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Amidation Reactions from the Direct Coupling of Metal Carboxylate Salts with Amines

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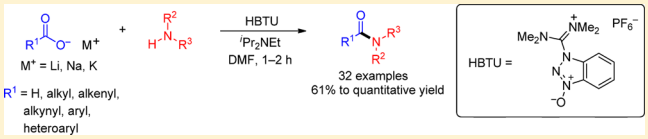
Supporting Information

ABSTRACT: A general method for the synthesis of amides involving the direct coupling of alkali metal carboxylate salts with amines is described. Amidation of a wide variety of carboxylate salts with either free amines or their ammonium hydrochloride salts can be achieved using HBTU as a coupling agent in combination with Hünig's base. The reaction is highly efficient and is generally complete in as little as 1−2 h, giving the products in good to excellent yields. The protocol is valuable for the coupling of carboxylates for which the corresponding carboxylic acids or acyl chlorides are unstable, less conveniently manipulated/isolated, or are not commercially available. For example, the coupling of amines and α-amino acids with lithium 5-bromo-1*H*-pyrrole-2-carboxylate, whose corresponding acid that is prone to decarboxylation, allowed for the synthesis of 5-bromo-1*H*-pyrrole-2-carboxamides, which are analogues of the pyrrole-2-aminoimidazole marine alkaloids. The protocol can be combined with other reactions in a sequenced fashion, as exemplified by the synthesis of acetylenic amides, in a one-pot procedure, via the coupling of a lithium carboxylate salt formed initially by the addition of carbon dioxide to a lithiated terminal alkyne.



INTRODUCTION

Carboxylic amides constitute one of the most important and ubiquitous of organic functional groups, occurring in natural products, both peptidic and nonpeptidic, pharmaceuticals, agrochemicals, materials, and polymers. The privileged nature of the amide functional group is apparent, for example, from its occurrence in an estimated 25% of available drugs.[1] Most amide bond formations utilize the reaction of amines in the presence of acylating agents, such as acyl chlorides,[2] or the reaction of carboxylic acids with amines in the presence of coupling agents.[3] The importance of amides has ensured continued advances in protocols and reagents based upon these approaches,[4] as well as the development of alternative methods for amide bond formation.[5]

In contrast to the use of carboxylic acids, acyl chlorides, and other activated acylating agents, metal carboxylate salts have found limited utility for the synthesis of amides. Indeed, the diminished nucleophilicity of the carboxylate functionality has enabled carboxylate salts of α-amino acids to be used as a protected carboxylic acid functionality in peptide couplings.[6] For example, alkaline earth metal carboxylate salts of α-amino acids have been used in reactions with Boc-protected α-amino acid activated esters (*N*-hydroxysuccinimidyl or *p*-nitrophenyl esters).[7] Similar approaches using tetraalkylammonium carboxylate salts for peptide couplings have also been reported.[8] Carboxylate salts have also been employed for the synthesis of amides via in situ acid chloride formation.[9] Finally, couplings of methyl red sodium carboxylate and other alkali metal dye carboxylates with amines using *N*,*N*-diisopropylcarbodiimide (DIC)/*N*-hydroxybenzotriazole (HOBt) have been achieved with PPTS (3 equiv)/tertiary amine (2 equiv of Hünig's base or *N*-methylmorpholine) additives.[10] Although effective, neither method is appropriate when the corresponding acyl chloride is unstable or the system is acid-sensitive. Herein, we report the first general method for the direct coupling of metal carboxylate salts with amines or amine hydrochloride salts. The newly developed protocol enables amidations using metal carboxylate salts for which the corresponding acids or acyl chlorides may be unstable or inconvenient to manipulate or isolate. Application of the method for the formation of acetylenic carboxamides, through a one-pot protocol involving an initial reaction of an acetylide anion with carbon dioxide, demonstrates its potential for multistep one-pot amidation reactions from metalated intermediates.[11]

RESULTS AND DISCUSSION

As part of our recent total synthesis of the marine alkaloid agelastatin A, a method for the formation of a bromopyrrole amide was required, which culminated in the development of a direct reaction between diammonium hydrochloride salt **1** with lithium bromopyrrole carboxylate salt **2**, in the presence of the uronium coupling reagent TPTU (2-(2-pyridon-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate), to give amide **3** with good regioselectivity in 54% yield (Scheme 1).[12] Encouraged by the success of this preliminary study, we became interested in whether a general protocol for the direct coupling of alkali metal carboxylate salts could be developed. A method that

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Scheme 1. Selective Acylation of Diammonium Hydrochloride 1 with Lithium Bromopyrrole Carboxylate 2 in the Total Synthesis of (±)-Agelastatin A

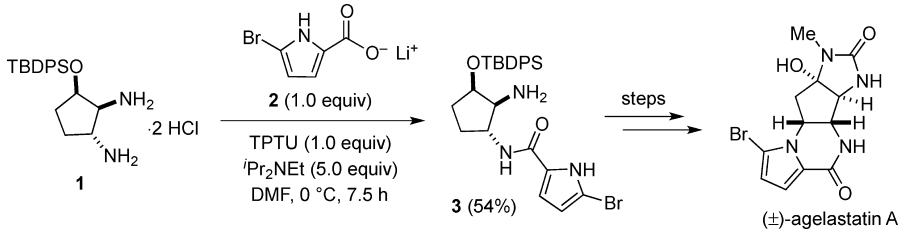
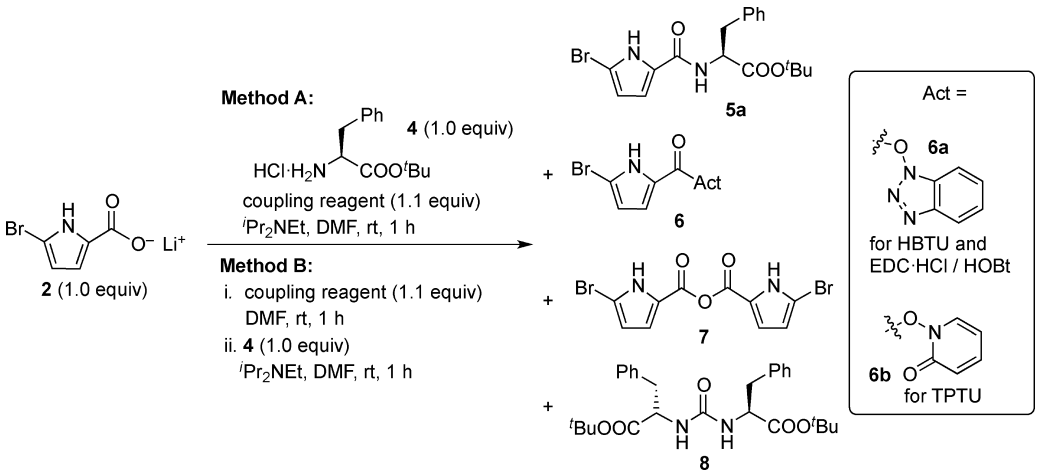


Table 1. Optimization Experiments for the Synthesis of Amide 5a Using Lithium Bromopyrrole Carboxylate 2 and Ammonium Salt 4



entry	method	coupling reagent	$^{i}Pr_2NEt$ (equiv)	4:5a:6:7:8[a]
1	A	HBTU	1.1	45:40:5:10:0
2	A	EDC·HCl	2.1	40:10:−:30:20
3[b]	A	EDC·HCl	2.1	20:55:0:15:10
4	A	PyBOP	1.1	20:35:0:25:20
5	B	HBTU	1.1	0:100:0:0:0
6	B	TPTU	1.1	20:60:15:5:5
7	B	EDC·HCl	2.1	50:15:−:30:5
8[b]	B	EDC·HCl	2.1	15:75:0:10:0
9	B	PyBOP	1.1	25:65:0:10:0

[a]Ratios determined by ^{1}H NMR analysis of the crude reaction mixtures and are reported to the nearest 5%. Ratios of compounds **4**, **5a**, and **8** were measured by integration of the H_α signals, whereas **6** and **7** were measured by integration of the H-4 and H-3 pyrrole signals, respectively. [b]1.0 equiv of HOBt was added to the reaction. HBTU = 1-[(dimethylamino)(dimethyliminio)methyl]-1*H*-benzo[*d*][1,2,3]triazole 3-oxide hexafluorophosphate, EDC·HCl = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, PyBOP = (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate.

utilizes such salts would be advantageous for a number of reasons. First, metal carboxylate salts can serve as bench-stable surrogates to free acids or acid chlorides that are unstable (prone to decarboxylation/decomposition pathways). For example, both the free acid and the acid chloride species of bromopyrrole **2** are reported to be unstable,[13−15] whereas the corresponding lithium carboxylate salt provides access to a bench-stable alternative that is stable for months.[15] Second, some carboxylic acids are more conveniently manipulated as the corresponding carboxylate salts, or the carboxylate salts are more readily available as precursors. Finally, direct (in situ) activation of a metal carboxylate salt using an appropriate coupling reagent will often be more time- and cost-effective than methods utilizing preformed activated esters (e.g., *N*-hydroxysuccinimidyl or pentafluorophenyl esters), which require additional steps to synthesize.

