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

Jordan D. Goodreid, Petar A. Duspara, Caroline Bosch, and Robert A. Batey*

Davenport Research Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, ON, Canada, MSS 3H6

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 S-bromo-1H-pyrrole-2-carboxylate, whose corresponding acid that is prone to decarboxylation, allowed for the synthesis of S-bromo-1H-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. Most amide bond formations utilize the reaction of amines in the presence of acylating agents, such as acyl chlorides, or the reaction of carboxylic acids with amines in the presence of coupling agents. The importance of amides has ensured continued advances in protocols and reagents based upon these approaches, as well as the development of alternative methods for amide bond formation.

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. 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). Similar approaches using tetraalkylammonium carboxylate salts for peptide couplings have also been reported. Carboxylate salts have also been employed for the synthesis of amides via in situ acid chloride formation. Finally, couplings of methyl red sodium carboxylate and other alkali metal dicyanamides 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. 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.

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 carbonate 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). 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...
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 are reported to be unstable, whereas the corresponding lithium carboxylate salt provides access to a bench-stable alternative that is stable for months. 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-hydroxysuccinimidy 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, but the corresponding pyrrole-2-carboxylic acids have poor stability profiles, limiting their application in some syntheses. Lithium 5-bromo-1H-pyrrole-2-carboxylate was thus chosen for the initial optimization study. Coupling of 2 with L-phenylalanine tert-butylester hydrochloride 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 Hunig’s base (Method A) resulted in poor conversion to the desired amide. In addition to significant amounts of remaining amine, anhydride and urea were also formed as side-products (Table 1, entries 1–4).
Formation of anhydride 7 presumably proceeds through the homocoupling of carboxylate 2 via an activated ester species. 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 Hüning’s base, but did form through the analogous reaction with HBTU (27% conversion by 1H 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, Hüning’s base, and PyBOP in the presence of carbon dioxide gas (57% conversion by 1H NMR) (Scheme 2, Eq 2). 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, Hüning’s base, and PyBOP in the presence of carbon dioxide gas (57% conversion by 1H 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 was observed (20% conversion by 1H 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 Hüning’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 1H NMR experiment utilizing DMF-d7 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 Hüning’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...
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−5k) and secondary (5l−5m) 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

### Table 3. Base-Free Synthesis of Amides 5g−5k Using Lithium Bromopyrrole Carboxylate 2 and Various Amines (Method B)""̈̈asaki et al. 2014, 79, 943−954

<table>
<thead>
<tr>
<th>entry</th>
<th>carboxylate</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>amide</th>
<th>yield (%)</th>
<th>dr (L,L:D,L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12a</td>
<td>rt</td>
<td>1</td>
<td>14a</td>
<td>quant</td>
<td>97.3</td>
</tr>
<tr>
<td>2</td>
<td>12a</td>
<td>0−10</td>
<td>33</td>
<td>14a</td>
<td>quant</td>
<td>99:1</td>
</tr>
<tr>
<td>3</td>
<td>12b</td>
<td>rt</td>
<td>33</td>
<td>14b</td>
<td>97</td>
<td>95:5</td>
</tr>
<tr>
<td>4</td>
<td>12b</td>
<td>0−10</td>
<td>33</td>
<td>14b</td>
<td>96</td>
<td>97:3</td>
</tr>
</tbody>
</table>

"Isolated yields after column chromatographic purification. 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 (Method A)

<table>
<thead>
<tr>
<th>entry</th>
<th>carboxylate</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>amide</th>
<th>yield (%)</th>
<th>dr (L,L:D,L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12a</td>
<td>rt</td>
<td>1</td>
<td>14a</td>
<td>quant</td>
<td>97.3</td>
</tr>
<tr>
<td>2</td>
<td>12a</td>
<td>0−10</td>
<td>33</td>
<td>14a</td>
<td>quant</td>
<td>99:1</td>
</tr>
<tr>
<td>3</td>
<td>12b</td>
<td>rt</td>
<td>33</td>
<td>14b</td>
<td>97</td>
<td>95:5</td>
</tr>
<tr>
<td>4</td>
<td>12b</td>
<td>0−10</td>
<td>33</td>
<td>14b</td>
<td>96</td>
<td>97:3</td>
</tr>
</tbody>
</table>

