (970 mg, 3.96 mmol, 92%). The ^1H and ^{13}C data were consistent with those reported in the literature.¹⁷ ^1H NMR

(400.0 MHz; CDCl_3) δ_{H} : 7.56 (d, $J = 7.9$ Hz, 1H_{Ar}), 7.54–7.39 (m, 1H_{Ar}), 7.28–7.24 (m, 1H_{Ar}), 7.11–7.07 (m, 1H_{Ar}), 3.87 (s, 2H), 2.90 (sept, $J = 6.7$ Hz, 1H), 1.30 (d, $J = 6.7$ Hz, 6H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 138.3 (C_{qAr}), 133.2 (CH_{Ar}), 130.8 (CH_{Ar}), 128.6 (CH_{Ar}), 127.6 (CH_{Ar}), 124.5 (C_{qAr}), 35.5 (CH_2), 35.2 (CH), 23.5 (CH_3).

2-(2-Bromobenzyl)thiophene (9f). Following general procedure B, **9f** was obtained from 2-thienylboronic acid (365 mg, 2.85 mmol) as a colorless oil (642 mg, 2.54 mmol, 89%). TLC $R_f = 0.53$ (pentane: 100%). ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.61 (d, $J = 8.4$ Hz, 1H_{Ar}), 7.30–7.25 (m, 2H_{Ar}), 7.19–7.17 (m, 1H_{Ar}), 7.14–7.10 (m, 1H_{Ar}), 6.97–6.94 (m, 1H_{Ar}), 6.85–6.84 (m, 1H_{Ar}), 4.31 (s, 2H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 144.2 (C_{qAr}), 139.9 (C_{qAr}), 133.0 (CH_{Ar}), 130.8 (CH_{Ar}), 128.4 (CH_{Ar}), 127.7 (CH_{Ar}), 127.0 (CH_{Ar}), 125.8 (CH_{Ar}), 124.5 (C_{qAr}), 124.2 (CH_{Ar}), 36.3 (CH_2). ν_{max} (neat, cm^{-1}): 3067, 2914, 1734, 1588, 1568, 1475, 1467, 1437, 1233, 1107, 1037, 1024. HRMS (EI+) m/z : $[\text{M}^{+}]$ calcd for $\text{C}_{11}\text{H}_9^{79}\text{BrS}$, 251.9608; found, 251.9601.

3-(2-Bromobenzyl)thiophene (9g). Following general procedure B, **9g** was obtained from 3-thienylboronic acid (365 mg, 2.85 mmol) as a colorless oil (700 mg, 2.62 mmol, 92%). TLC $R_f = 0.52$ (pentane: 100%). ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.57 (dd, $J = 8.0, 1.2$ Hz, 1H_{Ar}), 7.28 (d, $J = 3.2$ Hz, 1H_{Ar}), 7.24–7.22 (m, 1H_{Ar}), 7.18–7.16 (m, 1H_{Ar}), 7.09 (dt, $J = 7.2, 1.2$ Hz, 1H_{Ar}), 6.95 (m, 2H_{Ar}), 4.10 (s, 2H). ^{13}C NMR (400.0 MHz; CDCl_3) δ_{C} : 140.2 (C_{qAr}), 139.8 (C_{qAr}), 133.0 (CH_{Ar}), 130.8 (CH_{Ar}), 128.5 (CH_{Ar}), 128.1 (CH_{Ar}), 127.7 (CH_{Ar}), 125.7 (CH_{Ar}), 124.7 (C_{qAr}), 121.9 (CH_{Ar}), 36.8 (CH_2). ν_{max} (neat, cm^{-1}): 3058, 2923, 2853, 1567, 1467, 1439, 1386, 1235, 1157, 1113, 1080, 1024, 939, 860, 833. Elemental analysis: Anal. Calcd for $\text{C}_{11}\text{H}_9\text{BrS}$: C, 52.19; H, 3.58; S, 12.67. Found: C, 52.51; H, 3.56; S, 12.35.

1-Benzyl-2-bromobenzene (9i). To a solution of 2-bromobenzyl bromide (1 g, 4 mmol) in 12 mL of benzene was injected AlCl_3 (336.6 mg, 4 mmol) dissolved in 4 mL of nitrobenzene under an argon atmosphere. The mixture was refluxed for 5 h. After cooling to room temperature, the mixture was extracted with Et_2O (2×20 mL), dried over MgSO_4 , and evaporated under vacuum. The obtained yellow crude product was submitted to Kugelrohr distillation where the nitrobenzene was removed and pure product **9i** was obtained as a colorless oil (889 mg, 3.6 mmol, 90%). The ^1H and ^{13}C data were consistent with those reported in the literature.¹⁸ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.57 (dd, $J = 8.0, 4.0$ Hz, 1H_{Ar}), 7.37–7.30 (m, 2H_{Ar}), 7.29–7.20 (m, 5H_{Ar}), 7.18–7.11 (m, 2H_{Ar}), 4.18 (s, 2H). ^{13}C NMR (400.0 MHz; CDCl_3) δ_{C} : 140.5 (C_{qAr}), 139.6 (C_{qAr}), 133.0 (CH_{Ar}), 131.2 (CH_{Ar}), 129.1 (CH_{Ar}), 128.6 (CH_{Ar}), 128.0 (CH_{Ar}), 127.6 (CH_{Ar}), 126.4 (CH_{Ar}), 121.9 (C_{qAr}), 41.6 (CH_2).

2-Bromothiophene (10). To a mixture of thiophene (50.4 g, 0.6 mol) and HBr (224 g, 2.76 mol, 150 mL, 48% aqueous) in 90 mL of Et_2O at -20 °C was added H_2O_2 (50 g, 1.47 mol) in ten portions over 40 min while the temperature slowly increased to 0 °C. Then, the reaction mixture was stirred for 15 min at room temperature. The organic and aqueous layers were separated, and the aqueous layer was extracted with pentane (4×50 mL). The combined organic layers were washed with water (2×50 mL), brine (20 mL), dried over MgSO_4 , and concentrated under vacuum to give the crude product, which was further purified by vacuum distillation (100 mmbar, 78 °C) to yield the desired product as a yellow oil (46.38 g, 0.28 mol, 47%). The ^1H and ^{13}C characterization data were consistent with those reported in the literature.¹⁹ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.43 (dd, $J = 5.6, 1.2$ Hz, 1H_{Ar}), 7.27 (dd, $J = 3.6, 1.2$ Hz, 1H_{Ar}), 7.08 (dd, $J = 8.0, 4.0$ Hz, 1H_{Ar}). ^{13}C NMR (400.0 MHz; CDCl_3) δ_{C} : 129.9 (CH_{Ar}), 127.7 (CH_{Ar}), 127.1 (CH_{Ar}), 112.2 (C_{qAr}).

2-(Bromophenyl)(thiophen-2-yl)methanol (11). To a suspension of magnesium (2.67 g, 110 mmol) in 10 mL of THF at rt were added a crystal of iodine and three drops of 2-bromothiophene. After the reaction started, a solution of 2-bromothiophene **10** (9.7 mL, 16.3 g, 100 mmol) in THF (80 mL) was added dropwise to maintain a gentle reflux. Then, the reaction mixture was cooled to rt and further stirred for 1 h before being cooled to 0 °C. To this cooled mixture (0 °C), a solution of 2-bromobenzaldehyde (8.75 mL, 13.9 g, 75 mmol) in THF

(75 mL) was added dropwise, and the reaction mixture was stirred at 0 °C for 30 min before being warmed slowly to rt for 1 h. HCl (3M, 150 mL) was added at 0 °C, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated under vacuum. The crude mixture was purified by column chromatography on silica gel and eluted with pentane/EtOAc (10:1) to give title product **11** as a colorless oil (11.96 g, 44 mmol, 59%). The ¹H and ¹³C characterization data were consistent with those reported in the literature.²⁰ ¹H NMR (400.0 MHz; CDCl₃) δ_H: 7.69 (dd, *J* = 7.9, 1.2 Hz, 1H_{Ar}), 7.55 (dd, *J* = 7.9, 0.9 Hz, 1H_{Ar}), 7.37 (t, *J* = 7.9 Hz, 1H_{Ar}), 7.27 (dd, *J* = 5.0, 1.0 Hz, 1H_{Ar}), 7.18 (dd, *J* = 7.9, 0.9 Hz, 1H_{Ar}), 6.94 (m, 1H_{Ar}), 6.91 (m, 1H_{Ar}), 6.34 (s, 1H), 3.28 (br s, 1H). ¹³C NMR (400.0 MHz; CDCl₃) δ_C: 146.3 (C_{qAr}), 142.1 (C_{qAr}), 132.8 (CH_{Ar}), 129.4 (CH_{Ar}), 127.9 (CH_{Ar}), 126.7 (CH_{Ar}), 125.6 (CH_{Ar}), 125.5 (CH_{Ar}), 122.4 (C_{qAr}), 71.0 (CH).

(2-Bromophenyl)(thiophen-2-yl)methanone (12). To a solution of the aryl bromide **11** (11 g, 40.8 mmol) in CH₂Cl₂ at rt was added MnO₂ (35.5 g, 409 mmol) and stirred at reflux overnight. The reaction mixture was cooled to rt, filtered over Celite, and washed with CH₂Cl₂. The combined filtrates were concentrated under vacuum to give title product **12** as a brown oil, which was pure enough to be used in the next step (10 g, 37.4 mmol, 92%). The ¹H and ¹³C data were consistent with those reported in the literature.¹⁸ ¹H NMR (400.0 MHz; CDCl₃) δ_H: 7.72 (dd, *J* = 4.9, 0.6 Hz, 1H_{Ar}), 7.60 (d, *J* = 7.8 Hz, 1H_{Ar}), 7.40–7.33 (m, 3H_{Ar}), 7.33–7.28 (m, 1H_{Ar}), 7.07 (t, *J* = 4.3 Hz, 1H_{Ar}). ¹³C NMR (400.0 MHz; CDCl₃) δ_C: 87.8 (C=O), 143.4 (C_{qAr}), 140.4 (C_{qAr}), 136.2 (CH_{Ar}), 135.8 (CH_{Ar}), 133.4 (CH_{Ar}), 131.4 (CH_{Ar}), 128.8 (CH_{Ar}), 128.5 (CH_{Ar}), 127.2 (CH_{Ar}), 119.4 (C_{qAr}).