4- and 5-monobromo and 4,5-dibromopyrrole-2-carboxamides are present in a large family of structurally complex and bioactive pyrrole-2-aminoimidazole (P2AI) marine alkaloids,[16] but the corresponding pyrrole-2-carboxylic acids have poor stability profiles, limiting their application in some syntheses. Lithium 5-bromo-1*H*-pyrrole-2-carboxylate **2** was thus chosen for the initial optimization study. Coupling of **2** with L-phenylalanine *tert*-butylester hydrochloride **4** was employed as a model reaction for optimization studies, using aminium (HBTU), uronium (TPTU), phosphonium (PyBOP), and carbodiimide (EDC·HCl) coupling reagents (Table 1). Proton NMR analysis of the crude reaction mixtures after 1 h revealed that premixing of the starting materials and coupling reagent(s) prior to the addition of Hünig's base (Method A) resulted in poor conversion to the desired amide **5a**. In addition to significant amounts of remaining amine **4**, anhydride **7** and urea **8** were also formed as side-products (Table 1, entries 1−4).[17]

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Scheme 2. Control Experiments for Urea Formation

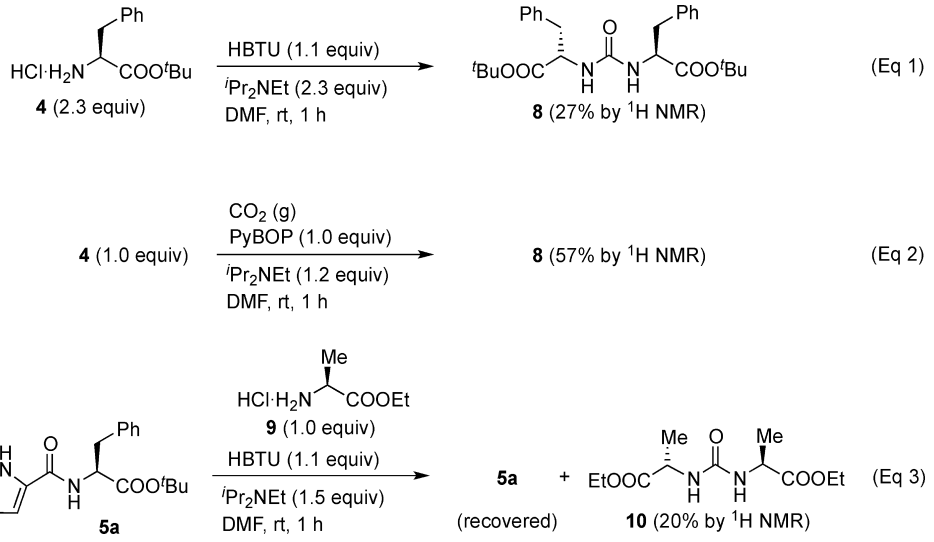
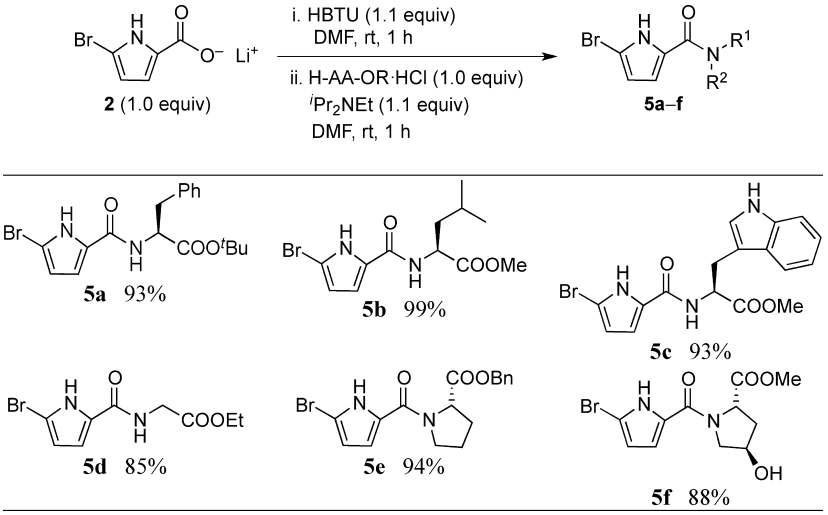


Table 2. One-Pot Synthesis of Amides 5a–5f Using Lithium Bromopyrrole Carboxylate 2 and Various α-Amino Ester Hydrochloride Salts (Method B)[a]



[a]Isolated yields after column chromatographic purification.

Formation of anhydride **7** presumably proceeds through the homocoupling of carboxylate **2** via an activated ester species.[18,19] Control experiments carried out under similar conditions demonstrate that urea **8** did not result through the reaction of excess ammonium salt **4** with EDC·HCl in the presence of Hünig's base, but did form through the analogous reaction with HBTU (27% conversion by ^{1}H NMR) (Scheme 2, Eq 1). Formation of urea **8** could instead occur from in situ decarboxylation of **2** and subsequent reaction with **4** using PyBOP or EDC·HCl. Support for this hypothesis is provided by the formation of **8** in the reaction of ammonium salt **4**, Hünig's base, and PyBOP in the presence of carbon dioxide gas (57% conversion by ^{1}H NMR) (Scheme 2, Eq 2). Finally, in order to test the stability of the pyrrole amide, **5a** was resubjected to the reaction conditions using L-alanine ethyl ester hydrochloride **9**; however, only the formation of urea **10**[20] was observed (20% conversion by ^{1}H NMR) without appreciable **5a** decomposition or unsymmetrical urea formation (Scheme 2, Eq 3).

Further optimization revealed that activation of **2** with the coupling reagent prior to the addition of ammonium salt **4** and Hünig's base (Method B) was essential in obtaining a higher conversion to amide **5a** (Table 1, entries 5–9). The order of addition was found to greatly suppress the formation of anhydride **7** and resulted in improved yields of amide **5a**. Use of this method, with HBTU as a coupling reagent, resulted in full conversion to **5a** while avoiding the formation of anhydride **7** entirely (Table 1, entry 5). HBTU was thus chosen as the standard reagent for all further amidation reactions. This result was confirmed in an analogous ^{1}H NMR experiment utilizing DMF-d_7 as solvent. After 45 min, the reaction between **2** and HBTU showed full conversion to activated ester **6a** (with no detectable amounts of anhydride **7**), which subsequently was reacted with ammonium salt **4** and Hünig's base to give **5a** as the sole product.

Application of this improved procedure (Method B) led to the formation of various primary (**5a–5d**) and secondary (**5e**,**5f**) amides in excellent isolated yields via the one-pot coupling of lithium carboxylate **2** with α-amino ester

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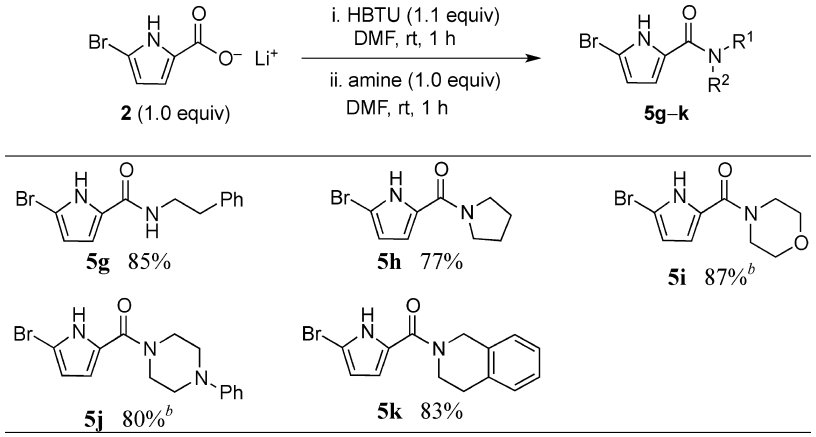
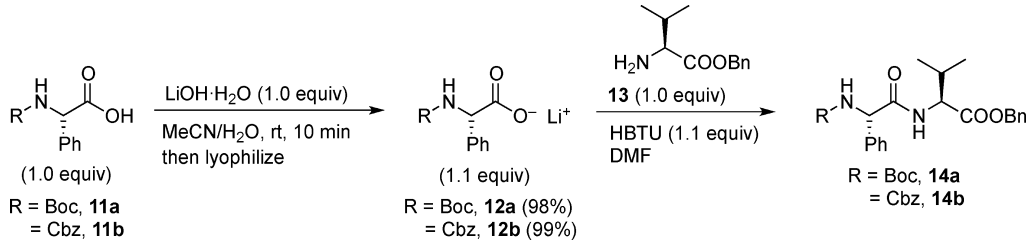
Table 3. Base-Free Synthesis of Amides 5g−5k Using Lithium Bromopyrrole Carboxylate 2 and Various Amines (Method B)[a,b]



[a]Isolated yields after column chromatographic purification. [b]1.5 equiv of amine was used.

Table 4. Base-Free Synthesis of Amides 14a,14b Using Lithium Carboxylate Salts 12a,12b and Amine 13[a] (Method A)



entry	carboxylate	temp (°C)	time (h)	amide	yield (%)[b]	dr (L,L:D,L)[c]
1	**12a**	rt	1	**14a**	quant	97:3
2	**12a**	0−10	33	**14a**	quant	99:1
3	**12b**	rt	1	**14b**	97	95:5
4	**12b**	0−10	33	**14b**	96	97:3

[a]Free base **13** was obtained by treatment of H-Val-OBn·HCl with saturated Na_2CO_3 (aq) and extraction into CH_2Cl_2, followed by drying over $MgSO_4$ and concentration in vacuo. [b]Isolated yields after column chromatographic purification. [c]Diastereomeric ratio determined by reversed-phase HPLC (C-18 column) of the purified product. These ratios were found to be consistent with those measured initially by ^1H NMR of the crude reaction mixtures (i.e., diastereomeric enrichment was not observed upon purification).[23]

ammonium hydrochloride salts (Table 2). Reaction workup involves simply concentrating the reaction mixture with an air stream to yield a crude residue that is purified directly by column chromatography. This operationally simple workup procedure is less wasteful since it does not require extraction prior to chromatography, and also could possibly enable the use of semiautomated techniques. In an effort to expand the reaction scope, lithium carboxylate **2** was also coupled to a series of medicinally relevant free amines, giving primary (**5g**) and secondary (**5h−5k**) amides in good yields (Table 3). In contrast to the examples using amine hydrochloride salts (Table 2), the addition of Hünig's base was not necessary in the reactions using free amines.

To test whether this base-free approach could be applied to more sensitive amide couplings that have been shown to suffer from epimerization,[21] the lithium carboxylate salts of Boc- and Cbz-L-phenylglycine (**12a,12b**) were prepared as model substrates and coupled with the sterically encumbered amine L-valine benzyl ester **13** (Table 4). Formation of amides **14a,14b** proceeded smoothly in 1 h at room temperature in excellent yields with minimal epimerization of the phenylglycine residue (Table 4, entries 1 and 3).[22] For amide **14b**, the observed level of epimerization (5%) at room temperature (Table 4, entry 3) is comparable to a related protocol that employs an EDC/HOBt mediated coupling requiring prolonged reaction times at low temperature (24 h, 0−5 °C).[21a] Performing the same reactions at lower temperatures for prolonged reaction times gave comparable yields of **14a,14b** to those obtained at room temperature with reduced loss of stereochemical integrity about the phenylglycine residue (Table 4, entries 2 and 4).