Free base 13 was obtained by treatment of H-Val-OBn·HCl with saturated Na2CO3 (aq) and extraction into CH2Cl2, followed by drying over MgSO4 and concentration in vacuo. Isolated yields after column chromatographic purification. 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
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·H₂O via a modified literature procedure. 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

Table 5. Synthesis of Amides 16a−16m Using Metal Carboxylates 15a−15m and Ammonium Salt 4 (Method A)\(^{a,b}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carboxylate</th>
<th>Amide</th>
<th>Yield (%)(^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15a</td>
<td>16a</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>15a</td>
<td>16a</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>15b</td>
<td>16b</td>
<td>quant</td>
</tr>
<tr>
<td>4</td>
<td>15c</td>
<td>16c</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>15d</td>
<td>16d</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>15e</td>
<td>16e</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>15f</td>
<td>16f</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>15g</td>
<td>16g</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>15h</td>
<td>16h</td>
<td>56</td>
</tr>
<tr>
<td>10</td>
<td>15k</td>
<td>16i</td>
<td>quant</td>
</tr>
<tr>
<td>11</td>
<td>15l</td>
<td>16j</td>
<td>98</td>
</tr>
<tr>
<td>12</td>
<td>15m</td>
<td>16k</td>
<td>quant</td>
</tr>
<tr>
<td>13</td>
<td>15n</td>
<td>16l</td>
<td>86</td>
</tr>
<tr>
<td>14</td>
<td>15o</td>
<td>16m</td>
<td>quant</td>
</tr>
</tbody>
</table>

\(^{a}\)Isolated yields after column chromatographic purification. \(^{b}\)2.0 equiv of carboxylate salt and HBTU 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. Amidations using free acetylenic acids, such as propionic acid or but-2-ynoic acid, with peptide coupling reagents provide one classical approach to their synthesis. For example, isolated 3-(triisopropylsilyl)propionic acid (synthesized via the corresponding acetylide addition to carbon dioxide) was used in a PyBOP mediated coupling with DL-serine methyl ester hydrochloride. An alternative approach to their synthesis utilizes low-temperature trapping of a lithiated acetylide with phenyl isocyanate or a magnesium acetylide with Me₃SiNCO. 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 BuLi 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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne</th>
<th>Amide</th>
<th>Yield (%)d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17a</td>
<td>18a</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>17b</td>
<td>18b</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>17c</td>
<td>18c</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>17d</td>
<td>18d</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>17e</td>
<td>18e</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>17f</td>
<td>18f</td>
<td>53 quant</td>
</tr>
</tbody>
</table>

“Isolated yields after column chromatographic purification. aAlkyne 17e (1.0 equiv), BuLi (1.0 equiv), and 4 (1.0 equiv) were used. bAlkyne 17f (1.6 equiv), BuLi (1.0 equiv), and 4 (1.6 equiv) were used.
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 hydrochloric acid. 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 alkyynes, "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 lamp. Solvent ratios for chromatography and reagent gradients for HPLC were 1:10 and 1:5, respectively. Flash chromatography on silica gel (60 Å, 230–400 mesh) was performed with reagent-grade solvents. The mass of the neutral species (not corrected for the mass of an added salt) was obtained as a crystalline solid; mp 50 °C (CHCl₃); Rf 0.25 (4:1 hexanes:EtOAc; [α]D = −15.4 (1.04, CHCl₃); IR (thin film in CHCl₃) ν max 3287 (br), 3196 (br), 2976, 2961, 2926, 2855, 1717, 1626, 1546, 1367, 1153 cm⁻¹; 1H NMR (400 MHz, CDCl₃); 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). 13C NMR (125 MHz, CDCl₃) δ 174.0, 160.0, 126.0, 112.0, 111.3, 104.3, 52.6, 50.7, 41.9, 25.1, 23.0, 22.1; HRMS (DART) mass calcd for C₁₇H₁₇BrN₃O₃ [M + H]+: 390.0452, found 390.0453.