2-(1-(2-Bromophenyl)vinyl)thiophene (9j). To a suspension of methyltriphenylphosphonium iodide (9.7 g, 24 mmol) in 30 mL of THF at 0 °C was *n*-BuLi (2.1 M in hexanes, 10.8 mL, 22.8 mmol) added dropwise, and the red reaction mixture was stirred at 0 °C for 30 min. This mixture was cannulated into a precooled (0 °C) solution of the aryl bromide **11** (3.2 g, 12 mmol) in THF (10 mL), and the reaction mixture was further stirred at 0 °C for 30 min before being slowly warmed to rt over 2 h. HCl (1M, 100 mL) was added to the reaction mixture, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated under vacuum. The crude mixture was purified by column chromatography on silica gel and eluted with pentane (100%) to give the title product **9j** as a colorless oil (2.66 g, 10 mmol, 84%). *Caution:* this is a photosensitive product that turns purple upon exposure to light. TLC *R_f* = 0.48 (pentane: 100%). ¹H NMR (400.0 MHz; CDCl₃) δ_H: 7.55 (d, *J* = 8.0 Hz, 1H_{Ar}), 7.28–7.20 (m, 2H_{Ar}), 7.18–7.11 (m, 2H_{Ar}), 6.84 (dd, *J* = 5.0, 3.8 Hz, 1H_{Ar}), 6.56 (d, *J* = 3.8 Hz, 1H_{Ar}), 5.73 (s, 1H), 5.03 (s, 1H). ¹³C NMR (400.0 MHz; CDCl₃) δ_C: 144.2 (C_{qAr}), 142.7 (C=CH₂), 142.1 (C_{qAr}), 133.1 (CH_{Ar}), 131.2 (CH_{Ar}), 129.4 (CH_{Ar}), 127.6 (CH_{Ar}), 127.4 (CH_{Ar}), 126.2 (CH_{Ar}), 125.3 (CH_{Ar}), 123.3 (C_{qAr}), 144.6 (C=CH₂). *ν*_{max} (neat, cm⁻¹): 2359, 2341, 1469, 1430, 1023, 892, 852, 831, 763, 732, 695, 668. HRMS (EI+) *m/z*: [M⁺] calcd for C₁₂H₉⁷⁹BrS, 263.9608; found, 263.9593.

2-(1-(2-Bromophenyl)ethyl)thiophene (9k). To a solution of the aryl bromide **9j** (500 mg, 1.9 mmol, 1.0 equiv) in 20 mL of EtOH was added Pd/C (10%, 600 mg), and the mixture was vigorously stirred at rt under an atmosphere of H₂ overnight. Pd/C (10%, 150 mg) was further added, and the reaction mixture was stirred for an additional 72 h. The reaction mixture was filtered over Celite, washed with EtOH, and the combined filtrates were concentrated under vacuum. The crude mixture was purified by column chromatography on silica gel and eluted with pentane (100%) to give title product **9k** as a colorless oil (260 mg, 0.97 mmol, 52%). TLC *R_f* = 0.58 (pentane: 100%). ¹H NMR (400.0 MHz; CDCl₃) δ_H: 7.57 (d, *J* = 8.0 Hz, 1H_{Ar}), 7.28–7.24 (m, 2H_{Ar}), 7.18 (dd, *J* = 5.0, 0.9 Hz, 1H_{Ar}), 7.11–7.05 (m, 1H_{Ar}), 6.95 (dd, *J* = 5.0, 1.4 Hz, 1H_{Ar}), 6.88–6.86 (m, 1H_{Ar}), 4.89 (q, *J* = 7.0 Hz, 1H), 1.70 (d, *J* = 7.0 Hz, 3H). ¹³C NMR (400.0 MHz; CDCl₃) δ_C: 149.2 (C_{qAr}), 145.2 (C_{qAr}), 133.0 (CH_{Ar}), 128.7 (CH_{Ar}), 128.2 (CH_{Ar}), 127.9 (CH_{Ar}), 126.7 (CH_{Ar}), 124.3 (CH_{Ar}), 124.1 (C_{qAr}),

123.8 (CH_{Ar}), 39.6 (CH), 22.6 (CH₃). *ν*_{max} (neat, cm⁻¹): 2359, 2468, 2437, 1019, 850, 828, 1019, 850, 828, 755, 744, 668. Elemental analysis: Anal. Calcd for C₁₂H₁₁BrS: C, 53.94; H, 4.15; S, 12.00. Found: C, 54.31; H, 4.29; S, 11.61.

2-(1-(2-Bromophenyl)cyclopropyl)thiophene (9l). To a solution of Et₂Zn (1 M in hexanes, 6 mL, 6 mmol) in 4 mL of CH₂Cl₂ at 0 °C was trifluoroacetic acid (460.0 μL, 684.1 mg, 6 mmol) added dropwise in CH₂Cl₂ (2 mL), and the reaction mixture was stirred at 0 °C for 20 min. CH₂I₂ (483.3 μL, 1.6 g, 6 mmol) in CH₂Cl₂ (2 mL) was added dropwise, and the reaction mixture was further stirred at 0 °C for 20 min. To the cooled solution, the aryl bromide **9j** (530.3 mg, 2 mmol) in CH₂Cl₂ (2 mL) was added dropwise, and the reaction mixture was allowed to warm slowly to rt overnight. HCl (1M, 20 mL) was added to the reaction mixture, which was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel and eluted with pentane (100%) to give title product **9l** as a colorless oil (92.7 mg, 0.33 mmol, 17%). *Caution:* this is a photosensitive product that turns purple and decomposes upon light and air exposure. TLC *R_f* = 0.55 (pentane: 100%). ¹H NMR (400.0 MHz; CDCl₃) δ_H: 7.58 (dd, *J* = 7.6, 1.2 Hz, 1H_{Ar}), 7.54 (dd, *J* = 7.6, 1.7 Hz, 1H_{Ar}), 7.32 (dt, *J* = 7.6, 1.2 Hz, 1H_{Ar}), 7.15 (dt, *J* = 7.6, 1.7 Hz, 1H_{Ar}), 7.04 (dd, *J* = 5.1, 1.2 Hz, 1H_{Ar}), 6.84 (dd, *J* = 5.1, 3.5 Hz, 1H_{Ar}), 6.63 (dd, *J* = 3.5, 1.2 Hz, 1H_{Ar}), 1.53–1.49 (m, 2H), 1.45–1.42 (m, 2H). ¹³C NMR (400.0 MHz; CDCl₃) δ_C: 150.7 (C_{qAr}), 143.3 (C_{qAr}), 133.5 (CH_{Ar}), 132.8 (CH_{Ar}), 128.8 (CH_{Ar}), 127.6 (CH_{Ar}), 126.8 (C_{qAr}), 126.7 (CH_{Ar}), 123.6 (CH_{Ar}), 122.6 (CH_{Ar}), 28.2 (Cq), 19.8 (CH₂). *ν*_{max} (neat, cm⁻¹): 3068, 3004, 2341, 1469, 1423, 1220, 1038, 1020, 849, 802, 762, 689. HRMS (ESI-TOF) *m/z*: [M – H][–] calcd for C₁₃H₁₀BrS, 276.9692; found, 276.9673.

General Procedure C for the Boronic Acids Syntheses. To a solution of the aryl bromide (1 equiv) in dry THF at –78 °C and under argon atmosphere was *n*-BuLi (1.1 equiv) added dropwise. The colored reaction mixture was then stirred for ~40 min, while the temperature rose slowly to –50 °C. The temperature was decreased again to –78 °C, and an excess of B(OMe)₃ (9.5 equiv) was added. The resulting solution was allowed to warm slowly to room temperature and stirred overnight. After the addition of distilled water, the mixture was acidified with HCl (1 M) and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated under vacuum. Recrystallization from pentane usually yielded the desired pure product. However, purification by column chromatography on silica gel and preparative TLC plates were required for some products.

[1,1'-Biphenyl]-2-ylboronic Acid (7a). A solution of KMnO₄ (474 mg, 3 mmol) in 100 mL of benzene/AcOH (10:1) was stirred under reflux at 100 °C until the purple color of permanganate turned brown (15–30 min). To this solution was added (2-bromophenyl)boronic acid (201 mg, 1 mmol), and reflux was continued for 24 h. The progress of the reaction was monitored by TLC with pentane (100%) as the eluent. After all of the starting material was consumed, the reaction mixture was neutralized with a saturated aqueous NaHCO₃ solution and extracted with diethyl ether. The combined organic phases were dried over MgSO₄, filtered through a pad of silica, and concentrated under vacuum. The resulting yellow oil consisted of **9a** slightly contaminated with 1,2-dibromobenzene (<2%).²¹ The presence of **9a** was confirmed by ¹H NMR with a multiplet at δ_H = 7.77–7.67, corresponding to H_{Ar} at the proximity of the boron atom.

Crude **9a** (203 mg, 0.87 mmol) was dissolved in 9.3 mL of dry THF and *n*-BuLi (0.38 mL, 0.94 mmol, 2.48 M in hexane), and B(OMe)₃ (0.57 mL, 8.15 mmol) was added according to general procedure C. Triturating the resulting yellowish solid with acetonitrile yielded desired pure boronic acid **7a** as an off-white solid (142 mg, 0.72 mmol, 83% from **9a**). The ¹H and ¹³C data were consistent with those reported in the literature.²² This compound is also available commercially. ¹H NMR (400.0 MHz; Acetone-*d*₆ + D₂O) δ_H: (d, *J* = 8.0 Hz, 1H_{Ar}), 7.44–7.35 (m, 5H_{Ar}), 7.33–7.27 (m, 3H_{Ar}), 3.69 (br s, OH). ¹³C NMR (100.6 MHz; Acetone-*d*₆ + D₂O) δ_C: 146.1 (C_{qAr}),

144.2 (Cq_{Ar}), 133.8 (CH_{Ar}), 129.5 (CH_{Ar}), 129.24 (CH_{Ar}), 129.20 (CH_{Ar}), 128.9 (CH_{Ar}), 127.56 (CH_{Ar}), 126.9 (CH_{Ar}).