The reaction scope was further evaluated using a variety of alkali metal salts **15a−15m** in couplings with ammonium salt **4**, giving the product amides **16a−16m** in good to excellent isolated yields (Table 5). In contrast to the examples using lithium carboxylate **2**, preactivation of the metal carboxylate was not necessary in these cases and generally had a negligible effect on the reaction outcome for the majority of the substrates; hence, Method A was employed for convenience. *N*-Formylation of **4** using 1.0 equiv of sodium formate **15a** resulted in a low yield of **16a** (Table 5, entry 1), and a gaseous byproduct (presumably carbon monoxide) was observed upon addition of coupling reagent. The use of 2.0 equiv of HBTU and **15a** led to a modest improvement in the yield of **16a** (Table 5, entry 2). Amidation of **4** with ethyl potassium malonate **15b** gave amide **16b** in quantitative yield (Table 5, entry 3), with **15b** serving as both a less toxic and cost-effective substitute to the use of ethyl malonyl chloride. Coupling of

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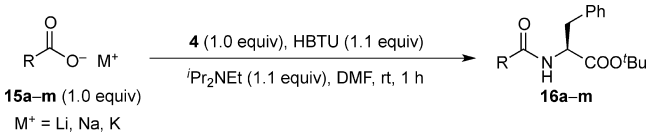
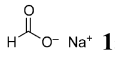
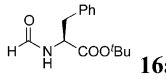
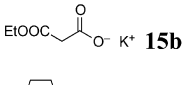
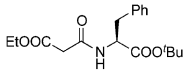
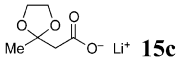
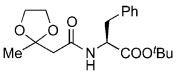
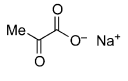
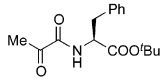
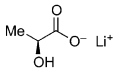
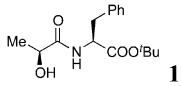
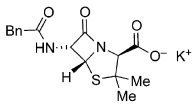
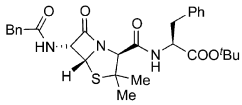
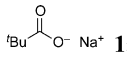
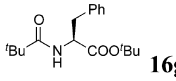
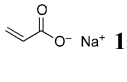
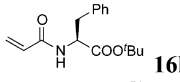
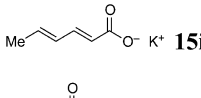
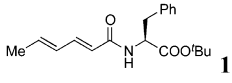
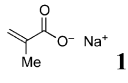
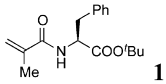
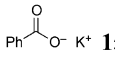
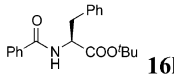
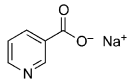
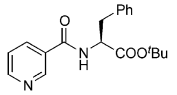
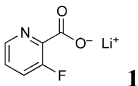
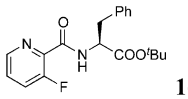
Table 5. Synthesis of Amides 16a–16m Using Metal Carboxylates 15a–15m and Ammonium Salt 4 (Method A)[a,b]



Entry	Carboxylate	Amide	Yield (%)[a]
1	 **15a**	 **16a**	48
2[b]			61
3	 **15b**	 **16b**	quant
4	 **15c**	 **16c**	90
5	 **15d**	 **16d**	77
6	 **15e**	 **16e**	85
7	 **15f**	 **16f**	80
8	 **15g**	 **16g**	84
9			56
10[b]	 **15h**	 **16h**	61
11	 **15i**	 **16i**	quant
12	 **15j**	 **16j**	98
13	 **15k**	 **16k**	quant
14	 **15l**	 **16l**	86
15	 **15m**	 **16m**	quant

[a]Isolated yields after column chromatographic purification. [b]2.0 equiv of carboxylate salt and HBTU were used.

ketal-protected lithium carboxylate **15c** resulted in a 90% yield of amide **16c** (Table 5, entry 4). Carboxylate **15c**, which is bench-stable for several months, was prepared in 89% yield by hydrolysis of the corresponding ethyl ester derivative with 1.0 equiv of $LiOH·H_2O$ via a modified literature procedure.[24] Attempts to couple the corresponding unprotected keto derivative of **15c** proved unsuccessful, yielding only urea **8** in 54% yield. The ability of the unprotected keto acid derivative of **15c** to undergo decarboxylation under these conditions is necessary in order for urea **8** to form, just as was observed for reaction of **2**, which can similarly decarboxylate, leading to the formation of **8** (Table 1 and Scheme 2). Reaction of unprotected lithium L-lactate **15e** gave amide **16e** in 85% yield via Method A (Table 5, entry 6), whereas Method B was unsuccessful. Penicillin G potassium carboxylate **15f**, which is only sold commercially as the carboxylate salt for stability reasons, was coupled smoothly to give amide **16f** in 80% yield (Table 5, entry 7). This example provides further evidence that late stage amidation reactions of structurally complex carboxylate salts can be accomplished even in the presence of highly reactive functionalities, such as β-lactams. Coupling of 1.0 equiv of sodium acrylate **15h** proceeded in low yield and only via Method A (Table 5, entry 9) due to a competing polymerization pathway. As was the case for the reaction of sodium formate, increasing the number of equivalents of **15h** and HBTU had a minimal effect on the outcome of the reaction (Table 5, entry 10). Conversely, coupling reactions of other unsaturated carboxylate salts, namely, potassium sorbate **15i**

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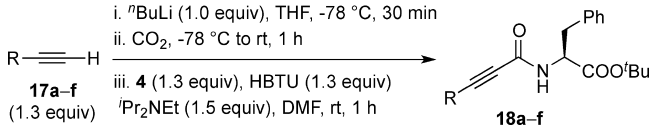
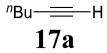
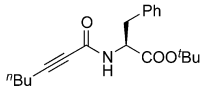
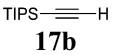
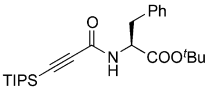
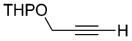
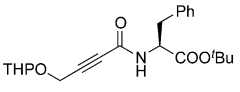
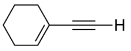
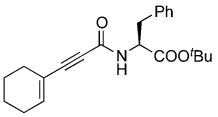
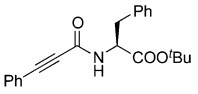
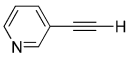
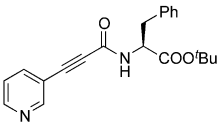
Table 6. One-Pot Synthesis of Acetylenic Amides 18a–18f from Terminal Alkynes 17a–17f (Method C)[a,b,c]



Entry	Alkyne	Amide	Yield (%)[a]
1	 **17a**	 **18a**	97
2	 **17b**	 **18b**	96
3	 **17c**	 **18c**	76
4	 **17d**	 **18d**	95
5[b]	 **17e**	 **18e**	84
6 7[c]	 **17f**	 **18f**	53 quant

[a]Isolated yields after column chromatographic purification. [b]Alkyne **17e** (1.0 equiv), nBuLi (1.0 equiv), and **4** (1.0 equiv) were used. [c]Alkyne **17f** (1.6 equiv), nBuLi (1.0 equiv), and **4** (1.6 equiv) were used.

and sodium methacrylate **15j**, proceeded smoothly and in excellent yields (Table 5, entries 11 and 12). Coupling of aryl carboxylate salts **15k–15m** also occurred in excellent yields (Table 5, entries 13–15) even for electron-deficient nicotinic and picolinic acid derivatives **15l** and **15m**, respectively.

Since there are many reactions that form carboxylate salts in situ, it was also of interest to evaluate whether sequenced or domino transformations could be combined with the newly developed amidation protocol. To evaluate the feasibility of such a strategy, the reaction of in situ generated acetylenic carboxylate salts for the formation of acetylenic amides was chosen as a model study. Acetylenic amides serve as useful building blocks in the synthesis of heterocycles as well as other functionalities.[25] Amidations using free acetylenic acids, such as propiolic acid or but-2-ynoic acid, with peptide coupling reagents provide one classical approach to their synthesis. For example, isolated 3-(triisopropylsilyl)propiolic acid (synthesized via the corresponding acetylide addition to carbon dioxide) was used in a PyBOP mediated coupling with DL-serine methyl ester hydrochloride.[26] An alternative approach to their synthesis utilizes low-temperature trapping of a lithiated acetylide with phenyl isocyanate or a magnesium acetylide with Me_3SiNCO.[27] Although these methods have proven useful, their application can be limited by the lack of access to appropriate starting materials or low product yields.

A more general synthetic approach to acetylenic amides utilizing trapping of metalated acetylides with carbon dioxide to generate carboxylate salt intermediates, followed by in situ coupling with amines, would, therefore, be of considerable interest. Accordingly, a variety of terminal alkynes **17a–17f** were lithiated using nBuLi and then reacted with carbon dioxide to give the intermediate lithium carboxylate salts, which could then be directly coupled with amine **4** in their crude state to give amides **18a–18f** (Table 6). Good overall yields of the acetylenic amides could be obtained using a slight excess of **4**, **17**, and HBTU (1.3 equiv). The carboxylate salt derived from phenylacetylene **17e** on the other hand was coupled in 84% overall yield using only a stoichiometric amount of reagents (Table 6, entry 5). Using the standard conditions (1.3 equiv of reagents), the carboxylate salt derived from 3-ethynylpyridine **17f** was only coupled in modest yield; however, a quantitative isolated yield was obtained by employing additional reagent equivalents (Table 6, entries 6 and 7).

In summary, this study represents the first general investigation into the direct use of metal carboxylate salts in amidation reactions with amines. The full scope of this reaction was explored through the coupling of a wide variety of alkali metal carboxylate salts with various amine or ammonium hydrochloride salts using HBTU as a coupling reagent. The amide products were obtained in good to excellent yields, using

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one of two reaction protocols depending upon the carboxylate salt used. The first protocol involves the direct reaction of all of the reagents, while the second protocol employs the initial reaction of the carboxylate salt and coupling reagent, followed by subsequent addition of the amine or hydrochloride salt. Extension of the method to a three-step one-pot synthesis of acetylenic amides was possible using an approach in which acetylenic carboxylates were synthesized from terminal alkynes, ^{n}BuLi, and carbon dioxide. Further application of this reaction can be envisaged for related amide formations, including multistep variants and cyclization reactions of carboxylate salts.

EXPERIMENTAL SECTION

All reactions were performed under nitrogen in flame-dried glassware. Tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl under nitrogen. Dichloromethane was freshly distilled from calcium hydride under nitrogen. Anhydrous dimethylformamide was obtained as ≥99.9% pure and stored under argon. Flash chromatography on silica gel (60 Å, 230−400 mesh) was performed with reagent grade solvents. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel plates and visualized with a UV_{254} lamp. Solvent ratios for chromatography and R_f values are reported as v/v ratios. Melting points are uncorrected and obtained on >95% pure compounds without any further recrystallization. All 1-D (^{1}H, ^{13}C) NMR spectra were obtained on 300, 400, 500, and 600 MHz spectrometers as solutions in deuterated solvents. Chemical shifts are reported in δ parts per million (ppm) values. Proton chemical shifts were internally referenced to tetramethylsilane (δ 0.00) for $CDCl_3$ or to the residual proton resonance in CD_3OD (δ 3.31) and DMSO-d_6 (δ 2.49). Carbon chemical shifts were internally referenced to the solvent resonances in $CDCl_3$ (δ 77.16 ppm), CD_3OD (δ 49.15 ppm), or DMSO-d_6 (δ 39.51 ppm). Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; J, coupling constant in Hz (rounded to the nearest 0.5 Hz). Exact mass measurements were performed on quadrupole time-of-flight mass spectrometers utilizing electrospray ionization (ESI-QTOF) or direct analysis in real-time ionization (DART-TOF). Both the measured and the calculated m/z values for ESI-QTOF correspond to the ionic species of interest (are corrected for the mass of an electron), whereas those for DART correspond to the mass of the neutral species (not corrected for the mass of an electron).