**(S)-Methyl-2-(5-bromo-1H-pyrrole-2-carboxamido)-3-(1H-indol-5-yl)propanoate (5a).** Beige solid (103.2 mg, 93%); mp 77–80 °C (CHCl₃); Rf 0.22 (2:1 hexanes:EtOAc; [α]D = +49.5 (0.56, CHCl₃); IR (thin film in CHCl₃) ν max 3287 (br), 3196 (br), 2976, 2961, 2926, 2855, 1744, 1592, 1448, 1414, 1207 cm⁻¹; 1H NMR (400 MHz, CDCl₃; note: the amide and pyrrole NH signals were not observed due to deuterium exchange) δ 6.76–6.71 (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); 13C NMR (100 MHz, CDCl₃) 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 C₁₇H₁₇BrN₃O₃ [M − H]−: 375.0052, found 375.0054.

**(S)-Benzyl-2-(5-bromo-1H-pyrrole-2-carboxamido)pyrrolidine-2-carboxylate (5e).** White foam (91.6 mg, 94%); Rf 0.37 (2:1 hexanes:EtOAc; [α]D = −54.5 (0.89, MeOH); IR (thin film in CHCl₃) ν max 3182 (br), 3070, 3033, 2958, 2879, 1744, 1592, 1448, 1386, 1169 cm⁻¹; 1H NMR (400 MHz, CDCl₃; note: the pyrrole NH signal was not observed due to deuterium exchange) δ 7.42–7.22 (SH, 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), 3.28 (2H, m), 2.34–2.21 (1H, m), 2.14–1.90 (3H, m); 13C NMR (100 MHz, CDCl₃) 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 (ESI −) mass calcd for C₁₇H₁₇BrN₃O₃ [M − H]−: 377.0501, found 377.0503.

**(25R)-Methyl-1-(5-bromo-1H-pyrrole-2-carboxamido)-4-hydroxy-pyrrolidine-2-carboxylate (5f).** Light yellow solid (76.6 mg, 88%); decomposition temp 170 °C; Rf 0.41 (EtOAc); [α]D = +58.5 (0.76, MeOH); IR (solid) ν max 3416, 3130, 2957, 2925, 1732, 1616, 1431, 1215, 1184 cm⁻¹; 1H NMR (400 MHz, CDCl₃; 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); 13C NMR (100 MHz, CDCl₃) δ 174.7, 162.4, 127.9, 116.4, 112.9, 110.5, 71.5, 60.3, 58.3, 52.9, 38.1; HRMS (DART) mass calcd for C₁₉H₁₉BrN₃O₄ [M + H]+: 317.0137, found 317.0140.
**Bromo-1H-pyrole-2-carboxylic anhydride (7).** Synthesized via the same procedure as for compound 6a except 2.3 equiv of lithium 5-bromo-1H-pyrole-2-carboxylic acid was used. LiH (1.06 equiv) was dissolved in THF (2 mL) and the solution was then carefully added to 5.0 mmol of the carboxylic acid under dry nitrogen. The reaction mixture was stirred for 12 h at room temperature. The crude reaction mixture was then concentrated down to a thick residue. Flash chromatography (2:1 hexanes:EtOAc) of the crude residue a m/z calcd for C_{15}H_{15}BrN_3O_2 [M+H]^+ 282.9713, found 282.9712.