(2-(Thiophen-2-yl)phenyl)boronic Acid (**7b**). Following general procedure C, the title compound was prepared using aryl bromide **9b** (100 mg, 0.42 mmol) in 9.8 mL of dry THF, *n*-BuLi (0.28 mL, 0.46 mmol, 2.2 M in hexane), and B(OMe)₃ (0.45 mL, 3.99 mmol). Recrystallization from pentane yielded desired pure product **7b** as a colorless solid (67 mg, 0.33 mmol, 79%). Mp 75–77 °C. ¹H NMR (400.0 MHz; Acetone-*d*⁶ + D₂O) δ_H: 7.51 (d, *J* = 6.8 Hz, 1H_{Ar}), 7.41–7.39 (m, 2H_{Ar}), 7.37–7.33 (m, 1H_{Ar}), 7.29–7.325 (m, 1H_{Ar}), 7.19 (d, *J* = 3.2 Hz, 1H_{Ar}), 7.05 (dd, *J* = 4.8, 3.6 Hz, 1H_{Ar}), 3.46 (br s, OH). ¹³C NMR (100.6 MHz; Acetone-*d*⁶ + D₂O) δ_C: 146.5 (Cq_{Ar}), 138.0 (Cq_{Ar}), 133.6 (CH_{Ar}), 129.5 (CH_{Ar}), 129.2 (CH_{Ar}), 128.4 (CH_{Ar}), 127.5 (CH_{Ar}), 126.2 (CH_{Ar}), 126.1 (CH_{Ar}). ¹¹B NMR (160.4 MHz; Acetone-*d*⁶ + D₂O) δ_B: 30.1 (br s). ν_{max} (neat, cm^{−1}): 3303 (br), 1713, 1592, 1481, 1423, 1331, 1277, 1162, 1121, 1009, 831, 804. HRMS (ESI-TOF) *m/z*: [M − H][−] calcd for C₁₀H₈BO₂S, 203.0344; found, 203.0330.

(2-((Methylthio)methyl)phenyl)boronic Acid (**7c**). Following general procedure C, the title compound was prepared using aryl bromide **9c** (282 mg, 1.3 mmol) in 30 mL of dry THF, *n*-BuLi (0.65 mL, 1.43 mmol, 2.2 M in hexane), and B(OMe)₃ (1.4 mL, 12.35 mmol). The crude mixture was purified by flash chromatography on silica gel and eluted with cyclohexane then cyclohexane/EtOAc (80:20) to yield desired product **7c** as a colorless solid (125 mg, 0.69 mmol, 53%). TLC *R*_f = 0.2 (cyclohexane/EtOAc: 80/20). Mp 80–82 °C. ¹H NMR (400.0 MHz; Acetone-*d*⁶ + D₂O) δ_H: 7.62 (d, *J* = 7.2, 1H_{Ar}), 7.29–7.21 (m, 2H_{Ar}), 7.17–7.15 (m, 1H_{Ar}), 3.95 (s, 2H), 3.43 (br s, OH), 1.91 (s, 3H). ¹³C NMR (100.6 MHz; Acetone-*d*⁶ + D₂O) δ_C: 144.1 (Cq_{Ar}), 135.3 (CH_{Ar}), 130.2 (CH_{Ar}), 129.8 (CH_{Ar}), 126.7 (Cq_{Ar}), 38.3 (CH₂), 14.7 (CH₃). ¹¹B NMR (160.4 MHz; Acetone-*d*⁶ + D₂O) δ_B: 29.3 (br s). ν_{max} (neat, cm^{−1}): 3283 (br), 1738, 1596, 1485, 1438, 1422, 1302, 1176, 1126, 1086, 1013, 983, 806. HRMS (ESI-TOF) *m/z*: [M − H][−] calcd for C₈H₁₀BO₂S, 181.0501; found, 181.0497.

(2-((Ethylthio)methyl)phenyl)boronic Acid (**7d**). Following general procedure C, the title compound was prepared using aryl bromide **9d** (600 mg, 2.6 mmol) in 60 mL of dry THF, *n*-BuLi (1.3 mL, 2.86 mmol, 2.2 M in hexane), and B(OMe)₃ (2.8 mL, 24.7 mmol). Recrystallization from pentane yielded desired pure product **7d** as a colorless solid (310 mg, 1.58 mmol, 61%). Mp 58–60 °C. ¹H NMR (400.0 MHz; Acetone-*d*⁶ + D₂O) δ_H: 7.61 (d, *J* = 7.7 Hz, 1H_{Ar}), 7.48–7.23 (m, 2H_{Ar}), 7.18–7.16 (m, 1H_{Ar}), 3.99 (s, 2H), 3.45 (br s, OH), 2.39 (q, *J* = 7.6 Hz, 2H), 1.15 (t, *J* = 5.6 Hz, 3H). ¹³C NMR (100.6 MHz; Acetone-*d*⁶ + D₂O) δ_C: 144.2 (Cq_{Ar}), 135.2 (CH_{Ar}), 130.1 (CH_{Ar}), 129.8 (CH_{Ar}), 126.6 (CH_{Ar}), 36.1 (CH₂), 25.6 (CH₂), 14.8 (CH₃). ¹¹B NMR (160.4 MHz; Acetone-*d*⁶ + D₂O) δ_B: 29.4 (br s). ν_{max} (neat, cm^{−1}): 3284 (br), 1739, 1596, 1485, 1439, 1422, 1350, 1229, 1217, 1116, 1084, 807. HRMS (ESI-TOF) *m/z*: [M − H][−] calcd for C₉H₁₂BO₂S, 195.0657; found, 195.0659.

(2-((Isopropylthio)methyl)phenyl)boronic Acid (**7e**). Following general procedure C, the title compound was prepared using aryl bromide **9e** (400 mg, 1.63 mmol) in 38 mL of dry THF, *n*-BuLi (0.82 mL, 1.79 mmol, 2.2 M in hexane), and B(OMe)₃ (1.74 mL, 15.48 mmol). Recrystallization from pentane yielded desired pure product **7e** as a colorless solid (280 mg, 1.33 mmol, 82%). Mp 56–57 °C. ¹H NMR (400.0 MHz; Acetone-*d*⁶ + D₂O) δ_H: 7.61 (d, *J* = 7.7 Hz, 1H_{Ar}), 7.28–7.27 (m, 2H_{Ar}), 7.19–7.15 (m, 1H_{Ar}), 4.03 (s, 2H), 3.49 (br s, OH), 2.90 (sept, *J* = 6.8 Hz, 1H), 1.20 (t, *J* = 5.6 Hz, 3H). ¹³C NMR (100.6 MHz; Acetone-*d*⁶ + D₂O) δ_C: 144.1 (Cq_{Ar}), 135.2 (CH_{Ar}), 130.0 (CH_{Ar}), 129.8 (CH_{Ar}), 126.6 (CH_{Ar}), 35.5 (CH₂), 35.1 (CH), 23.5 (CH₃). ¹¹B NMR (160.4 MHz; Acetone-*d*⁶ + D₂O) δ_B: 29.9 (br s). ν_{max} (neat, cm^{−1}): 3302 (br), 1738, 1597, 1484, 1439, 1350, 1299, 1171, 1156, 1107, 1078, 1008, 785. HRMS (ESI-TOF) *m/z*: [M − H][−] calcd for C₁₀H₁₄BO₂S, 209.0813; found, 209.0811.

(2-(Thiophen-2-ylmethyl)phenyl)boronic Acid (**7f**). Following general procedure C, the title compound was prepared using aryl bromide **9f** (1.472 g, 5.81 mmol) in 133.6 mL of dry THF, *n*-BuLi (2.56 mL, 6.39 mmol, 2.5 M in hexane), and B(OMe)₃ (6.22 mL, 55.2 mmol). Recrystallization from pentane yielded desired pure product **7f** as a colorless solid (1.12 g, 5.1 mmol, 88%). Mp 112–113 °C. ¹H

NMR (400.0 MHz; Acetone-*d*⁶ + D₂O) δ_H: 7.63 (d, *J* = 7.2 Hz, 1H_{Ar}), 7.26 (dd, *J* = 7.2, 1.2 Hz, 1H_{Ar}), 7.18–7.11 (m, 3H_{Ar}), 6.85 (m, 1H_{Ar}), 6.79 (d, 1H, *J* = 2.8 Hz, 1H_{Ar}), 4.44 (s, 2H), 3.68 (br s, OH). ¹³C NMR (100.6 MHz; Acetone-*d*⁶ + D₂O) δ_C: 146.4 (Cq_{Ar}), 135.2 (CH_{Ar}), 130.3 (CH_{Ar}), 128.0 (CH_{Ar}), 127.3 (CH_{Ar}), 126.1 (CH_{Ar}), 125.6 (CH_{Ar}), 124.3 (CH_{Ar}), 35.8 (CH₂). ¹¹B NMR (160.4 MHz; Acetone-*d*⁶ + D₂O) δ_B: 29.7 (br s). ν_{max} (neat, cm^{−1}): 3206 (br), 1737, 1596, 1567, 1483, 1444, 1339, 1307, 1288, 1256, 1194, 1063, 1034, 831. HRMS (ESI-TOF) *m/z*: [M − H][−] calcd for C₁₁H₁₀BO₂S 217.0500; found, 217.0489.

(2-(Thiophen-3-ylmethyl)phenyl)boronic Acid (**7g**). Following general procedure C, the title compound was prepared using aryl bromide **9g** (280 mg, 1.11 mmol) in 11.8 mL of dry THF, *n*-BuLi (0.51 mL, 1.22 mmol, 2.4 M in hexane), and B(OMe)₃ (1.18 mL, 10.55 mmol). Recrystallization from pentane yielded desired pure product **7g** as a colorless solid (198 mg, 0.91 mmol, 82%). Mp 95–96 °C. ¹H NMR (400.0 MHz; Acetone-*d*⁶ + D₂O) δ_H: 7.60 (d, *J* = 6.8 Hz, 1H_{Ar}), 7.28 (dd, *J* = 4.8, 3.2 Hz, 1H_{Ar}), 7.23 (d, *J* = 7.2 Hz, 1H_{Ar}), 7.15–7.10 (m, 2H_{Ar}), 7.00 (s, 1H_{Ar}), 6.94 (d, *J* = 4.8 Hz, 1H_{Ar}), 4.24 (s, 2H), 3.45 (br s, OH). ¹³C NMR (100.6 MHz; Acetone-*d*⁶ + D₂O) δ_C: 146.3 (Cq_{Ar}), 143.9 (CH_{Ar}), 134.9 (CH_{Ar}), 130.1 (CH_{Ar}), 130.0 (CH_{Ar}), 129.5 (CH_{Ar}), 125.9 (CH_{Ar}), 125.8 (CH_{Ar}), 121.4 (CH_{Ar}), 36.5 (CH₂). ¹¹B NMR (160.4 MHz; Acetone-*d*⁶ + D₂O) δ_B: 30.0 (br s). ν_{max} (neat, cm^{−1}): 3214 (br), 1739, 1598, 1564, 1481, 1444, 1431, 1333, 1193, 1160, 1103, 1072, 1044, 995, 781, 749. HRMS (ESI-TOF) *m/z*: [M − H][−] calcd for C₁₁H₁₀BO₂S, 217.0500; found, 217.0493.