Amides Synthesized via General Procedure B. *Representative Procedure: (S)-tert-Butyl-2-(5-bromo-1H-pyrrole-2-carboxamido)-3-phenylpropanoate (**5a**).* In a flame-dried vial with a stir bar were loaded lithium 5-bromo-1*H*-pyrrole-2-carboxylate **2** (14.8 mg, 0.075 mmol, 1.0 equiv) and DMF (1 mL). To the resulting solution was added HBTU (31.8 mg, 0.084 mmol, 1.1 equiv), and the mixture was stirred for 1 h at room temperature. A second vial was prepared with L-phenylalanine *tert*-butyl ester hydrochloride **4** (19.6 mg, 0.076 mmol, 1.0 equiv) and it was slurried in DMF (1 mL) before dropwise addition of Hünig's base (15 μL, 0.086 mmol, 1.1 equiv). This solution was then cannula transferred to the carboxylate/HBTU mixture, and the reaction mixture was stirred for an additional 1 h at room temperature. The crude reaction mixture was then concentrated down to a thick residue using an air stream before being loaded directly onto a silica column. Flash chromatography (3:1 hexanes:EtOAc) of the crude residue afforded **5a** (27.9 mg, 93% yield) as a light yellow crystalline solid; mp 50−51 °C (CH_2Cl_2); R_f 0.61 (3:1 hexanes:EtOAc); $[\alpha]_D^{23}$ +73.2 (c 0.83, $CHCl_3$); IR (thin film in CH_2Cl_2) ν_{max} 3287 (br), 3196 (br), 2976, 2961, 2926, 2855, 1717, 1626, 1456, 1367, 1153 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD; note: the amide and pyrrole NH signals were not observed due to deuterium exchange) δ 7.30−7.17 (5H, m), 6.76 (1H, d, J = 4.0 Hz), 6.12 (1H, d, J = 4.0 Hz), 4.68 (1H, dd, J = 8.5, 6.5 Hz), 3.16 (1H, dd, J = 14.0, 6.5 Hz), 3.06 (1H, dd, J = 14.0, 8.5 Hz), 1.40 (9H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 172.7, 162.3, 138.6, 130.5, 129.6, 128.3, 127.9, 114.1, 112.6, 104.8, 83.1, 56.0, 38.8, 28.3; HRMS (ESI$^+$) m/z calcd for $C_{18}H_{22}BrN_2O_3$ $[M + H]^+$: 393.0808, found 393.0813.

*(S)-Methyl-2-(5-bromo-1H-pyrrole-2-carboxamido)-4-methylpentanoate (**5b**).* Yellow crystalline solid (81.5 mg, 99%); mp 92−93 °C (CH_2Cl_2); R_f 0.25 (4:1 hexanes:EtOAc); $[\alpha]_D^{25}$ −15.4 (c 1.04, MeOH); IR (thin film in CH_2Cl_2) ν_{max} 3312 (br), 3181 (br), 2957, 1728, 1634, 1558, 1526, 1439, 1207 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.40 (1H, br s), 6.57 (1H, dd, J = 4.0, 2.5 Hz), 6.42 (1H, br d, J = 8.5 Hz), 6.15 (1H, dd, J = 4.0, 2.5 Hz), 4.88 (1H, ddd, J = 8.5, 8.5, 5.0 Hz), 3.75 (3H, s), 1.77−1.59 (3H, m), 0.97 (3H, d, J = 6.5 Hz), 0.95 (3H, d, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 160.0, 126.7, 112.0, 111.3, 104.3, 52.6, 50.7, 41.9, 25.1, 23.0, 22.1; HRMS (DART) mass calcd for $C_{12}H_{18}BrN_2O_3$ [M + H]: 317.0501, found 317.0494.

*(S)-Methyl-2-(5-bromo-1H-pyrrole-2-carboxamido)-3-(1H-indol-3-yl)propanoate (**5c**).* Beige solid (103.2 mg, 93%); mp 77−78 °C (CH_2Cl_2); R_f 0.22 (2:1 hexanes:EtOAc); $[\alpha]_D^{26}$ +49.5 (c 0.56, $CHCl_3$); IR (thin film in CH_2Cl_2) ν_{max} 3416 (br), 2953, 2926, 1728, 1624, 1558, 1456 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD; note: the amide, pyrrole, and indole NH signals were not observed due to deuterium exchange) δ 7.55−7.51 (1H, m), 7.34−7.30 (1H, m), 7.10−7.06 (2H, m), 7.02−6.97 (1H, m), 6.72 (1H, d, J = 4.0 Hz), 6.11 (1H, d, J = 4.0 Hz), 4.87 (1H, dd, J = 7.5, 6.0 Hz), 3.67 (3H, s), 3.37 (1H, ddd, J = 14.5, 6.0, 0.5 Hz), 3.27 (1H, ddd, J = 14.5, 7.5, 0.5 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 174.4, 162.3, 138.2, 128.8, 128.3, 124.5, 122.6, 120.0, 119.3, 114.2, 112.7, 112.5, 111.0, 104.9, 55.0, 52.8, 28.6; HRMS (DART) mass calcd for $C_{17}H_{17}BrN_3O_3$ [M + H]: 390.0453, found 390.0464.

*Ethyl-2-(5-bromo-1H-pyrrole-2-carboxamido)acetate (**5d**).* Beige crystalline solid (50.8 mg, 85%); mp 143−145 °C (CH_2Cl_2); R_f 0.43 (2:1 hexanes:EtOAc); IR (thin film in CH_2Cl_2) ν_{max} 3400, 3175 (br), 2984, 1730, 1639, 1472, 1393 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD; note: the amide and pyrrole NH signals were not observed due to deuterium exchange) δ 6.76 (1H, d, J = 4.0 Hz), 6.15 (1H, d, J = 4.0 Hz), 4.19 (2H, q, J = 7.5 Hz), 4.04 (2H, s), 1.26 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 171.8, 163.0, 128.3, 113.8, 112.7, 104.9, 62.4, 42.0, 14.6; HRMS (ESI$^+$) m/z calcd for $C_9H_{12}BrN_2O_3$ [M + H]$^+$: 275.0025, found 275.0034.

*(S)-Benzyl-1-(5-bromo-1H-pyrrole-2-carbonyl)pyrrolidine-2-carboxylate (**5e**).* White foam (91.6 mg, 94%); R_f 0.37 (2:1 hexanes:EtOAc); $[\alpha]_D^{26}$ −54.5 (c 0.89, MeOH); IR (thin film in CH_2Cl_2) ν_{max} 3182 (br), 3070, 3033, 2958, 2879, 1744, 1592, 1448, 1386, 1169 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD; note: the pyrrole NH signal was not observed due to deuterium exchange) δ 7.42−7.22 (5H, m), 6.69 (1H, d, J = 3.0 Hz), 6.20 (1H, d, J = 3.0 Hz), 5.16 (2H, s), 4.64 (1H, dd, J = 7.5, 4.5 Hz), 3.94−3.78 (2H, m), 2.34−2.21 (1H, m), 2.14−1.90 (3H, m); ^{13}C NMR (100 MHz, CD_3OD) δ 173.9, 161.8, 137.5, 129.7, 129.4, 129.2, 128.1, 116.3, 113.0, 105.5, 68.0, 61.8, 50.1, 29.8, 26.4; HRMS (DART) mass calcd for $C_{17}H_{18}BrN_2O_3$ [M + H]: 377.0501, found 377.0503.

*(2S,4R)-Methyl-1-(5-bromo-1H-pyrrole-2-carbonyl)-4-hydroxypyrrolidine-2-carboxylate (**5f**).* Light yellow solid (76.6 mg, 88%); decomposition temp 170 °C; R_f 0.41 (EtOAc); $[\alpha]_D^{23}$ −58.5 (c 0.76, MeOH); IR (solid) ν_{max} 3416, 3130, 2957, 2925, 1732, 1616, 1431, 1215, 1184 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD; note: the pyrrole NH and alcohol OH signals were not observed due to deuterium exchange) δ 6.67 (1H, d, J = 4.0 Hz), 6.21 (1H, d, J = 4.0 Hz), 4.71 (1H, dd, J = 9.0, 9.0 Hz), 4.53 (1H, br s), 3.98 (1H, dd, J = 11.0, 4.0 Hz), 3.82 (1H, d, J = 11.0 Hz), 3.73 (3H, s), 2.34−2.23 (1H, m), 2.05 (1H, ddd, J = 13.0, 9.0, 4.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 174.7, 162.4, 127.9, 116.4, 112.9, 105.5, 71.5, 60.3, 58.3, 52.9, 38.1; HRMS (DART) mass calcd for $C_{11}H_{14}BrN_2O_4$ [M + H]: 317.0137, found 317.0140.

*5-Bromo-N-phenethyl-1H-pyrrole-2-carboxamide (**5g**).* White solid (63.2 mg, 85%); mp 134−135 °C (CH_2Cl_2); R_f 0.50 (2:1 hexanes:EtOAc); IR (solid) ν_{max} 3363 (br), 3219 (br), 3026, 2924, 2849, 1615, 1599, 1551, 1453, 1395 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD; note: the amide and pyrrole NH signals were not observed due to deuterium exchange) δ 7.31−7.14 (5H, m), 6.67 (1H, d, J = 4.0 Hz), 6.11 (1H, d, J = 4.0 Hz), 3.55−3.47 (2H, m), 2.90−2.82 (2H,

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m); ^{13}C NMR (75 MHz, CD_3OD) δ 162.7, 140.8, 130.0, 129.6, 128.9, 127.5, 113.2, 112.5, 104.3, 42.2, 37.0; HRMS (ESI$^+$) m/z calcd for $C_{13}H_{14}BrN_2O$ $[M + H]^+$: 293.0284, found 293.0294.

*(5-Bromo-1H-pyrrol-2-yl)(pyrrolidin-1-yl)methanone (**5h**).* White solid (49.0 mg, 77%); sublimation temp 190 °C; R_f 0.20 (2:1 hexanes:EtOAc); IR (solid) ν_{max} 3137, 2969, 1582, 1445, 1386, 831 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 12.15 (1H, br s), 6.56 (1H, dd, J = 3.5, 2.5 Hz), 6.16 (1H, dd, J = 3.5, 2.5 Hz), 3.70−3.55 (2H, m), 3.53−3.38 (2H, m), 2.00−1.70 (4H, m); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 158.9, 127.8, 113.4, 111.0, 102.6, 47.6, 46.6, 26.2, 23.4; HRMS (DART) mass calcd for $C_9H_{12}BrN_2O$ $[M + H]$: 243.0133, found 243.0137.