**Lithium (2)-(tetrabutoxy)carbonylaminophenol (12a).** In a 150 mL lyophilization flask were loaded 0.5 mmol of 5-bromo-1H-pyrole-2-carboxylic acid (5 mL) 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 (1.02 g, 98% as a white solid; mp 113–115 °C (CHCl_3); R_f 0.49 (3:1 hexanes:EtOAc); 3-phenylglycine (203.2 mg, 0.788 mmol, 1.8 equiv) and it was slurried in CH_2Cl_2 (5 mL) before being loaded directly onto a silica column. Flash chromatography (3:1 hexanes:EtOAc) gave the crude residue a m/z calcd for C_{15}H_{15}BrN_3O_2 [M+H]^+ 269.9269, found 269.9264.
Amides Synthesized via General Procedure A. Representative Procedure: (S)-Benzy1-2(2S)-2-[(tert-butoxycarbonyl)amino]-2-phencylacetoamido)-3-methylbutanoate (14a).29 In a flame-sealed vial with a stir bar were added 300 mg of benzyl ester 13 (73.3 mg, 0.349 mmol, 1.0 equiv) and DMF (3 mL). The solution was cooled to 0 °C before the addition of lithium Boc-phenylglycine carbonate 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; Rf 0.44 (3:1 hexanes:EtOAC); HPLC (C18 column, 4.6 × 250 mm (5 μm), 45% H2O/MeCN, 0.5 mL/min, 23 °C, 210 nm, tR tot (min): 51.85 min, tR α (min): 54.44 min; [α]236 = +483 (c 1.00, CHCl3) [lit.25] [α]236 = +268 (c 0.94, CHCl3); IR (thin film in CHCl3) νmax 3317, 2969, 1739, 1715, 1663, 1525, 1498, 1367, 1246, 1169 cm−1; 1H NMR (400 MHz, CDCl3) δ 7.40 (10H, m), 7.18–7.12 (7H, m), 7.08–7.02 (1H, m), 6.24 (1H, d, J = 17.0 Hz), 5.74 (1H, d, J = 7.5 Hz), 5.56 (1H, d, J = 4.5 Hz), 4.73 (1H, d, J = 14.0, 6.0 Hz), 3.17–3.04 (2H, m), 1.36–1.30 (9H, s), 0.83 (3H, d, J = 7.0 Hz); δ13C NMR (100 MHz, CDCl3) δ 171.3, 170.3, 168.5, 136.5, 129.6, 128.5, 128.5, 128.3, 127.3, 80.3, 67.2, 58.9, 57.5, 31.5, 28.4, 19.0, 17.7; HRMS (ESI+) m/z calcd for C30H34N4O8 [M + H]+: 441.2384, found 441.2386.

(S)-Benzy1-2(2S)-2-[(benzoxyl)]carbonyl amino)-2-phencylacetoamido)-3-methylbutanoate (14b).29 White solid (176.3 mg, 96%, dr 97:3 by HPLC); Rf 0.32 (3:1 hexanes:EtOAC); HPLC (C18 column, 4.6 × 250 mm (5 μm), 45% H2O/MeCN, 0.5 mL/min, 23 °C, 210 nm, tR tot (min): 51.85 min, tR α (min): 54.44 min; [α]236 = +483 (c 1.00, CHCl3) [lit.25] [α]236 = +268 (c 0.94, CHCl3); IR (thin film in CHCl3) νmax 3306, 2979, 2972, 1785, 1730, 1615, 1524, 1454, 1376, 1154 cm−1; 1H NMR (500 MHz, CDOD, note: the amide NH signals were not observed due to deuteration exchange) δ 7.33–7.18 (10H, m), 5.56 (1H, d, J = 4.5 Hz), 5.45 (1H, d, J = 4.5 Hz), 4.73 (1H, d, J = 14.0, 6.0 Hz), 3.03 (1H, d, J = 14.0, 5.0 Hz), 2.95 (1H, d, J = 14.0, 6.5 Hz), 1.49 (9H, s), 1.14 (9H, s), 0.82 (3H, d, J = 7.0 Hz); δ13C NMR (100 MHz, CDCl3) δ 170.9, 168.9, 168.3, 136.5, 130.5, 129.7, 129.0, 128.0, 128.8, 83.1, 73.2, 68.1, 65.6, 59.5, 55.8, 43.2, 38.9, 28.3, 27.5; HRMS (ESI+) m/z calcd for C29H32N4O8 [M + H]+: 439.2087, found 439.2091.