(2-(Furan-2-ylmethyl)phenyl)boronic Acid (**7h**). To a solution of furan (0.91 mL, 12.48 mmol) in 25 mL of anhydrous Et₂O at 0 °C was added *n*-BuLi (5.27 mL, 115.59 mmol, 2.2 M in hexane). The solution was heated under reflux for 4 h. The reaction mixture was then cooled to 0 °C, and a solution of 2-bromobenzyl bromide (2.75 g, 11 mmol) in anhydrous ether (7.5 mL) was added dropwise. The solution was further heated under reflux for 16 h. After cooling, the mixture was poured onto crushed ice. The ether layer was separated, washed with brine, and dried to give a brown orange oil (1.56 g) constituted of an inseparable combination of **9h** and 2-bromobenzyl bromide (ratio 2:1) used without further purification in the next step.²³ The presence of **9h** was confirmed by ¹H NMR [δ_H 4.10 (s, 2H)]. To crude **9h** (200 mg) in 19.5 mL of dry THF were added *n*-BuLi (1 mL, 1.87 mmol, 1.9 M in hexane) and B(OMe)₃ (1 mL, 8.08 mmol) according to general procedure C. Recrystallization from pentane yielded desired pure product **7h** as an off-white solid (85 mg, 0.42 mmol, 75%). *Caution*: this is a hygroscopic and air sensitive product. Mp 77–78 °C. ¹H NMR (400.0 MHz; Acetone-*d*⁶ + D₂O) δ_H: 7.60 (d, *J* = 8.0 Hz, 1H_{Ar}), 7.33 (d, *J* = 4.0 Hz, 1H_{Ar}), 7.26–7.22 (m, 2H_{Ar}), 7.12 (td, *J* = 8.0, 4 Hz, 1H_{Ar}), 6.24 (d, *J* = 4.0 Hz, 1H_{Ar}), 5.94 (d, *J* = 4.0 Hz, 1H_{Ar}), 4.23 (s, 2H), 3.45 (br s, OH). ¹³C NMR (100.6 MHz; Acetone-*d*⁶ + D₂O) δ_C: 156.6 (Cq_{Ar}), 143.6 (Cq_{Ar}), 141.8 (CH_{Ar}), 134.9 (CH_{Ar}), 130.0 (CH_{Ar}), 129.8 (CH_{Ar}), 126.1 (CH_{Ar}), 110.8 (CH_{Ar}), 106.5 (CH_{Ar}), 34.3 (CH₂). ¹¹B NMR (160.4 MHz; Acetone-*d*⁶ + D₂O) δ_B: 29.3 (br s). ν_{max} (neat, cm^{−1}): 3285 (br), 1599, 1568, 1506, 1487, 1441, 1342, 1264, 1148, 1124, 1086, 1071, 1008, 935, 895, 883, 797. HRMS (ESI-TOF) *m/z*: [M − H][−] calcd for C₁₁H₁₀BO₃, 201.0728; found, 201.0712.

(2-Benzylphenyl)boronic Acid (**7i**). Following general procedure C, the title compound was prepared using aryl bromide **9i** (565 mg, 2.28 mmol) in 53 mL of dry THF, *n*-BuLi (2.5 M in hexane, 1 mL, 2.5 mmol), and B(OMe)₃ (2.41 mL, 21.7 mmol, 9.5 equiv). Recrystallization from pentane yielded desired pure product **7i** as a colorless solid (380 mg, 1.79 mmol, 79%). Mp 122–123 °C. ¹H NMR (400.0 MHz; Acetone-*d*⁶ + D₂O) δ_H: 7.61 (d, *J* = 8.0 Hz, 1H_{Ar}), 7.26–7.19 (m, 5H_{Ar}), 7.19–7.11 (m, 3H_{Ar}), 4.27 (s, 2H), 3.22 (s, OH). ¹³C NMR (100.6 MHz; Acetone-*d*⁶ + D₂O) δ_C: 146.5 (Cq_{Ar}), 143.4 (Cq_{Ar}), 134.9 (Cq_{Ar}), 130.2 (CH_{Ar}), 130.1 (CH_{Ar}), 129.7 (CH_{Ar}), 128.9 (CH_{Ar}), 126.3 (CH_{Ar}), 125.8 (CH_{Ar}), 41.6 (CH₂). ¹¹B NMR (160.4 MHz; Acetone-*d*⁶ + D₂O) δ_B: 29.7 (br s). ν_{max} (neat, cm^{−1}): 3304 (br), 1738, 1596, 1566, 1494, 1483, 1443, 1345, 1292, 1182, 1165, 1115, 1073, 1055, 1043, 747, 696. HRMS (ESI-TOF) *m/z*: [M − H][−] calcd for C₁₃H₁₂BO₂, 211.0936; found, 211.0929.

2-(1-(Thiophen-2-yl)vinyl)phenylboronic Acid (7j). Following general procedure C with an optimized amount of B(OMe)₃, the title compound was prepared using aryl bromide **9j** (443 mg, 1.7 mmol) in 10 mL of dry THF, *n*-BuLi (2.1 M in hexane, 0.95 mL, 2 mmol), and B(OMe)₃ (0.38 mL, 3.4 mmol, 2 equiv) in dry THF (1 mL). The crude mixture was purified by preparative TLC on silica and eluted with cyclohexane/EtOAc (60:40) to give title product **7j** as a brown oil (165 mg, 0.73 mmol, 43%). TLC *R*_f = 0.69 (cyclohexane/EtOAc: 70:30). ¹H NMR (500.0 MHz; Acetone-*d*⁶ + D₂O) δ _H: 7.64 (dd, *J* = 7.2, 1.5 Hz, 1H_{Ar}), 7.36 (dt, *J* = 7.5, 1.5 Hz, 1H_{Ar}), 7.34–7.29 (m, 2H_{Ar}), 7.23 (dd, *J* = 7.5, 1.1 Hz, 1H_{Ar}), 6.92 (dd, *J* = 5.0, 3.6 Hz, 1H_{Ar}), 6.73 (dd, *J* = 3.6, 0.7 Hz, 1H_{Ar}), 5.63 (s, 1H), 5.01 (s, 1H), 3.23 (br s, OH). ¹³C NMR (125.7 MHz; Acetone-*d*⁶ + D₂O) δ _C: 146.4 (C_{qAr}), 146.0 (C=CH₂), 145.8 (C_{qAr}), 134.2 (CH_{Ar}), 129.6 (CH_{Ar}), 129.5 (CH_{Ar}), 128.2 (CH_{Ar}), 127.8 (CH_{Ar}), 127.4 (CH_{Ar}), 126.2 (CH_{Ar}), 113.4 (C=CH₂). ¹¹B NMR (160.4 MHz; Acetone-*d*⁶ + D₂O) δ _B: 29.8 (br s). ν _{max} (neat, cm⁻¹): 3396 (br), 1606, 1412, 1322, 1292, 1055, 1020, 890, 760, 640. HRMS (ESI-TOF) *m/z*: [M – H][–] calcd for C₁₂H₁₀BO₂S, 229.0500; found, 229.0489.

2-(1-(Thiophen-2-yl)ethyl)phenylboronic Acid (7k). Following general procedure C with an optimized amount of B(OMe)₃, the title compound was prepared using aryl bromide **9k** (159 mg, 0.6 mmol) in 10 mL of dry THF, *n*-BuLi (2.1 M in hexane, 0.31 mL, 0.66 mmol), and B(OMe)₃ (0.13 mL, 1.2 mmol, 2 equiv) in dry THF (1 mL). The crude mixture was purified by preparative TLC on silica and eluted with cyclohexane/EtOAc (60:40) to give title product **7k** as a light pink solid (105 mg, 0.45 mmol, 75%). TLC *R*_f = 0.72 (cyclohexane/EtOAc: 60:40). Mp 108–110 °C. ¹H NMR (500.0 MHz; Acetone-*d*⁶ + D₂O) δ _H: 7.60 (dd, *J* = 7.5, 1.3 Hz, 1H_{Ar}), 7.26 (dt, *J* = 7.5, 1.3 Hz, 1H_{Ar}), 7.20 (m, 1H_{Ar}), 7.18 (dd, *J* = 5.1, 1.2 Hz, 1H_{Ar}), 7.13 (dt, *J* = 7.5, 1.3 Hz, 1H_{Ar}), 6.89 (dd, *J* = 5.1, 3.5 Hz, 1H_{Ar}), 6.87 (dt, *J* = 3.5, 1.2 Hz, 1H_{Ar}), 5.17 (q, *J* = 7.0 Hz, 1H), 2.44 (br s, OH), 1.64 (d, *J* = 7.0 Hz, 3H). ¹³C NMR (125.7 MHz; Acetone-*d*⁶ + D₂O) δ _C: 152.3 (C_{qAr}), 151.7 (C_{qAr}), 134.5 (CH_{Ar}), 130.2 (CH_{Ar}), 127.2 (CH_{Ar}), 126.9 (CH_{Ar}), 126.0 (CH_{Ar}), 124.3 (CH_{Ar}), 124.0 (CH_{Ar}), 39.2 (CH), 24.1 (CH₃). ¹¹B NMR (160.4 MHz; Acetone-*d*⁶ + D₂O) δ _B: 29.9 (br s). ν _{max} (neat, cm⁻¹): 2968 (br), 1596, 1441, 1280, 1292, 1235, 1045, 691. HRMS (ESI-TOF) *m/z*: [M – H][–] calcd for C₁₂H₁₀BO₂S, 231.0657; found, 231.0640.