*(5-Bromo-1H-pyrrol-2-yl)(morpholino)methanone (**5i**).* White solid (49.7 mg, 87%); mp 170−172 °C ($CHCl_3$); R_f 0.18 (2:1 hexanes:EtOAc); IR (solid) ν_{max} 3192 (br), 2961, 2917, 2850, 1583, 1465, 1430, 1114, 966, 813 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.62 (1H, br s), 6.42 (1H, dd, J = 3.5, 2.5 Hz), 6.17 (1H, dd, J = 3.5, 2.5 Hz), 3.92−3.81 (4H, m), 3.79−3.70 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 125.8, 114.0, 111.7, 103.8, 67.0, 45.5; HRMS (DART) mass calcd for $C_9H_{12}BrN_2O_2$ $[M + H]$: 259.0082, found 259.0088.

*(5-Bromo-1H-pyrrol-2-yl)(4-phenylpiperazin-1-yl)methanone (**5j**).* White solid (71.6 mg, 80%); mp 196−197 °C ($CHCl_3$); R_f 0.68 (2:1 hexanes:EtOAc); IR (solid) ν_{max} 3132, 3086, 2966, 2857, 1597, 1465, 1442, 1387, 1370, 1289, 1224, 1203, 1027 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 12.22 (1H, br s), 7.26−7.19 (2H, m), 6.97−6.92 (2H, m), 6.83−6.77 (1H, m), 6.50 (1H, d, J = 3.5 Hz), 6.17 (1H, d, J = 3.5 Hz), 3.83−3.72 (4H, m), 3.20−3.13 (4H, m); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 160.5, 150.7, 129.0, 126.1, 119.2, 115.7, 113.4, 110.5, 102.2, 48.5, 44.2; HRMS (ESI$^+$) m/z calcd for $C_{15}H_{17}BrN_3O$ $[M + H]^+$: 334.0549, found 334.0534.

*(5-Bromo-1H-pyrrol-2-yl)(3,4-dihydroisoquinolin-2(1H)-yl)-methanone (**5k**).* Light yellow solid (70.3 mg, 83%); mp 120−121 °C (CH_2Cl_2); R_f 0.56 (2:1 hexanes:EtOAc); IR (thin film in CH_2Cl_2) ν_{max} 3177 (br), 3078, 3024, 2961, 2934, 2847, 1595, 1447, 1387 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.23 (1H, br s), 7.25−7.14 (4H, m), 6.60 (1H, d, J = 4.0 Hz), 6.20 (1H, d, J = 4.0 Hz), 4.79 (2H, s), 3.85 (2H, t, J = 6.0 Hz), 2.88 (2H, t, J = 6.0 Hz); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 160.7, 134.8, 133.4, 128.4, 126.5, 126.35, 126.33, 126.2, 113.4, 110.6, 102.2, 46.3, 42.7, 28.4; HRMS (DART) mass calcd for $C_{14}H_{14}BrN_2O$ $[M + H]$: 305.0289, found 305.0276.

*1H-Benzo[d][1,2,3]triazol-1-yl 5-bromo-1H-pyrrole-2-carboxylate (**6a**).* In a flame-dried vial with a stir bar were loaded lithium 5-bromo-1*H*-pyrrole-2-carboxylate **2** (65.4 mg, 0.334 mmol, 1.0 equiv) and DMF (2 mL). HBTU (130.0 mg, 0.343 mmol, 1.0 equiv) was added, and the mixture was stirred for 1 h at room temperature. The crude reaction mixture was then concentrated down to a thick residue using an air stream before being loaded directly onto a silica column. Flash chromatography (4:1 hexanes:EtOAc) of the crude residue afforded **6a** (79.5 mg, 78% yield) as a light orange solid; mp 161−163 °C (CH_2Cl_2); R_f 0.35 (4:1 hexanes:EtOAc); IR (solid) ν_{max} 3050, 2955, 2232, 1761, 1420, 1366, 1075 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD; note: the pyrrole NH signal was not observed due to deuterium exchange) δ 8.05 (1H, ddd, J = 8.5, 1.0, 1.0 Hz), 7.66−7.60 (2H, m), 7.55−7.48 (1H, m), 7.33 (1H, d, J = 4.0 Hz), 6.43 (1H, d, J = 4.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 157.0, 144.7, 130.5, 130.4, 126.6, 122.5, 120.9, 118.9, 115.1, 111.8, 110.1; HRMS (ESI$^+$) m/z calcd for $C_{11}H_8BrN_4O_2$ $[M + H]^+$: 306.9825, found 306.9824.

*2-Oxopyridin-1(2H)-yl 5-bromo-1H-pyrrole-2-carboxylate (**6b**).* Synthesized via the same procedure as for compound **6a** except TPTU was used in place of HBTU. Note: product **6b** contains a 1,1,3,3-tetramethylurea (TMU) impurity (approximately 5% w/w by ^{1}H NMR). White solid (110.8 mg, 71%); decomposition temp 70 °C; R_f 0.36 (1:1 hexanes:EtOAc); IR (solid) ν_{max} 3113, 3059, 2953, 1754, 1650, 1577, 1534, 1378, 1152, 1030 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD; note: the pyrrole NH signal was not observed due to deuterium exchange) δ 7.85 (1H, dd, J = 7.0, 2.0 Hz), 7.65−7.57 (1H, m), 7.14 (1H, d, J = 4.0 Hz), 6.73 (1H, dd, J = 9.0, 2.0 Hz), 6.44 (1H, ddd, J = 7.0, 7.0, 2.0 Hz), 6.33 (1H, d, J = 4.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 160.0, 157.1, 142.2, 138.2, 122.7, 121.3, 120.1, 114.4, 110.1, 107.8; HRMS (ESI$^+$) m/z calcd for $C_{10}H_8BrN_2O_3$ $[M + H]^+$: 282.9713, found 282.9712.

*5-Bromo-1H-pyrrole-2-carboxylic anhydride (**7**).* Synthesized via the same procedure as for compound **6a** except 2.3 equiv of lithium 5-bromo-1*H*-pyrrole-2-carboxylate **2** was used. Light orange solid (18.8 mg, 16%); mp 84−86 °C (CH_2Cl_2); R_f 0.07 (2:1 hexanes:EtOAc); IR (solid) ν_{max} 3184, 2923, 1643, 1430, 1378, 1187, 1031 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD; note: the pyrrole NH signal was not observed due to deuterium exchange) δ 6.79 (2H, d, J = 4.0 Hz), 6.15 (2H, d, J = 4.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 163.4, 125.9, 118.0, 113.1, 106.0; HRMS (ESI$^-$) m/z calcd for $C_{10}H_5Br_2N_2O_3$ $[M - H]^-$: 358.8672, found 358.8672.

*(2S,2′S)-di-tert-Butyl 2,2′-(carbonylbis(azanediyl))bis(3-phenyl-propanoate) (**8**).* In a flame-dried 25 mL flask with a stir bar was loaded L-phenylalanine *tert*-butyl ester hydrochloride **4** (203.2 mg, 0.788 mmol, 1.8 equiv) and it was slurried in CH_2Cl_2 (5 mL) before dropwise addition of Hünig's base (140 μL, 0.804 mmol, 1.9 equiv), followed by addition of 1,1′-carbonyldiimidazole (70.0 mg, 0.432 mmol, 1.0 equiv). The reaction mixture was stirred for 12 h at room temperature before being concentrated in vacuo to give a crude residue. Flash chromatography (3:1 hexanes:EtOAc) of the crude residue afforded **8** (160.5 mg, 79% yield) as a white solid; mp 136−137 °C (CH_2Cl_2); R_f 0.49 (3:1 hexanes:EtOAc); $[\alpha]_D^{23}$ +70.3 (*c* 1.06, $CHCl_3$); IR (solid) ν_{max} 3303 (br), 2977, 1730, 1623, 1563, 1364, 1445, 1104 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD; note: the amide NH signal was not observed due to deuterium exchange) δ 7.30−7.24 (4H, m), 7.23−7.17 (6H, m), 4.45−4.38 (2H, m), 3.00 (2H, dd, J = 14.0, 6.5 Hz), 2.95 (2H, dd, J = 14.0, 7.0 Hz), 1.37 (18H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 173.2, 159.6, 138.3, 130.7, 129.5, 127.9, 82.9, 56.3, 39.5, 28.4; HRMS (ESI$^+$) m/z calcd for $C_{27}H_{37}N_2O_5$ $[M + H]^+$: 469.2697, found 469.2694.

*Lithium (S)-2-((tert-butoxycarbonyl)amino)-2-phenylacetate (**12a**).* In a 150 mL lyophilization flask were loaded Boc-L-phenylglycine **11a** (1.019 g, 4.06 mmol) and 3:2 MeCN/H_2O (25 mL). To this solution was added LiOH·H_2O (170.5 mg, 4.06 mmol), and the mixture was stirred vigorously for 10 min (LiOH should be completely dissolved) before removing the stir bar and cooling the solution to −78 °C until the mixture became completely solid. Removal of the solvents by lyophilization overnight afforded **12a** (1.022 g, 98%) as a white solid; decomposition temp 80 °C; $[\alpha]_D^{21}$ +102.8 (*c* 1.01, MeOH); IR (solid) ν_{max} 2977, 1684, 1601, 1390, 1366, 1165 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD; note: mixture of rotamers and the carbamate NH signal was not observed due to deuterium exchange) δ 7.42 (2H, d, J = 7.5 Hz), 7.27 (2H, t, J = 7.5 Hz), 7.20 (1H, t, J = 7.5 Hz), 5.00−4.78 (1H, m), 1.50−1.20 (9H, m); ^{13}C NMR (100 MHz, CD_3OD; note: mixture of rotamers) δ 177.2, 157.1, 142.5, 129.3, 128.23, 128.14, 81.2, 80.4, 62.7, 61.6, 28.9, 28.6; HRMS (ESI$^-$) m/z calcd for $C_{13}H_{16}NO_4$ $[M - Li]^-$: 250.1085, found 250.1088.