(S-tert-Butyl-2(2S)-2-oxopropanamido)-3-phenylpropanoate (16a).21 White crystalline solid (147.6 mg, 85%); mp 72–73 °C (CH2Cl2); Rf 0.41 (1:1 hexanes:EtOAc); [α]236 = +48.4 (c 1.11, CHCl3) [lit.26] [α]236 = +68.6 (c 1.0, CHCl3), dr ≥20:1; IR (thin film in CH2Cl2) νmax 3306 (br), 3032, 2979, 2974, 1729, 1512, 1454, 1376, 1155 cm−1; 1H NMR (400 MHz, CDCl3) δ 7.38–7.19 (2H, m), 7.18–7.10 (2H, m), 4.68 (1H, dd, J = 8.5, 5.5 Hz), 3.17–3.04 (2H, m), 2.44 (3H, s), 1.40 (9H, s); δ13C NMR (75 MHz, CDCl3) 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 C19H23NO3 [M + H]+: 292.1543, found 292.1544.

(S)-tert-Butyl-2-(2(S)-2-oxopropanamido)-3-phenylpropanoate (16b).21 White crystalline solid (147.6 mg, 85%); mp 72–73 °C (CH2Cl2); Rf 0.41 (1:1 hexanes:EtOAc); [α]236 = +48.4 (c 1.11, CHCl3) [lit.26] [α]236 = +68.6 (c 1.0, CHCl3), dr ≥20:1; IR (thin film in CH2Cl2) νmax 3306 (br), 3032, 2979, 2974, 1729, 1512, 1454, 1376, 1155 cm−1; 1H NMR (400 MHz, CDCl3) δ 7.38–7.19 (2H, m), 7.18–7.10 (2H, m), 4.68 (1H, dd, J = 8.5, 5.5 Hz), 3.17–3.04 (2H, m), 2.44 (3H, s), 1.40 (9H, s); δ13C NMR (75 MHz, CDCl3) 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 C19H23NO3 [M + H]+: 292.1543, found 292.1544.


This article is protected by copyright. All rights reserved.  

The Journal of Organic Chemistry
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); 13C NMR (75 MHz, CDCl3) δ 170.9, 165.7, 141.8, 138.3, 136.4, 129.78, 129.73, 128.4, 127.1, 122.8, 82.5, 53.7, 38.3, 28.1, 18.7; HRMS (ESI) m/z calc for C19H23N2O3 [M + H]+: 316.1907, found 316.1910.

Amines Synthesized via General Procedure C. Representative Procedure: (S)-tert-Butyl-2-(3-phenoxypropanoate) (16a). 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 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 CO2 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: If a flask with sufficient head space must be used and fitted with an exit bubbler prior to the addition of CO2 gas to avoid overpressurizing the vessel, especially as it warms to room temperature.

After the solution was warmed to room temperature, the flow of CO2 was stopped and the solution was concentrated to dryness in vacuo to yield the crude carbonate. To this flask was added 1-phenylalanine tert-butyl ester hydrochloride 4 (25.6 g, 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; Rf 0.56 (4:1 hexanes:EtOAc); HRMS (ESI+) m/z calcd for C20H24NO3 [M + H]: 322.1751, found 322.1756.