2-(1-(Thiophen-2-yl)cyclopropyl)phenylboronic Acid (7l). Following general procedure C with an optimized amount of B(OMe)₃, the title compound was prepared using the aryl bromide **9l** (85 mg, 0.3 mmol) in 8 mL of dry THF, *n*-BuLi (2.1 M in hexane, 0.16 mL, 0.33 mmol), and B(OMe)₃ (0.13 mL, 1.2 mmol, 4 equiv) in dry THF (1 mL). The crude mixture was purified by preparative TLC on silica and eluted with cyclohexane/EtOAc (70:30) to give title product **7l** as a colorless solid (21 mg, 0.087 mmol, 29%). TLC *R*_f = 0.42 (cyclohexane/EtOAc: 70:30). Mp 94–95 °C. ¹H NMR (400.0 MHz; Acetone-*d*⁶ + D₂O) δ _H: 7.54 (d, *J* = 7.6 Hz, 1H_{Ar}), 7.44 (d, *J* = 7.6 Hz, 1H_{Ar}), 7.32 (t, *J* = 7.6 Hz, 1H_{Ar}), 7.20 (t, *J* = 7.6 Hz, 1H_{Ar}), 7.09 (d, *J* = 5.2 Hz, 1H_{Ar}), 6.78 (dd, *J* = 5.2, 3.5 Hz, 1H_{Ar}), 6.01 (d, *J* = 3.5 Hz, 1H_{Ar}), 2.45 (br s, OH), 1.40–1.35 (m, 2H), 1.33–1.29 (m, 2H). ¹³C NMR (100.6 MHz; Acetone-*d*⁶ + D₂O) δ _C: 153.6 (C_{qAr}), 148.3 (C_{qAr}), 134.6 (CH_{Ar}), 131.3 (CH_{Ar}), 129.9 (CH_{Ar}), 127.4 (CH_{Ar}), 127.0 (CH_{Ar}), 124.0 (CH_{Ar}), 123.6 (CH_{Ar}), 28.4 (Cq), 19.9 (CH₂). ¹¹B NMR (160.4 MHz; Acetone-*d*⁶ + D₂O) δ _B: 30.0 (br s). ν _{max} (neat, cm⁻¹): 3056 (br), 1660, 1600, 1585, 1573, 1494, 1448, 1332, 1309, 1087, 1008, 995, 982, 828, 719, 690. HRMS (ESI-TOF) *m/z*: [2 M – H₂O – H][–] calcd for C₂₆H₂₃B₂O₃S₂, 469.1280; found, 469.1263.

General Procedure D for Boronic Acid-Catalyzed Amide Synthesis. Under an argon atmosphere were mixed carboxylic acid (0.55 mmol, 1.1 equiv), 2-(thiophen-2-ylmethyl) phenyl boronic acid **7f** (10.9 mg, 0.05 mmol, 10 mol %), and 1 g of powdered and activated 5 Å molecular sieves. Dry CH₂Cl₂ (7 mL) was added, and the suspension was vigorously stirred for 15 min. Then, the amine (0.5 mmol) was added, and the resulting mixture was further stirred for 24 h (rt–50 °C). The suspension was filtered through a pad of Celite and washed with CH₂Cl₂ (3 × 5 mL). The filtrate was extracted twice with an aqueous solution of HCl (1M, 10 mL), twice with an aqueous

solution of NaOH (1M, 10 mL), and brine (10 mL). The organic layer was collected, dried over anhydrous MgSO₄, filtered, and evaporated under reduced pressure to yield the title compound as a pure product unless otherwise stated.

N-Benzyl-2-phenylacetamide (8a). The title compound is known and described. It was prepared at room temperature after 16 h using general procedure D and isolated as a light yellow solid (111 mg, 99% yield). The ¹H and ¹³C data were consistent with those reported in the literature.²⁴ ¹H NMR (400.0 MHz; CDCl₃) δ _H: 7.35–7.23 (m, 8H_{Ar}), 7.16 (d, *J* = 8 Hz, 2H_{Ar}), 5.70 (br s, NH), 4.39 (d, *J* = 8 Hz, 2H), 3.61 (s, 2H). ¹³C NMR (100.6 MHz; CDCl₃) δ _C: 171.0 (C=O), 138.2 (C_{qAr}), 134.9 (C_{qAr}), 129.5 (CH_{Ar}), 129.1 (CH_{Ar}), 128.7 (CH_{Ar}), 127.5 (CH_{Ar}), 127.5 (CH_{Ar}), 127.4 (CH_{Ar}), 43.8 (CH₂), 43.6 (CH₂).

(R)-2-Phenyl-N-(1-phenylethyl)acetamide (8b). The title compound is known and described. It was prepared at room temperature after 12 h using general procedure D and isolated as a white solid (66 mg, 55% yield). The ¹H and ¹³C data were consistent with those reported in the literature.^{3a,b} ¹H NMR (400.0 MHz; CDCl₃) δ _H: 7.37–7.21 (m, 8H_{Ar}), 7.18 (d, *J* = 7.2 Hz, 2H_{Ar}), 5.57 (br s, NH), 5.12 (quint, *J* = 7.2 Hz, 1H), 3.58 (s, 2H), 1.39 (d, *J* = 6.8 Hz, 3H). ¹³C NMR (100.6 MHz; CDCl₃) δ _C: 170.1 (C=O), 143.2 (C_{qAr}), 129.5 (CH_{Ar}), 129.2 (CH_{Ar}), 128.8 (CH_{Ar}), 127.5 (CH_{Ar}), 127.4 (C_{qAr}), 126.1 (CH_{Ar}), 48.9 (CH), 44.1 (CH₂), 21.9 (CH₃).

N-Isobutyl-2-phenylacetamide (8c). The title compound is known and described. It was prepared at room temperature after 24 h using general procedure D and isolated as a brown solid (92 mg, 96% yield). The ¹H and ¹³C data were consistent with those reported in the literature.^{6g} ¹H NMR (400.0 MHz; CDCl₃) δ _H: 7.35–7.24 (m, 5H_{Ar}), 5.72 (br, NH), 3.55 (s, 2H), 3.00 (l, *J* = 6.4 Hz, 2H), 1.67 (sept, *J* = 6.8 Hz, 1H), 0.79 (d, *J* = 6.8 Hz, 6H). ¹³C NMR (100.6 MHz; CDCl₃) δ _C: 171.1 (C=O), 135.2 (C_{qAr}), 129.4 (CH_{Ar}), 129.0 (CH_{Ar}), 127.3 (CH_{Ar}), 46.9 (CH₂), 43.9 (CH₂), 28.4 (CH), 20.0 (CH₃).

N-Benzyl-2-(4-methoxyphenyl)acetamide (13a). The title compound is known and described. It was prepared at room temperature after 2 h using general procedure D and isolated as a yellow solid (126 mg, 99% yield). The ¹H and ¹³C data were consistent with those reported in the literature.^{5a} ¹H NMR (400.0 MHz; CDCl₃) δ _H: 7.36–7.31 (m, 3H_{Ar}), 7.23–7.25 (m, 4H_{Ar}), 6.94–6.92 (m, 2H_{Ar}), 5.94 (br s, NH), 4.46 (d, *J* = 8 Hz, 2H), 3.85 (s, 3H), 3.61 (s, 2H). ¹³C NMR (100.6 MHz; CDCl₃) δ _C: 171.4 (C=O), 159.0 (C_{qAr}), 138.3 (C_{qAr}), 130.6 (CH_{Ar}), 128.7 (CH_{Ar}), 127.6 (CH_{Ar}), 127.5 (CH_{Ar}), 126.8 (C_{qAr}), 114.5 (CH_{Ar}), 55.4 (CH₃), 43.6 (CH₂), 42.9 (CH₂).

(R)-2-(4-Methoxyphenyl)-N-(1-phenylethyl)acetamide (13b). The title compound was prepared at room temperature after 8 h using general procedure D and isolated as a light yellow solid (133 mg, 99% yield). Mp 108–109 °C. ¹H NMR (400.0 MHz; CDCl₃) δ _H: 7.39–7.30 (m, 5H_{Ar}), 7.27 (d, *J* = 8.4 Hz, 2H_{Ar}), 6.98 (d, *J* = 8.4 Hz, 2H_{Ar}), 6.08 (br s, NH), 5.22 (q, *J* = 7.2 Hz, 1H), 3.90 (s, 3H), 3.60 (s, 2H), 1.50 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (100.6 MHz; CDCl₃) δ _C: 170.6 (C=O), 158.8 (C_{qAr}), 143.2 (C_{qAr}), 130.5 (CH_{Ar}), 128.6 (CH_{Ar}), 127.2 (CH_{Ar}), 127.0 (C_{qAr}), 114.4 (CH_{Ar}), 55.3 (CH₃), 48.7 (CH), 42.9 (CH₂), 21.9 (CH₃). ν _{max} (neat, cm⁻¹): 3299 (br), 2963, 1644, 1614, 1584, 1543, 1514, 1493, 1446, 1409, 1361, 1299, 1248, 1204, 1177, 1090, 1019, 957, 797. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₇H₂₀NO₂, 270.1489; found, 270.1493.

N-Isobutyl-2-(4-methoxyphenyl)acetamide (13c). The title compound was prepared at room temperature after 6 h using general procedure D and isolated as a light yellow solid (109 mg, 99% yield). Mp 125–126 °C. ¹H NMR (400.0 MHz; CDCl₃) δ _H: 7.15 (d, *J* = 8.4 Hz, 2H_{Ar}), 6.87 (d, *J* = 8.4 Hz, 2H_{Ar}), 5.43 (br s, NH), 3.79 (s, 3H), 3.50 (s, 2H), 3.00 (t, *J* = 6.6 Hz, 2H), 1.66 (sept, *J* = 6.8 Hz, 1H), 0.79 (d, *J* = 6.8 Hz, 6H). ¹³C NMR (100.6 MHz; CDCl₃) δ _C: 171.5 (C=O), 159.0 (C_{qAr}), 130.7 (CH_{Ar}), 127.1 (C_{qAr}), 114.6 (CH_{Ar}), 55.4 (CH₃), 47.0 (CH₂), 43.1 (CH₂), 28.5 (CH), 20.1 (CH₃). ν _{max} (neat, cm⁻¹): 3269 (br), 2954, 1641, 1611, 1558, 1514, 1457, 1445, 1368, 1305, 1241, 1178, 1025, 907, 815. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₃H₂₀NO₂, 222.1489; found, 222.1497.