*Lithium (S)-2-(((benzyloxy)carbonyl)amino)-2-phenylacetate (**12b**).* Synthesized via the same procedure as for compound **12a** except a 7:4 MeCN/H_2O solvent system was used for Cbz-L-phenylglycine **11b**. White solid; decomposition temp 240 °C; $[\alpha]_D^{21}$ +108.8 (*c* 1.14, DMSO); IR (solid) ν_{max} 3420, 3064, 3034, 2966, 1702, 1601, 1405, 1388, 1350, 1058 cm^{-1}; ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 7.40−7.09 (10H, m), 6.99 (1H, d, J = 6.5 Hz), 5.00 (1H, d, J = 12.5 Hz), 4.93 (1H, d, J = 12.5 Hz), 4.60 (1H, d, J = 6.5 Hz); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 166.0, 150.6, 138.6, 133.3, 124.4, 123.74, 123.68, 123.4, 122.7, 121.9, 61.1, 56.4; HRMS (ESI$^-$) m/z calcd for $C_{16}H_{14}NO_4$ $[M - Li]^-$: 284.0928, found 284.0937.

*Lithium 2-(2-methyl-1,3-dioxolan-2-yl)acetate (**15c**).* In a 100 mL Schlenk flask with a stir bar was loaded ethyl 2-(2-methyl-1,3-dioxolan-2-yl)acetate[28] (2.89 g, 17.11 mmol). A 1.05 M (aq) solution of LiOH (16.3 mL, 17.11 mmol) was then added, and the reaction mixture was stirred vigorously for 5 h at 50 °C. The solution was then carefully concentrated under reduced pressure at 50 °C to yield a thick white residue. Evaporation from toluene (2 × 30 mL) and further drying in vacuo afforded **15c** (2.31 g, 89% yield) as a white solid; decomposition temp 200 °C; IR (solid) ν_{max} 2905, 1597, 1418, 1201, 1151, 1049 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 4.01−3.88 (4H, m), 2.49 (2H, s), 1.47 (3H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 178.3, 110.0, 65.6,

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48.6, 24.7; HRMS (ESI$^-$) m/z calcd for $C_6H_9O_4$ [M − Li]$^-$: 145.0506, found 145.0503.

Amides Synthesized via General Procedure A. *Representative Procedure: (S)-Benzyl-2-((S)-2-((tert-butoxycarbonyl)amino)-2-phenylacetamido)-3-methylbutanoate (**14a**).*[29] In a flame-dried vial with a stir bar were loaded L-valine benzyl ester **13** (72.3 mg, 0.349 mmol, 1.0 equiv) and DMF (3 mL). The solution was cooled to 0 °C before the addition of lithium Boc-L-phenylglycine carboxylate **12a** (99.0 mg, 0.385 mmol, 1.1 equiv), followed by HBTU (151.0 mg, 0.398 mmol, 1.1 equiv). The mixture was stirred at 0 °C for 24 h before slowly warming to 10 °C (9 additional hours of reaction time). The reaction mixture was then concentrated down to a thick residue using an air stream, and then loaded directly onto a silica column. Flash chromatography (3:1 hexanes:EtOAc) of the crude residue afforded **14a** (153.6 mg, quantitative yield) as an inseparable mixture of diastereomers (dr 99:1 by HPLC). White foam; R_f 0.44 (3:1 hexanes:EtOAc); HPLC (C18 column, 4.6 × 250 mm (5 μm), 45% H_2O/MeCN, 0.5 mL/min, 23 °C, 210 nm, t_R (L,L): 51.58 min, t_R (D,L): 54.44 min); $[\alpha]_D^{21}$ +48.3 (c 1.00, $CHCl_3$) [lit.[29] $[\alpha]_D^{25}$ +26.8 (c 0.94, $CHCl_3$)]; IR (thin film in CH_2Cl_2) ν_{max} 3317, 2969, 1739, 1715, 1663, 1525, 1498, 1367, 1246, 1169 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (10H, m), 6.24 (1H, d, J = 8.5 Hz), 5.71 (1H, br s), 5.17 (1H, br s), 5.10 (1H, d, J = 12.0 Hz), 5.05 (1H, d, J = 12.0 Hz), 4.55 (1H, dd, J = 8.5, 4.5 Hz), 2.22−2.10 (1H, m), 1.41 (9H, s), 0.90 (3H, d, J = 7.0 Hz), 0.83 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.3, 155.3, 137.9, 135.3, 129.1, 128.7, 128.58, 128.55, 128.4, 127.3, 80.3, 67.2, 58.9, 57.5, 31.5, 28.4, 19.0, 17.7; HRMS (ESI$^+$) m/z calcd for $C_{25}H_{33}N_2O_5$ [M + H]$^+$: 441.2384, found 441.2386.

*(S)-Benzyl-2-((S)-2-(((benzyloxy)carbonyl)amino)-2-phenylacetamido)-3-methylbutanoate (**14b**).*[21a] White solid (176.3 mg, 96%, dr 97:3 by HPLC); R_f 0.32 (3:1 hexanes:EtOAc); HPLC (C18 column, 4.6 × 250 mm (5 μm), 45% H_2O/MeCN, 0.5 mL/min, 23 °C, 210 nm, t_R (L,L): 54.78 min, t_R (D,L): 59.52 min); $[\alpha]_D^{21}$ +53.2 (c 1.08, $CHCl_3$); IR (thin film in CH_2Cl_2) ν_{max} 3307, 2964, 1734, 1707, 1659, 1533, 1246, 1139 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.28 (13H, m), 7.27−7.22 (2H, m), 6.15 (1H, d, J = 8.5 Hz), 6.09−5.98 (1H, br m), 5.30−5.20 (1H, br m), 5.15−4.98 (4H, m), 4.54 (1H, dd, J = 8.5, 5.0 Hz), 2.23−2.10 (1H, m), 0.89 (3H, d, J = 7.0 Hz), 0.82 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 169.9, 155.8, 137.6, 136.3, 135.2, 129.2, 128.74, 128.72, 128.6 (2C), 128.5, 128.24, 128.20, 127.4, 67.2 (2C), 59.0, 57.6, 31.5, 19.0, 17.7; HRMS (ESI$^+$) m/z calcd for $C_{28}H_{31}N_2O_5$ [M + H]$^+$: 475.2227, found 475.2233.

*(S)-tert-Butyl-2-formamido-3-phenylpropanoate (**16a**).*[30] Colorless oil (69.6 mg, 61% yield); R_f 0.20 (2:1 hexanes:EtOAc); $[\alpha]_D^{23}$ +16.9 (c 1.20, EtOH) [lit.[30] $[\alpha]_D^{25}$ +16.0 (c 0.7, EtOH)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (1H, s), 7.33−7.20 (3H, m), 7.19−7.12 (2H, m), 6.11 (1H, br d, J = 6.0 Hz), 4.89−4.79 (1H, m), 3.16−3.06 (2H, m), 1.41 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 160.5, 135.9, 129.6, 128.5, 127.2, 82.8, 52.4, 38.1, 28.1; HRMS (DART) mass calcd for $C_{14}H_{20}NO_3$ [M + H]: 250.1438, found 250.1446.

*(S)-tert-Butyl-2-(3-ethoxy-3-oxopropanamido)-3-phenylpropanoate (**16b**).* Colorless oil (289.1 mg, quantitative yield); R_f 0.41 (2:1 hexanes:EtOAc); $[\alpha]_D^{23}$ +47.2 (c 0.94, $CHCl_3$); IR (neat) ν_{max} 3375 (br), 3088, 3064, 3031, 2981, 2935, 1731, 1653, 1367, 1151, 1033 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (1H, br d, J = 7.5 Hz), 7.32−7.11 (5H, m), 4.75 (1H, ddd, J = 7.5, 6.0, 6.0 Hz), 4.18 (2H, q, J = 7.0 Hz), 3.32 (1H, d, J = 17.5 Hz), 3.26 (1H, d, J = 17.5 Hz), 3.17−3.04 (2H, m), 1.40 (9H, s), 1.26 (3H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 168.9, 164.6, 136.3, 129.6, 128.5, 127.1, 82.5, 61.7, 54.0, 41.5, 38.1, 28.1, 14.2; HRMS (DART) mass calcd for $C_{18}H_{26}NO_5$ [M + H]: 336.1806, found 336.1819.

*(S)-tert-Butyl-2-(2-(2-methyl-1,3-dioxolan-2-yl)acetamido)-3-phenylpropanoate (**16c**).* White semisolid (280.1 mg, 90%); R_f 0.39 (1:1 hexanes:EtOAc); $[\alpha]_D^{23}$ +26.9 (c 1.27, $CHCl_3$); IR (thin film in CH_2Cl_2) ν_{max} 3377 (br), 2981, 2936, 2892, 1733, 1660, 1525, 1367, 1155, 1046 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.17 (5H, m), 6.91 (1H, br d, J = 7.5 Hz), 4.76 (1H, ddd, J = 7.5, 6.5, 6.5 Hz), 3.98−3.89 (3H, m), 3.88−3.82 (1H, m), 3.11 (1H, dd, J = 14.0, 6.5 Hz), 3.06 (1H, dd, J = 14.0, 6.5 Hz), 2.56 (2H, s), 1.40 (9H, s), 1.35 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 168.5, 136.5, 129.6, 128.5, 127.0, 107.9, 82.2, 64.72, 64.69, 53.6, 46.2, 38.3, 28.1, 24.0; HRMS (DART) mass calcd for $C_{19}H_{28}NO_5$ [M + H]: 350.1962, found 350.1971.

*(S)-tert-Butyl-2-(2-oxopropanamido)-3-phenylpropanoate (**16d**).* Light yellow oil (215.4 mg, 77%); R_f 0.46 (4:1 hexanes:EtOAc); $[\alpha]_D^{23}$ +33.4 (c 1.49, $CHCl_3$); IR (neat) ν_{max} 3397 (br), 3030, 3004, 2979, 2934, 1732, 1684, 1519, 1367, 1356, 1254, 1155 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.19 (4H, m), 7.18−7.10 (2H, m), 4.68 (1H, ddd, J = 8.0, 5.5, 5.5 Hz), 3.17−3.03 (2H, m), 2.44 (3H, s), 1.40 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 169.7, 159.6, 135.8, 129.5, 128.6, 127.3, 82.9, 53.8, 38.2, 28.0, 24.5; HRMS (DART) mass calcd for $C_{16}H_{22}NO_4$ [M + H]: 292.1543, found 292.1554.