White solid (701.3 mg, 96%); mp 50 °C (CHCl3); Rf 0.73 (4:1 hexanes:EtOAc); [α]D25 +67.1 (1.05, CHCl3); IR (thin film in CH2Cl2) δmax 3298 (br), 2944, 2866, 2164, 1733, 1662, 1496, 1368, 1257, 1124, 1154 cm−1; 1H NMR (400 MHz, CDCl3) δ 7.31–7.21 (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 (1H, m), 0.91 (3H, t, J = 7.5 Hz); 13C NMR (100 MHz, CDCl3) δ 170.2, 152.9, 136.0, 129.7, 128.5, 127.1, 89.3, 82.8, 54.0, 38.0, 29.8, 28.1, 21.1, 18.4, 13.6; HRMS (DART) mass calcd for C20H24NO3 [M + H]: 330.2069, found 330.2069.

White solid (170.5 mg, quantitative yield); mp 76–78 °C (CH2Cl2); Rf 0.74 (2:1 hexanes:EtOAc); [α]D24 +81.0 (c 1.49, CHCl3); 1H NMR (300 MHz, CDCl3) 67.78–7.69 (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 = 7.5, 5.5, 5.5 Hz), 3.30–3.16 (2H, m), 1.44 (9H, s); 13C NMR (75 MHz, CDCl3) δ 170.8, 166.9, 163.3, 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 C19H21FN2O3Na [M + Na]+: 367.1431, found 367.1432.

Beige crystalline solid (170.5 mg, quantitative yield); mp 76–78 °C (CH2Cl2); Rf 0.74 (2:1 hexanes:EtOAc); [α]D20 +81.0 (c 1.49, CHCl3); 1H NMR (300 MHz, CDCl3) δ 7.0, 6.0, 6.0 Hz), 3.16 (2H, m), 1.44 (9H, s); 13C NMR (75 MHz, CDCl3) δ 7.0, 6.0, 6.0 Hz), 3.16 (2H, m), 1.44 (9H, s); 13C NMR (75 MHz, CDCl3) 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 C20H28NO3 [M + H]+: 346.2175, found 346.2176.

Colorless oil (132.6 mg, quantitative yield); Rf 0.39 (2:1 hexanes:EtOAc); [α]D24 +55.4 (c 1.16, MeOH); IR (thin film in CH2Cl2) δmax 3325 (br), 2978, 1733, 1645, 1593, 1539, 1368, 1153 cm−1; 1H NMR (300 MHz, CD2OD; 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, dd, J = 8.0, 2.0 Hz), 7.51 (1H, dd, J = 8.0, 5.5 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); 13C NMR (75 MHz, CDCl3) 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 C19H21FN2O3Na [M + Na]+: 379.1462, found 379.1464.
ASSOCIATED CONTENT

Supporting Information
Copies of 1H, 13C, and 19F NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
E-mail: rbatey@chem.utoronto.ca. Phone/Fax: (416)-978-5059.

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors acknowledge financial support from a Natural Science and Engineering Research Council (NSERC) of Canada Discovery Grant and a Canadian Institutes of Health Research Emerging Team Grants for R.A.B. and a PGDS scholarship to J.D.G.

REFERENCES


(17) The structures of side products 7 and 8 were synthesized independently for confirmation. See the Supporting Information.
(18) Activated esters 6a and 6b were synthesized independently through the coupling of 2 with HBTU or TPTU, respectively. See the Supporting Information.

(19) Compound 6a was unambiguously determined to be the O-acetyl HOBT adduct via spectroscopic comparison with other known adducts. For more information on O- versus N-acylation regiochemistry observed in adduct formation, see: Brink, B. D.; DeFrancisco, J. R.; Hillner, J. A.; Linton, B. R. J. Org. Chem. 2011, 76, 5258–5263.
(22) As a control to unambiguously establish the identities of the diastereomers of 14a,14b by 1H NMR and HPLC, the analogous dipetidates were prepared by coupling racemic 11a,11b with the hydrochloride salt of 13 using HBTU and Hünig’s base.
(23) The δ dratios for 14a,14b were measured by integration of the CH3 signals of the t-valine residue in the crude 1H NMRs.