N-Cyclopropyl-2-(4-methoxyphenyl)acetamide (13d). The title compound was prepared at 45 °C after 24 h using general procedure D

and isolated as a light yellow solid (101 mg, 98%). Mp 128–129 °C. ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.10 (d, $J = 8.4$ Hz, 2H_{Ar}), 6.82 (d, $J = 8.4$ Hz, 2H_{Ar}), 5.89 (br s, NH), 3.75 (s, 3H), 3.41 (s, 2H), 2.59–2.65 (m, 1H), 0.66 (q, $J = 6.8$ Hz, 2H), 0.39–0.38 (m, 2H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 173.0 (C=O), 158.7 (Cq_{Ar}), 127.0 (Cq_{Ar}), 130.4 (CH_{Ar}), 114.3 (CH_{Ar}), 55.2 (CH₃), 42.7 (CH₂), 22.7 (CH), 6.48 (CH₂). ν_{max} (neat, cm^{-1}): 3229 (br), 2962, 1664, 1612, 1586, 1554, 1511, 1469, 1450, 1425, 1351, 1300, 1281, 1250, 1177, 1093, 1033, 1018, 1002, 861, 812, 788. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_2$, 206.1176; found, 206.1180.

***N*-Allyl-2-(4-methoxyphenyl)acetamide (13e).** The title compound is known and described. It was prepared at 45 °C after 24 h using general procedure D and isolated as a colorless solid (101 mg, 98%). The ^1H and ^{13}C data were consistent with those reported in the literature.²⁵ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.22 (d, $J = 8.4$ Hz, 2H_{Ar}), 6.88 (d, $J = 8.4$ Hz, 2H_{Ar}), 5.50 (br s, NH), 5.06–5.02 (m, 2H), 3.81 (s, 3H), 3.80 (t, 2H, $J = 5.6$ Hz), 3.53 (s, 2H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 171.3 (C=O), 159.0 (Cq_{Ar}), 134.2 (CH_{Ar}), 130.7 (CH_{Ar}), 126.8 (Cq_{Ar}), 116.1 (CH_{Ar}), 114.6 (CH_{Ar}), 55.4 (CH₃), 43.0 (CH₂), 41.9 (CH₃).

***N*-Benzyl-2,2-diphenylacetamide (14a).** The title compound is known and described. It was prepared at 45 °C after 48 h using general procedure D and isolated as a light yellow solid (123 mg, 82%). The ^1H and ^{13}C data were consistent with those reported in the literature.²⁶ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.32–7.18 (m, 13H_{Ar}), 7.17 (d, $J = 6.8$ Hz, 2H_{Ar}), 6.03 (br s, NH), 4.94 (s, 1H), 4.44 (d, $J = 6.0$ Hz, 2H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 171.9 (C=O), 139.5 (Cq_{Ar}), 138.2 (Cq_{Ar}), 129.0 (CH_{Ar}), 128.9 (CH_{Ar}), 128.8 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 127.4 (CH_{Ar}), 59.2 (CH), 43.9 (CH₂).

***N*-Isobutyl-2,2-diphenylacetamide (14c).** The title compound is known and described. It was prepared at 45 °C after 48 h using general procedure D and isolated as an off-white solid (87 mg, 55%). The ^1H and ^{13}C data were consistent with those reported in the literature.²⁷ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.35–7.31 (m, 4H_{Ar}), 7.28–7.25 (m, 6H_{Ar}), 5.6 (br s, NH), 4.95 (s, 1H), 3.11 (t, $J = 6.6$ Hz, 2H), 1.79–1.68 (m, 1H), 0.84 (d, $J = 6.8$ Hz, 6H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 171.9 (C=O), 139.7 (Cq_{Ar}), 129.0 (CH_{Ar}), 128.9 (CH_{Ar}), 127.4 (CH_{Ar}), 59.5 (CH), 47.2 (CH₂), 28.5 (CH), 20.1 (CH₃).

(*S*)-2-(4-isobutylphenyl)-*N*-((*R*)-1-phenylethyl)acetamide (15b). The title compound is known and described. It was prepared at 45 °C after 48 h using general procedure D and isolated as a brown solid (83 mg, 54%, ee > 99.9%). $[\alpha]_{\text{D}}^{25} -4.4$ (c 0.5, CHCl_3). Enantiomeric excess (ee) was determined by chiral HPLC on Daicel Chiralpak ASH 4.6 mm \times 250 mm, 5 μm , using 90% of *n*-heptane and 10% of 2-propanol with a flow rate of 1 mL/min at 20 °C. The ^1H and ^{13}C data were consistent with those reported in the literature.⁶⁸ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.31–7.27 (m, 3H_{Ar}), 7.25–7.18 (m, 4H_{Ar}), 7.13–7.11 (m, 2H_{Ar}), 5.59 (br s, NH), 5.08 (quint, $J = 7.3$ Hz, 1H), 3.52 (q, $J = 7.6$ Hz, 1H), 2.46 (d, $J = 7.2$ Hz, 2H), 1.86 (sept, $J = 6.8$ Hz, 1H), 1.51 (d, $J = 7.2$ Hz, 2H), 1.35 (d, $J = 6.8$ Hz, 2H), 0.90 (d, $J = 6.8$ Hz, 2H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 173.7 (C=O), 139.7 (Cq_{Ar}), 140.9 (Cq_{Ar}), 138.7 (Cq_{Ar}), 129.8 (CH_{Ar}), 128.7 (CH_{Ar}), 127.5 (CH_{Ar}), 127.4 (CH_{Ar}), 126.1 (CH_{Ar}), 48.8 (CH), 46.9 (CH), 45.1 (CH₂), 30.3 (CH), 22.5 (CH₃), 21.8 (CH₃), 18.6 (CH₃).

***N*-Benzyl-2-(furan-2-yl)acetamide (16a).** The title compound is known and described. It was prepared at room temperature after 4 h using general procedure D and isolated as a light yellow solid (98 mg, 91%). The ^1H and ^{13}C data were consistent with those reported in the literature.²⁸ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.33 (d, $J = 6.8$ Hz, H_{Ar}), 7.30–7.26 (m, 3H_{Ar}), 7.22 (d, $J = 6.8$ Hz, 2H_{Ar}), 6.35 (dd, $J = 2.8$, 2 Hz, 1H_{Ar}), 6.24 (d, $J = 2.8$ Hz, 1H_{Ar}), 5.97 (br s, NH), 4.44 (d, $J = 5.6$ Hz, 2H), 3.67 (s, 2H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 168.7 (C=O), 148.8 (Cq_{Ar}), 142.7 (CH_{Ar}), 138.2 (Cq_{Ar}), 128.9 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 111.0 (CH_{Ar}), 108.8 (CH_{Ar}), 43.8 (CH₂), 36.5 (CH₂).

***N*-Benzyl-2-(thiophen-2-yl)acetamide (17a).** The title compound is known and described. It was prepared at room temperature after 24 h using general procedure D and isolated as an off-white solid (114

mg, 99%). The ^1H and ^{13}C data were consistent with those reported in the literature.²⁹ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.30–7.24 (m, 6H_{Ar}), 7.02 (dd, $J = 3.2$, 1.6 Hz, 1H_{Ar}), 6.98 (dd, $J = 8.0$, 2.4 Hz, 1H_{Ar}), 6.28 (br s, NH), 4.45 (d, $J = 6.0$, 2H), 3.83 (s, 2H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 170.0 (C=O), 138.1 (Cq_{Ar}), 136.2 (Cq_{Ar}), 128.7 (CH_{Ar}), 127.6 (CH_{Ar}), 127.5 (CH_{Ar}), 127.4 (CH_{Ar}), 127.3 (CH_{Ar}), 125.6 (Cq_{Ar}), 43.6 (CH₂), 37.5 (CH₂).

***N*-Benzylheptanamide (18a).** The title compound is known and described. It was prepared at room temperature after 24 h using general procedure D and isolated as a yellow oil (103 mg, 94%). The ^1H and ^{13}C data were consistent with those reported in the literature.³⁰

^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.33–7.24 (m, 5H_{Ar}), 6.42 (s, NH), 4.39 (d, $J = 5.6$ Hz, 2H), 2.19 (t, $J = 8.0$ Hz, 2H), 1.62 (m, 2H), 1.32–1.29 (m, 6H), 0.90 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 173.3 (C=O), 138.6 (Cq_{Ar}), 128.6 (CH_{Ar}), 127.7 (CH_{Ar}), 127.3 (CH_{Ar}), 43.4 (CH₂), 36.7 (CH₂), 31.6 (CH₂), 29.0 (CH₂), 25.8 (CH₂), 22.5 (CH₂), 14.1 (CH₃).

***N*-Hexylheptanamide (19).** The title compound is known and described. It was prepared at room temperature after 24 h using general procedure D and isolated as a light yellow oil (90 mg, 84%). The ^1H and ^{13}C data were consistent with those reported in the literature.³¹ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 5.78 (s, NH), 3.19 (q, $J = 7.2$ Hz, 2H), 2.12 (t, $J = 8.0$ Hz, 2H), 1.58 (t, $J = 7.2$ Hz, 2H), 1.45 (t, $J = 6.4$ Hz, 2H), 1.29–1.25 (m, 12H), 0.84 (t, $J = 6.0$ Hz, 6H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 173.3 (C=O), 39.6 (CH₂), 36.9 (CH₂), 31.6 (CH₂), 31.6 (CH₂), 29.7 (CH₂), 29.1 (CH₂), 26.7 (CH₂), 25.9 (CH₂), 22.7 (CH₂), 22.6 (CH₂), 14.1 (CH₃), 14.0 (CH₃).

***N*-Hexyl-2-phenylacetamide (20).** The title compound is known and described. It was prepared at room temperature after 24 h using general procedure D and isolated as an off-white solid (94 mg, 86%). The ^1H and ^{13}C data were consistent with those reported in the literature.⁶⁸ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.36–7.32 (m, 2H_{Ar}), 7.28–7.24 (m, 3H_{Ar}), 5.59 (s, NH), 3.55 (s, 2H), 3.21–3.16 (m, 2H), 1.40 (t, $J = 6.8$ Hz, 2H), 1.26–1.20 (m, 6H), 0.85 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 171.0 (C=O), 135.2 (Cq_{Ar}), 129.5 (CH_{Ar}), 129.0 (CH_{Ar}), 127.3 (CH_{Ar}), 43.9 (CH₂), 39.7 (CH₂), 31.4 (CH₂), 29.5 (CH₂), 26.5 (CH₂), 22.6 (CH₂), 14.0 (CH₃).