*(S)-tert-Butyl-2-((S)-2-hydroxypropanamido)-3-phenylpropanoate (**16e**).*[31] White crystalline solid (147.6 mg, 85%); mp 72−73 °C (CH_2Cl_2); R_f 0.41 (1:1 hexanes:EtOAc); $[\alpha]_D^{23}$ +44.8 (c 1.11, $CHCl_3$) [lit.[31] $[\alpha]_D^{20}$ +36.8 (c 1.0, $CHCl_3$), dr >20:1]; IR (thin film in CH_2Cl_2) ν_{max} 3396 (br), 3032, 2979, 2934, 1729, 1651, 1524, 1367, 1155 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.20 (3H, m), 7.18−7.13 (2H, m), 6.89 (1H, br d, J = 7.5 Hz), 4.75 (1H, ddd, J = 7.5, 6.0, 6.0 Hz), 4.20 (1H, br qd, J = 7.0, 4.5 Hz), 3.13 (1H, dd, J = 14.0, 6.0 Hz), 3.08 (1H, dd, J = 14.0, 6.0 Hz), 2.73 (1H, br d, J = 4.5 Hz), 1.41 (9H, s), 1.35 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 170.7, 136.2, 129.6, 128.5, 127.1, 82.6, 68.5, 53.2, 38.2, 28.1, 21.3; HRMS (DART) mass calcd for $C_{16}H_{24}NO_4$ [M + H]: 294.1700, found 294.1711.

*(S)-tert-Butyl-2-((2S,5R,6R)-3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamido)-3-phenylpropanoate (**16f**).* Light yellow crystalline solid (125.7 mg, 80%); mp 62−63 °C (CH_2Cl_2); R_f 0.31 (2:1 hexanes:EtOAc); $[\alpha]_D^{23}$ +192.1 (c 1.21, $CHCl_3$); IR (thin film in CH_2Cl_2) ν_{max} 3303 (br), 3063, 3029, 2977, 2932, 1785, 1730, 1661, 1523, 1454, 1367, 1154 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD; note: the amide NH signals were not observed due to deuterium exchange) δ 7.33−7.18 (10H, m), 5.56 (1H, d, J = 4.5 Hz), 5.45 (1H, d, J = 4.5 Hz), 4.57 (1H, dd, J = 9.5, 5.5 Hz), 4.13 (1H, s), 3.60 (1H, d, J = 14.5 Hz), 3.56 (1H, d, J = 14.5 Hz), 3.16 (1H, dd, J = 14.0, 5.5 Hz), 2.95 (1H, dd, J = 14.0, 9.5 Hz), 1.56 (3H, s), 1.42 (9H, s), 1.31 (3H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 176.2, 174.0, 171.8, 169.8, 138.3, 136.5, 130.5, 130.3, 129.72, 129.70, 128.2, 128.0, 83.3, 73.1, 68.2, 65.6, 59.5, 55.8, 43.2, 38.3, 29.8, 28.3, 27.5; HRMS (ESI$^+$) m/z calcd for $C_{29}H_{36}N_3O_5S$ [M + H]$^+$: 538.2370, found 538.2347.

*(S)-tert-Butyl-3-phenyl-2-pivalamidopropanoate (**16g**).* White solid (242.1 mg, 84%); mp 71−72 °C (CH_2Cl_2); R_f 0.53 (4:1 hexanes:EtOAc); $[\alpha]_D^{23}$ +58.0 (c 1.33, $CHCl_3$); IR (thin film in CH_2Cl_2) ν_{max} 3316 (br), 3071, 3031, 2977, 2934, 2871, 1722, 1645, 1539, 1367, 1254, 1154 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.18 (3H, m), 7.17−7.10 (2H, m), 6.08 (1H, br d, J = 7.0 Hz), 4.73 (1H, ddd, J = 7.5, 6.0, 6.0 Hz), 3.14 (1H, dd, J = 14.0, 6.0 Hz), 3.07 (1H, dd, J = 14.0, 6.0 Hz), 1.42 (9H, s), 1.15 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 171.0, 136.4, 129.7, 128.4, 127.0, 82.4, 53.3, 38.8, 38.0, 28.1, 27.5; HRMS (DART) mass calcd for $C_{18}H_{28}NO_3$ [M + H]: 306.2064, found 306.2075.

*(S)-tert-Butyl-2-acrylamido-3-phenylpropanoate (**16h**).*[32] Colorless crystalline solid (76.7 mg, 61%); mp 35−36 °C (CH_2Cl_2); R_f 0.46 (2:1 hexanes:EtOAc); $[\alpha]_D^{24}$ +116.3 (c 0.91, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.19 (3H, m), 7.18−7.11 (2H, m), 6.28 (1H, dd, J = 17.0, 1.5 Hz), 6.16−6.02 (2H, m), 5.65 (1H, dd, J = 10.0, 1.5 Hz), 4.84 (1H, ddd, J = 8.0, 6.0, 6.0 Hz), 3.19−3.07 (2H, m), 1.41 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 164.9, 136.2, 130.7, 129.7, 128.5, 127.1, 127.0, 82.7, 53.6, 38.1, 28.1; HRMS (DART) mass calcd for $C_{16}H_{22}NO_3$ [M + H]: 276.1594, found 276.1600.

*(S)-tert-Butyl-2-((2E,4E)-hexa-2,4-dienamido)-3-phenylpropanoate (**16i**).* White solid (204.0 mg, quantitative yield); mp 119−120 °C (CH_2Cl_2); R_f 0.32 (4:1 hexanes:EtOAc); $[\alpha]_D^{24}$ +170.2 (c 1.14, $CHCl_3$); IR (thin film in CH_2Cl_2) ν_{max} 3286 (br), 3028, 2978, 2933, 1733, 1660, 1635, 1615, 1538, 1367, 1153, 998 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.11 (6H, m), 6.21−6.01 (2H, m), 5.96 (1H, br d, J = 7.5 Hz), 5.74 (1H, d, J = 15.0 Hz), 4.85 (1H, ddd, J =

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7.5, 6.0, 6.0 Hz), 3.19−3.05 (2H, m), 1.83 (3H, d, J = 5.5 Hz), 1.40 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 165.7, 141.8, 138.3, 136.4, 129.78, 129.73, 128.4, 127.0, 121.2, 82.5, 53.7, 38.3, 28.1, 18.7; HRMS (ESI$^+$) m/z calcd for $C_{19}H_{26}NO_3$ [M + H]$^+$: 316.1907, found 316.1910.

*(S)-tert-Butyl-2-methacrylamido-3-phenylpropanoate (**16j**).*[33] White solid (308.6 mg, 98%); mp 64−65 °C (CH_2Cl_2); R_f 0.39 (4:1 hexanes:EtOAc); $[\alpha]_D^{24}$ +69.6 (c 1.25, $CHCl_3$) [lit.[33] $[\alpha]_D$ +64.7 (c 1.0, $CHCl_3$)]; IR (thin film in CH_2Cl_2) ν_{max} 3349 (br), 2990, 2979, 1744, 1653, 1613, 1530, 1148, 940 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.20 (3H, m), 7.18−7.12 (2H, m), 6.26 (1H, br d, J = 7.0 Hz), 5.67 (1H, dq, J = 1.0, 1.0 Hz), 5.33 (1H, qd, J = 1.5, 1.0 Hz), 4.80 (1H, ddd, J = 7.0, 6.0, 6.0 Hz), 3.16−3.12 (2H, m), 1.94 (3H, dd, J = 1.5, 1.0 Hz), 1.42 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.6, 139.8, 136.3, 129.7, 128.5, 127.1, 120.1, 82.6, 53.6, 38.0, 28.1, 18.6; HRMS (DART) mass calcd for $C_{17}H_{24}NO_3$ [M + H]: 290.1751, found 290.1756.

*(S)-tert-Butyl-2-benzamido-3-phenylpropanoate (**16k**).*[34] Beige crystalline solid (170.5 mg, quantitative yield); mp 76−78 °C (CH_2Cl_2); R_f 0.74 (2:1 hexanes:EtOAc); $[\alpha]_D^{24}$ +81.0 (c 1.49, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.69 (2H, m), 7.54−7.46 (1H, m), 7.45−7.36 (2H, m), 7.32−7.23 (3H, m), 7.22−7.14 (2H, m), 6.66 (1H, br d, J = 7.0 Hz), 4.96 (1H, ddd, J = 7.0, 5.5, 5.5 Hz), 3.30−3.16 (2H, m), 1.44 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 166.9, 136.3, 134.2, 131.8, 129.7, 128.7, 128.5, 127.15, 127.09, 82.8, 54.0, 38.1, 28.1; HRMS (DART) mass calcd for $C_{20}H_{24}NO_3$ [M + H]: 326.1751, found 326.1761.

*(S)-tert-Butyl-2-(nicotinamido)-3-phenylpropanoate (**16l**).* In a flame-dried vial with a stir bar were loaded nicotinic acid sodium salt **15l** (79.0 mg, 0.544 mmol), L-phenylalanine *tert*-butyl ester hydrochloride **4** (140.0 mg, 0.543 mmol), and DMF (4.0 mL). Hünig's base (105 μL, 0.603 mmol) was added to the resulting solution dropwise, followed by HBTU (215.0 mg, 0.567 mmol). The reaction mixture was stirred for 1 h at room temperature, and then concentrated down to a thick residue using an air stream before being loaded directly onto a silica column. Flash chromatography (1:1 hexanes:EtOAc) of the crude residue yielded an inseparable mixture of **16l** and HOBt (235.0 mg, approximately 25% w/w HOBt by ^{1}H NMR). The mixture was taken up in $CHCl_3$ (5 mL) and sonicated for 1 min, producing a fine white precipitate (HOBt) that was subsequently removed by filtration over Celite directly into a 50 mL separatory funnel. Additional $CHCl_3$ was added (15 mL), and the organic layer was washed twice with saturated aqueous $NaHCO_3$ (2 × 20 mL) and dried over $MgSO_4$. Concentration in vacuo afforded pure **16l** (151.7 mg, 86% yield) as a colorless oil; R_f 0.27 (1:1 hexanes:EtOAc); $[\alpha]_D^{23}$ −30.2 (c 1.16, MeOH); IR (thin film in CH_2Cl_2) ν_{max} 3325 (br), 2978, 1733, 1645, 1593, 1539, 1368, 1153 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD; note: the amide NH signal was not observed due to deuterium exchange) δ 8.86 (1H, d, J = 2.0 Hz), 8.66 (1H, dd, J = 5.0, 2.0 Hz), 8.14 (1H, ddd, J = 8.0, 2.0, 2.0 Hz), 7.51 (1H, dd, J = 8.0, 5.0 Hz), 7.33−7.17 (5H, m), 4.75 (1H, dd, J = 9.0, 6.0 Hz), 3.25 (1H, dd, J = 14.0, 6.0 Hz), 3.09 (1H, dd, J = 14.0, 9.0 Hz), 1.43 (9H, s); ^{13}C NMR (75 MHz, CD_3OD) δ 172.3, 168.1, 152.9, 149.3, 138.6, 137.2, 131.9, 130.5, 129.6, 128.0, 125.2, 83.2, 56.7, 38.4, 28.3; HRMS (ESI$^+$) m/z calcd for $C_{19}H_{23}N_2O_3$ [M + H]$^+$: 327.1703, found 327.1707.

*(S)-tert-Butyl-2-(3-fluoropicolinamido)-3-phenylpropanoate (**16m**).* Colorless oil (132.6 mg, quantitative yield); R_f 0.39 (2:1 hexanes:EtOAc); $[\alpha]_D^{23}$ +55.4 (c 1.16, $CHCl_3$); IR (thin film in CH_2Cl_2) ν_{max} 3385 (br), 2979, 1730, 1685, 1507, 1454, 1443, 1367, 1155 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.38 (1H, ddd, J = 4.5, 1.5, 1.5 Hz), 8.32 (1H, br d, J = 8.0 Hz), 7.55 (1H, ddd, J = 10.0, 8.5, 1.5 Hz), 7.46 (1H, ddd, J = 8.5, 4.5, 4.0 Hz), 7.30−7.25 (2H, m), 7.24−7.20 (3H, m), 4.95 (1H, ddd, J = 8.0, 6.0, 6.0 Hz), 3.26−3.17 (2H, m), 1.41 (9H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 161.9 (d, J = 6.0 Hz), 159.4 (d, J = 273.0 Hz), 144.2 (d, J = 6.0 Hz), 137.5 (d, J = 4.0 Hz), 136.5, 129.7, 128.5, 128.1 (d, J = 5.0 Hz), 127.0, 126.3 (d, J = 20.0 Hz), 82.5, 53.7, 38.5, 28.1; ^{19}F NMR (564 MHz, $CDCl_3$) δ −119.2 (dd, J = 10.0, 4.5 Hz); HRMS (ESI$^+$) m/z calcd for $C_{19}H_{21}FN_2O_3Na$ [M + Na]$^+$: 367.1428, found 367.1431.

Amides Synthesized via General Procedure C. *Representative Procedure: (S)-tert-Butyl-2-(hept-2-ynamido)-3-phenylpropanoate (**18a**).* To a flame-dried 50 mL flask with a stir bar were loaded 1-hexyne **17a** (115 μL, 1.001 mmol) and THF (8 mL). The resultant solution was cooled to −78 °C, and ^{n}BuLi (1.96 M in hexanes, 400 μL, 0.784 mmol) was added dropwise. After the addition was complete, the solution was stirred at −78 °C for an additional 30 min. A small piece of dry ice (weighing approximately 15 g) was placed into a 250 mL flask fitted with a drying tube (packed with drierite), and CO_2 gas was bubbled continually into the above solution at −78 °C for 30 min before slowly warming to room temperature (30 min) with continued bubbling. ***Caution!**: A flask with sufficient head space must be used and fitted with an exit bubbler prior to the addition of CO_2 gas to avoid overpressurizing the vessel, especially as it warms to room temperature.* After the solution was warmed to room temperature, the flow of CO_2 was stopped and the solution was concentrated to dryness in vacuo to yield the crude carboxylate. To this flask was added L-phenylalanine *tert*-butyl ester hydrochloride **4** (258.6 mg, 1.003 mmol) and it was slurried in DMF (5 mL) before dropwise addition of Hünig's base (200 μL, 1.149 mmol), followed by HBTU (388.0 mg, 1.023 mmol). The crude reaction mixture was stirred for a further 1 h at room temperature, and then concentrated down to a thick residue using an air stream before being loaded directly onto a silica column. Flash chromatography (4:1 hexanes:EtOAc) of the crude residue afforded **18a** (249.6 mg, 97% yield) as a colorless oil; R_f 0.56 (4:1 hexanes:EtOAc); $[\alpha]_D^{26}$ +84.4 (c 1.26, $CHCl_3$); IR (neat) ν_{max} 3295 (br), 3063, 3029, 2961, 2935, 2873, 2235, 1731, 1651, 1368, 1155 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.21 (3H, m), 7.19−7.13 (2H, m), 6.23 (1H, br d, J = 7.5 Hz), 4.77 (1H, ddd, J = 7.5, 6.0, 6.0 Hz), 3.16−3.06 (2H, m), 2.28 (2H, t, J = 7.0 Hz), 1.58−1.48 (2H, m), 1.46−1.36 (11H, m), 0.91 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 152.9, 136.0, 129.7, 128.5, 127.1, 88.3, 82.8, 75.4, 53.9, 38.0, 29.8, 28.1, 22.1, 18.4, 13.6; HRMS (DART) mass calcd for $C_{20}H_{28}NO_3$ [M + H]: 330.2069, found 330.2069.

*(S)-tert-Butyl-3-phenyl-2-(3-(triisopropylsilyl)propiolamido)-propanoate (**18b**).* White solid (701.3 mg, 96%); mp 50−52 °C (CH_2Cl_2); R_f 0.73 (4:1 hexanes:EtOAc); $[\alpha]_D^{25}$ +67.1 (c 1.05, $CHCl_3$); IR (thin film in CH_2Cl_2) ν_{max} 3298 (br), 2944, 2866, 2164, 1733, 1662, 1496, 1368, 1257, 1224, 1154 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.21 (3H, m), 7.19−7.14 (2H, m), 6.29 (1H, br d, J = 8.0 Hz), 4.78 (1H, ddd, J = 8.0, 6.0, 5.5 Hz), 3.17−3.07 (2H, m), 1.40 (9H, s), 1.14−1.05 (21H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 152.0, 135.9, 129.7, 128.5, 127.2, 99.6, 89.3, 82.9, 54.0, 38.0, 28.1, 18.6, 11.1; HRMS (DART) mass calcd for $C_{25}H_{40}NO_3Si$ [M + H]: 430.2777, found 430.2784.

*(2S)-tert-Butyl-3-phenyl-2-(4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-ynamido) propanoate (**18c**).* Light yellow oil; (248.3 mg, 76%); R_f 0.33 (4:1 hexanes:EtOAc); $[\alpha]_D^{25}$ +59.7 (c 0.95, $CHCl_3$); IR (neat) ν_{max} 3288 (br), 3030, 2941, 2243, 1733, 1652, 1520, 1155, 1122, 1079, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$; note: mixture of diastereomers) δ 7.33−7.21 (3H, m), 7.19−7.13 (2H, m), 6.44−6.24 (1H, br d, J = 7.5 Hz), 4.83−4.70 (2H, m), 4.41−4.29 (2H, m), 3.86−3.76 (1H, m), 3.59−3.49 (1H, m), 3.16−3.02 (2H, m), 1.88−1.69 (2H, m), 1.68−1.48 (4H, m), 1.40 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$; note: mixture of diastereomers) δ 169.9, 152.0, 135.8, 129.7, 128.6, 127.2, 97.40, 97.38, 83.0, 82.55, 82.52, 79.7, 62.19, 62.16, 54.0, 53.9, 38.0, 30.2, 28.1, 25.4, 19.02, 19.00; HRMS (DART) mass calcd for $C_{22}H_{30}NO_5$ [M + H]: 388.2124, found 388.2130.

*(S)-tert-Butyl-2-(3-(cyclohex-1-en-1-yl)propiolamido)-3-phenyl-propanoate (**18d**).* Light yellow oil (292.4 mg, 95%); R_f 0.49 (4:1 hexanes:EtOAc); $[\alpha]_D^{26}$ +71.6 (c 1.03, $CHCl_3$); IR (neat) ν_{max} 3292 (br), 3063, 3030, 2981, 2929, 2859, 2205, 1731, 1642, 1078, 1045, 1032 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.21 (3H, m), 7.20−7.14 (2H, m), 6.37−6.33 (1H, m), 6.28 (1H, br d, J = 7.5 Hz), 4.79 (1H, ddd, J = 7.5, 6.0, 6.0 Hz), 3.18−3.06 (2H, m), 2.18−2.08 (4H, m), 1.70−1.52 (4H, m), 1.40 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 153.2, 140.7, 136.0, 129.7, 128.5, 127.1, 118.8, 87.5, 82.8, 80.7, 54.0, 38.1, 28.4, 28.1, 26.0, 22.1, 21.3; HRMS (DART) mass calcd for $C_{22}H_{28}NO_3$ [M + H]: 354.2069, found 354.2071.

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*(S)-tert-Butyl-3-phenyl-2-(3-phenylpropiolamido)propanoate (**18e**).* White solid (294.9 mg, 84%); mp 87−88 °C (CH_2Cl_2); R_f 0.34 (4:1 hexanes:EtOAc); $[\alpha]_D^{23}$ +96.8 (*c* 1.21, $CHCl_3$); IR (thin film in CH_2Cl_2) ν_{max} 3288 (br), 3063, 3030, 2979, 2932, 2215, 1733, 1647, 1533, 1498, 1368, 1217, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56−7.51 (2H, m), 7.45−7.39 (1H, m), 7.38−7.23 (5H, m), 7.22−7.17 (2H, m), 6.44 (1H, br d, *J* = 7.5 Hz), 4.84 (1H, ddd, *J* = 7.5, 6.0, 6.0 Hz), 3.22−3.10 (2H, m), 1.42 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 152.8, 135.9, 132.7, 130.3, 129.7, 128.64, 128.58, 127.2, 120.2, 85.4, 83.0, 82.9, 54.1, 38.1, 28.1; HRMS (DART) mass calcd for $C_{22}H_{24}NO_3$ [M + H]: 350.1756, found 350.1759.

*(S)-tert-Butyl-3-phenyl-2-(3-(pyridin-3-yl)propiolamido)-propanoate (**18f**).* Light yellow oil (220.7 mg, quantitative yield); R_f 0.18 (2:1 hexanes:EtOAc); $[\alpha]_D^{23}$ +93.6 (*c* 1.02, $CHCl_3$); IR (thin film in CH_2Cl_2) ν_{max} 3247 (br), 2978, 2220, 1730, 1646, 1534, 1368, 1152 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (1H, d, *J* = 1.5 Hz), 8.62 (1H, dd, *J* = 5.0, 1.5 Hz), 7.82 (1H, ddd, *J* = 8.0, 2.0, 2.0 Hz), 7.36−7.12 (6H, m), 6.58 (1H, br d, *J* = 8.0 Hz), 4.84 (1H, ddd, *J* = 8.0, 6.0, 6.0 Hz), 3.24−3.07 (2H, m), 1.43 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 153.1, 152.2, 150.4, 139.7, 135.8, 129.7, 128.6, 127.3, 123.3, 117.6, 85.8, 83.1, 81.7, 54.1, 38.0, 28.1; HRMS (ESI^+) *m*/*z* calcd for $C_{21}H_{23}N_2O_3$ $[M + H]^+$: 351.1703, found 351.1702.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H, ^{13}C, and ^{19}F NMR spectra. 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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