***N*-(*Sec*-butyl)-2-phenylacetamide (21).** The title compound is known and described. It was prepared at 45 °C after 24 h using general procedure D and isolated as a colorless solid (78 mg, 82%). The ^1H and ^{13}C data were consistent with those reported in the literature.²⁸ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.37–7.28 (m, 2H_{Ar}), 7.26–7.24 (m, 3H_{Ar}), 5.12 (br s, NH), 3.89 (m, 1H), 3.55 (s, 2H), 1.40–1.25 (m, 2H), 1.15 (d, $J = 6.4$ Hz, 3H), 0.80 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 170.5 (C=O), 135.2 (Cq_{Ar}), 129.5 (CH_{Ar}), 129.1 (CH_{Ar}), 127.4 (CH_{Ar}), 46.8 (CH), 44.2 (CH₂), 29.6 (CH₂), 20.4 (CH₃), 10.3 (CH₃).

2-Phenyl-1-(pyrrolidin-1-yl)ethanone (22). The title compound is known and described. It was prepared at room temperature after 24 h using general procedure D and isolated as a yellow oil (79 mg, 83%). The ^1H and ^{13}C data were consistent with those reported in the literature.³² ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.29–7.20 (m, 5H_{Ar}), 3.74 (s, 2H), 3.61 (s, 4H), 3.45 (t, $J = 6.8$ Hz, 2H), 3.38 (t, $J = 6.8$ Hz, 2H), 1.90–1.77 (m, 4H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 169.6 (C=O), 135.0 (Cq_{Ar}), 129.0 (CH_{Ar}), 128.7 (CH_{Ar}), 126.8 (CH_{Ar}), 47.0 (CH₂), 46.0 (CH₂), 42.4 (CH₂), 26.2 (CH₂), 24.4 (CH₂).

1-(Piperidin-1-yl)heptan-1-one (23). The title compound is known and described. It was prepared at room temperature after 24 h using general procedure D and isolated as a yellow oil (80 mg, 81%). The ^1H and ^{13}C data were consistent with those reported in the literature.³³ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 3.54 (t, $J = 5.6$ Hz, 2H), 3.38 (t, $J = 5.2$ Hz, 2H), 2.3 (t, $J = 7.6$ Hz, 2H), 1.50–1.63 (m, 8H), 1.24–1.34 (m, 6H), 0.87 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 171.7 (C=O), 46.9 (CH₂), 42.7 (CH₂), 33.6 (CH₂), 31.8 (CH₂), 29.3 (CH₂), 26.7 (CH₂), 25.7 (CH₂), 25.6 (CH₂), 24.7 (CH₂), 22.7 (CH₂), 14.2 (CH₃).

1-(Pyrrolidin-1-yl)heptan-1-one (24). The title compound is known and described. It was prepared at room temperature after 24 h using general procedure D and isolated as a brown oil (91 mg, 99%).

The ^1H and ^{13}C data were consistent with those reported in the literature.³⁴ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 3.35 (quint, $J = 7.2$ Hz, 4H), 2.17 (t, $J = 7.6$ Hz, 2H), 1.87 (t, $J = 6.8$ Hz, 3H), 1.76 (t, $J = 6.8$ Hz, 3H), 1.59–1.51 (m, 2H), 1.29–1.17 (m, 2H), 0.79 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 171.9 (C=O), 46.6 (CH_2), 45.5 (CH_2), 34.8 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 26.1 (CH_2), 24.9 (CH_2), 24.4 (CH_2), 22.5 (CH_2), 14.0 (CH_3).

1-Morpholinoheptan-1-one (25). The title compound is known and described. It was prepared at room temperature after 24 h using general procedure D and isolated as a pale yellow oil (83 mg, 83%). The ^1H and ^{13}C data were consistent with those reported in the literature.³⁵ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 3.63–3.57 (m, 6H), 3.42 (t, $J = 5.2$ Hz, 2H), 2.27 (t, $J = 8.0$ Hz, 2H), 1.62–1.54 (m, 2H), 1.31–1.21 (m, 6H), 0.84 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 172.0 (C=O), 67.0 (CH_2), 66.7 (CH_2), 46.1 (CH_2), 41.9 (CH_2), 33.2 (CH_2), 31.6 (CH_2), 29.2 (CH_2), 25.3 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

1-Morpholino-2-phenylethanone (26). The title compound is known and described. It was prepared at room temperature after 24 h using general procedure D and isolated as an off-white solid (62 mg, 60%). The ^1H and ^{13}C data were consistent with those reported in the literature.³⁶ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.35–7.32 (m, 2H_{Ar}), 7.28–7.24 (m, 3H_{Ar}), 3.74 (s, 2H), 3.65 (s, 4H), 3.48–3.43 (m, 4H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 169.7 (C=O), 134.9 (C_{qAr}), 128.9 (CH_{Ar}), 128.6 (CH_{Ar}), 127.0 (CH_{Ar}), 66.9 (CH_2), 66.5 (CH_2), 46.6 (CH_2), 42.2 (CH_2), 40.9 (CH_2).

N-Benzyl-2-(4-methoxyphenyl)-N-methylacetamide (27). The title compound is known and described. It was prepared at 45 °C after 48 h using general procedure D and isolated as a yellow solid (133 mg, 99%). The ^1H and ^{13}C data were consistent with those reported in the literature.³⁷ The presence of two rotamers was observed in NMR. ^1H NMR (400.0 MHz; CDCl_3) major rotamer, δ_{H} : 7.39–7.19 (m, 7H_{Ar}), 6.91–6.87 (m, 2H_{Ar}), 4.63 (s, 2H), 3.81 (s, 3H), 3.75 (s, 2H), 2.94 (s, 3H). ^1H NMR (400.0 MHz; CDCl_3) minor rotamer, δ_{H} : 7.39–7.19 (m, 5H_{Ar}), 7.13 (d, $J = 8.4$ Hz, 2H_{Ar}), 6.91–6.87 (m, 2H_{Ar}), 4.56 (s, 2H), 3.80 (s, 3H), 3.72 (s, 2H), 2.98 (s, 3H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 171.8 (m, C=O), 171.4 (M, C=O), 158.5 (m, C_{qAr}), 158.4 (M, C_{qAr}), 137.3 (M, C_{qAr}), 136.5 (m, C_{qAr}), 129.8 (M, CH_{Ar}), 129.8 (m, CH_{Ar}), 128.8 (m, CH_{Ar}), 128.5 (M, CH_{Ar}), 128.0 (M, CH_{Ar}), 127.6 (m, CH_{Ar}), 127.3 (m, CH_{Ar}), 127.1 (m, C_{qAr}), 126.9 (M, C_{qAr}), 126.3 (M, CH_{Ar}), 114.1 (m, CH_{Ar}), 114.0 (m, CH_{Ar}), 55.2 (M, CH₃), 53.5 (m, CH₂), 50.9 (M, CH₂), 40.2 (M, CH₂), 39.8 (m, CH₂), 35.1 (M, CH₃), 33.9 (m, CH₃).

N-(2-(1H-Indol-3-yl)ethyl)-2-(4-methoxyphenyl)acetamide (28). The title compound is known and described. It was prepared at a temperature of 45 °C after 48 h using general procedure D and isolated as a yellow solid (66 mg, 43%). The ^1H and ^{13}C data were consistent with those reported in the literature.³⁸ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 8.02 (br s, NH), 7.53 (d, $J = 8.0$ Hz, 1H_{Ar}), 7.36 (d, $J = 8.0$ Hz, 1H_{Ar}), 7.26 (s, 1H_{Ar}), 7.20 (t, $J = 7.6$ Hz, 1H_{Ar}), 7.11 (t, $J = 7.2$ Hz, 1H_{Ar}), 7.03 (d, $J = 8.4$ Hz, 2H_{Ar}), 6.82–6.78 (3, 3H_{Ar}), 5.44 (br s, NH), 3.79 (s, 3H), 3.53 (q, $J = 6.8$ Hz, 2H), 3.45 (s, 2H), 2.90 (t, $J = 6.8$ Hz, 2H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 171.5 (C=O), 158.9 (C_{qAr}), 136.5 (C_{qAr}), 130.7 (CH_{Ar}), 127.4 (C_{qAr}), 127.0 (C_{qAr}), 122.3 (CH_{Ar}), 122.1 (CH_{Ar}), 119.6 (CH_{Ar}), 118.8 (CH_{Ar}), 114.5 (CH_{Ar}), 112.9 (C_{qAr}), 111.3 (CH_{Ar}), 55.5 (CH₃), 43.1 (CH₂), 39.9 (CH₂), 25.2 (CH₂).

2-Phenyl-N-(pyridin-3-yl)methylacetamide (29). The title compound is known and described. It was prepared at 45 °C after 48 h using general procedure D with 20 mol % of **7f** and isolated as a colorless crystalline solid (101 mg, 89%). The ^1H and ^{13}C data were consistent with those reported in the literature.³⁹ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.56 (d, $J = 7.6$ Hz, 1H_{Ar}), 7.37–7.34 (m, 3H_{Ar}), 7.31 (s, 1H_{Ar}), 7.29–7.25 (m, 4H_{Ar}), 6.20 (br s, NH), 4.41 (d, $J = 8.0$ Hz, 2H), 3.62 (s, 2H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 171.3 (C=O), 148.4 (C_{qAr}), 148.3 (CH_{Ar}), 135.9 (C_{qAr}), 134.7 (CH_{Ar}), 129.5 (CH_{Ar}), 129.2 (CH_{Ar}), 128.6 (CH_{Ar}), 127.6 (CH_{Ar}), 127.0 (CH_{Ar}), 43.7 (CH₂), 41.1 (CH₂).

N-Benzylfuran-2-carboxamide (30). The title compound is known and described. It was prepared at a temperature of 45 °C after 48 h

using general procedure D with 20 mol % of **7f** and isolated as a light yellow solid (62 mg, 62%). The ^1H and ^{13}C data were consistent with those reported in the literature.⁴⁸ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.41 (d, $J = 1.6$ Hz, 1H_{Ar}), 7.36–7.26 (m, 5H_{Ar}), 7.15 (d, $J = 3.2$ Hz, 1H_{Ar}), 6.66 (br s, NH), 6.50 (dd, $J = 3.6$, 1.6 Hz, 1H_{Ar}), 4.61 (d, $J = 1.6$ Hz, 2H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 158.4 (C=O), 148.0 (C_{qAr}), 144.0 (CH_{Ar}), 138.1 (C_{qAr}), 128.9 (CH_{Ar}), 128.0 (CH_{Ar}), 127.8 (CH_{Ar}), 114.6 (CH_{Ar}), 112.3 (CH_{Ar}), 43.3 (CH₂).

N-Benzyl-4-iodobenzamide (31). The title compound is known and described. It was prepared at 45 °C after 48 h using general procedure D with 20 mol % of **7f** and toluene as the solvent and isolated as a colorless crystalline solid (57 mg, 34%). The ^1H and ^{13}C data were consistent with those reported in the literature.⁴⁸ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.79 (d, $J = 8.4$ Hz, 2H_{Ar}), 7.52 (d, $J = 8.4$ Hz, 2H_{Ar}), 7.37–7.31 (m, 5H_{Ar}), 6.33 (br s, NH), 4.64 (d, $J = 5.6$ Hz, 2H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 166.7 (C=O), 139.0 (CH_{Ar}), 138.0 (C_{qAr}), 133.9 (C_{qAr}), 129.0 (CH_{Ar}), 128.7 (CH_{Ar}), 128.2 (CH_{Ar}), 128.0 (CH_{Ar}), 98.7 (CH_{Ar}), 44.4 (CH₂).

N-Benzyl-2-hydroxy-2-phenylacetamide (32). The title compound is known and described. It was prepared at 65 °C after 48 h using general procedure D with 1,2-DCE as the solvent and isolated as an off-white solid (119 mg, 99%). The ^1H and ^{13}C data were consistent with those reported in the literature.⁴⁰ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.33–7.24 (m, 8H_{Ar}), 7.14 (d, $J = 6.8$ Hz, 2H_{Ar}), 6.84 (br s, NH), 4.96 (s, 1H), 4.34 (dd, $J = 5.6$, 3.2 Hz, 2H). ^{13}C NMR (100.6 MHz; CDCl_3) δ_{C} : 172.5 (C=O), 139.6 (C_{qAr}), 137.8 (C_{qAr}), 128.8 (CH_{Ar}), 128.7 (CH_{Ar}), 128.6 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 126.8 (CH_{Ar}), 74.2 (CH), 43.4 (CH₂).

General Procedure E for the Direct Amidation of N-Protected and/or C-Protected Amino Acids. Under an argon atmosphere were added carboxylic acid (0.46 mmol), boronic acid **7f** (26 mg, 0.115 mmol, 25 mol %), and 1 g of activated powdered 5 Å molecular sieves. Fluorobenzene (6.7 mL) was added, and the mixture was vigorously stirred for 15 min at 65 °C. Then, the amine (0.46 mmol, 1 equiv) was added, and the resulting suspension was further stirred for 24 h at 65 °C. The suspension was filtered through a pad of Celite and washed with EtOAc (3 × 5 mL). The filtrate was evaporated, and the residue was dissolved in CH_2Cl_2 , washed with an aqueous solution of HCl (1M) (2 × 10 mL), an aqueous solution of NaOH (1M) (2 × 10 mL), and brine (10 mL). The organic layer was dried over MgSO_4 , filtered, and evaporated. The pure product was obtained by recrystallization.

(S)-N-Boc-proline Benzylamide (33). The title compound is known and described. It was prepared according to general procedure E using N-Boc-proline and isolated as a colorless solid by recrystallization from a mixture of toluene and pentane (129 mg, 92%, ee > 99.9%). $[\alpha]_{\text{D}}^{25}$ –64.5 (c 1.0, CHCl_3). Enantiomeric excess (ee) was determined by chiral HPLC on Daicel Chiralpak ASH 4.6 mm, 250 mm, 5 μm , using 60% of *n*-heptane and 40% of 2-propanol with a flow rate of 1 mL/min at 20 °C. The ^1H and ^{13}C data were consistent with those reported in the literature.⁹ ^1H NMR (500.0 MHz; $\text{DMSO}-d_6$, 80 °C) δ_{H} : 8.01 (br s, NH), 7.31–7.26 (m, 4H_{Ar}), 7.24–7.21 (m, 1H_{Ar}), 7.24–7.20 (m, 1H), 4.34 (d, $J = 6.2$ Hz, 1H), 4.25 (d, $J = 5.8$ Hz, 1H), 4.15 (d, $J = 3.1$ Hz, 1H), 3.44–3.39 (m, 1H), 3.36–3.31 (m, 1H), 2.14–2.10 (m, 1H), 1.89–1.76 (m, 3H), 1.36 (s, 9H). ^{13}C NMR (125.7 MHz; $\text{DMSO}-d_6$, 80 °C) δ_{C} : 171.8 (C=O), 153.1 (C=O), 139.1 (C_{qAr}), 127.5 (CH_{Ar}), 126.7 (CH_{Ar}), 126.0 (CH_{Ar}), 78.1 (Cq), 59.5 (CH), 46.1 (CH₂), 41.7 (CH₂), 30.1 (CH₂), 27.6 (CH₃), 22.9 (CH₂).

(S)-N-Boc-phenylalanine Benzylamide (34). The title compound is known and described. It was prepared according to general procedure E using N-Boc-phenylalanine and isolated as an off-white solid by recrystallization from a mixture of toluene and pentane (98 mg, 60%, ee > 99.9%). $[\alpha]_{\text{D}}^{25}$ +2.4 (c 1.0, CHCl_3). Enantiomeric excess (ee) was determined by chiral HPLC on Daicel Chiralpak ASH 4.6 mm, 250 mm, 5 μm , using 80% of *n*-heptane and 20% of 2-propanol with a flow rate of 1 mL/min at 20 °C. The ^1H and ^{13}C data were consistent with those reported in the literature.⁹ ^1H NMR (400.0 MHz; CDCl_3) δ_{H} : 7.30–7.26 (m, 6H_{Ar}), 7.24–7.10 (m, 2H_{Ar}), 7.10 (s, 2H_{Ar}), 6.22 (s, NH), 5.12 (s, NH), 4.36 (d, $J = 4.0$ Hz, 1H), 3.09 (t, $J = 8.0$ Hz, 2H), 1.39 (s, 9H). ^{13}C NMR (101.6 MHz; CDCl_3) δ_{C} : 171.1 (C=O), 155.4 (C=O), 137.6 (C_{qAr}), 136.6 (C_{qAr}), 129.3 (CH_{Ar}), 128.7

(CH_{Ar}), 128.6 (CH_{Ar}), 127.6 (CH_{Ar}), 127.4 (CH_{Ar}), 126.9 (CH_{Ar}), 80.2 (Cq), 56.0 (CH), 43.4 (CH₂), 38.6 (CH₂), 28.2 (CH₃).

(S)-N-Phenylacetyl-phenylalanine Methyl Ester (**35**). The title compound is known and described. It was prepared according to general procedure E using phenylalanine methyl ester and isolated as a colorless solid by recrystallization from a mixture of acetone and pentane (129 mg, 94%, ee = 94%). [α]_D²⁵ +37.5 (c 1.06, CHCl₃). Enantiomeric excess (ee) was determined by chiral HPLC on Daicel Chiralpak ASH 4.6 mm, 250 mm, 5 μ m, using 60% of *n*-heptane and 40% of 2-propanol with a flow rate of 1 mL/min at 20 °C. The ¹H and ¹³C data were consistent with those reported in the literature.⁹ ¹H NMR (400.0 MHz; CDCl₃) δ _H: 7.35–7.25 (m, 3H_{Ar}), 7.22–7.18 (m, 5H_{Ar}), 6.89–6.86 (m, 2H_{Ar}), 5.81–5.80 (br s, NH), 4.87–4.82 (dt, *J* = 8.0, 5.8 Hz, 1H), 3.69 (s, 3H), 3.54 (s, 2H), 3.06 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.99 (dd, *J* = 13.6, 5.6 Hz, 1H). ¹³C NMR (101.6 MHz; CDCl₃) δ _C: 171.8 (C=O), 170.5 (C=O), 135.6 (C_{qAr}), 134.5 (C_{qAr}), 129.4 (CH_{Ar}), 129.2 (CH_{Ar}), 129.0 (CH_{Ar}), 128.6 (CH_{Ar}), 127.4 (CH_{Ar}), 127.1 (CH_{Ar}), 53.0 (CH), 52.3 (CH), 43.6 (CH₂), 37.6 (CH₂).

(S,S)-N-Boc-Phe-Val methyl ester (**36**). The title compound is known and described. It was prepared according to general procedure E using N-Boc-phenylalanine and isolated as a colorless solid and single diastereomer (87 mg, 50%). The ¹H and ¹³C data were consistent with those reported in the literature.⁹ [α]_D²⁵ –7.0 (c 1.04, CHCl₃). ¹H NMR (400.0 MHz; CDCl₃) δ _H: 7.35–7.25 (m, 5H_{Ar}), 6.45 (d, *J* = 8.0 Hz, 2H), 5.04 (br s, NH), 4.51 (q, *J* = 4.0 Hz, 1H), 4.40 (d, *J* = 8.0 Hz, NH), 3.73 (s, 3H), 3.12 (d, *J* = 8.0 Hz, 2H), 2.19–2.10 (m, 1H), 1.46 (s, 9H), 0.90 (dd, *J* = 12.8, 6.8 Hz, 6H). ¹³C NMR (101.6 MHz; CDCl₃) δ _C: 171.9 (C=O), 171.2 (C=O), 155.5 (C_{qAr}), 136.7 (C_{qAr}), 129.4 (CH_{Ar}), 128.8 (CH_{Ar}), 127.0 (CH_{Ar}), 80.3 (Cq), 57.3 (CH₃), 56.0 (CH), 52.2 (CH₃), 38.1 (CH₂), 31.4 (CH₃), 28.4 (CH₃), 18.9 (CH₃), 17.8 (CH).

■ ASSOCIATED CONTENT

● Supporting Information

Optimization studies and copies of NMR and chiral HPLC spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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