'Umpolung' Reactivity in Semiaqueous Amide and Peptide Synthesis

Bo Shen, **Dawn M. Makley**, and **Jeffrey N. Johnston**[*]

Department of Chemistry & Vanderbilt Institute of Chemical Biology, Vanderbilt University, Nashville, TN 37235-1822

Abstract

The amide functional group is one of Nature's key functional and structural elements, most notably within peptides. Amides are also key intermediates in the preparation of a diverse range of therapeutic small molecules. Its construction using available methods focuses principally upon dehydrative approaches, although oxidative and radical-based methods are representative alternatives. During the carbon-nitrogen bond forming step in most every example, the carbon and nitrogen bear electrophilic and nucleophilic character, respectively. Here we show that activation of amines and nitroalkanes with an electrophilic iodine source in wet THF can lead directly to amide products. Preliminary observations support a mechanistic construct in which reactant polarity is reversed (umpolung) during C-N bond formation relative to traditional approaches. The use of nitroalkanes as acyl anion equivalents provides a conceptually innovative approach to amide and peptide synthesis, and one that might ultimately provide for efficient peptide synthesis that is fully reliant on enantioselective methods.

Nature achieves great structural diversity in protein synthesis through the rather straightforward condensation of amino acids (dehydrative amide synthesis). Large and complex, yet functionally precise proteins are formed in this manner from a remarkably small number of naturally occurring amino acids. The formation of the amide bond is the strategic lynchpin, one that is often mirrored in the laboratory through condensative methods for the preparation of amides and peptides. The reliance on condensative amide synthesis further benefits from the widespread availability of simple carboxylic acids and amines.[1] This otherwise solid foundation often weakens as the size of the target increases, or when the steric, functional and stereochemical complexity places a greater demand on the condensative acyl carbon-nitrogen bond forming reaction. For example, the use of disubstituted amines, aryl glycines, or peptidic amine/carboxylic acid combinations are often

met with low conversion and/or epimerization of the carboxylic acid prior to coupling. In addition to solid phase peptide synthesis, [2], [3] which often utilizes reagent excess to drive the condensation to completion, alternatives to conventional amide synthesis have emerged recently to address these practical challenges, including highly innovative approaches.[4] Among these, Staudinger ligation,[5], [6], [7], [8], [9] native chemical ligation,[10] hydrative amide synthesis through alkyne-azide coupling,[11], [12] oxidative amidation of alcohols,[13], [14] aldehydes,[15], [16] or alkynes,[17] and ketoacid-hydroxylamine ligation[18] are of contemporary importance.[19]

In this report, we describe a new preparation of amides and peptides that offers not only the advantages of convenience desired by the practitioner, but also a strategic divergence from traditional approaches. This amide synthesis utilizes the same amine feedstock as condensative amide synthesis, but explores new chemical space for the (chiral) acyl donor through the implementation of nitroalkanes, a compound class whose population and structural diversity is expanding at a rapid pace.[20], [21], [22], [23], [24] Unlike traditional amide bond forming reactions which engage a nucleophilic amine with an electrophilic active ester derivative, this amide synthesis employs an α-halo nitroalkane as an acyl donor for a variety of common amines. A halonium ion source (e.g. *N*-iodo succinimide, NIS) is used to activate the amine, and base is employed to maintain mildly alkaline conditions. Our preliminary investigation into the mechanism of this transformation suggests an uncommon chemotype wherein the inherent polarity of the acyl donor and amine are reversed (*umpolung*)[25], [26], [27] from conventional variants (Figure 1).

Our study of the basic bond forming reaction began with the hypothesis that an α-bromo nitroalkane (e.g. **1a**) might provide the proper oxidation state for coupling to an amine. This design was guided by the knowledge that the nonbrominated parent of **1a** is readily converted to the corresponding aldehyde using the Nef reaction in a two step sequence involving nitronate formation (NaOMe, MeOH), followed by its treatment with aqueous acid (H_2SO_4, H_2O).[28], [29] The inclusion of water (3:1 THF:H_2O = 93 equivalents) was based on the perceived need to hydrolyze the putative α-amino nitroalkane intermediate. By simply mixing α-bromo nitroalkane **1a** with secondary amine **2**, a trace amount of the desired amide (**3a**) could be identified after 10 days at room temperature (Table 1, entry 1). Addition of an exogenous base did not improve the conversion (Table 1, entry 2). Alongside this small amount of amide product, the formation of debrominated nitroalkane was detected. This observation led to the hypothesis that an *N*-halo amine and nitronate pair, formed through bromonium transfer from **1a** to **2**, might be key intermediates in the desired transformation.[30], [31] We therefore examined the action of *N*-iodo succinimide (NIS) as an electrophilic halogen source and found that conversion (>95%) and isolated chemical yield (61%) were improved substantially (Table 1, entry 3).

Use of potassium carbonate when water is a cosolvent provided a biphasic reaction mixture wherein the equivalents of amine could be reduced from 2 to 1.2 relative to α-bromo nitroalkane (c.f. entries 3–4, Table 1). When the amount of water was reduced further to 5 equivalents, a heterogeneous mixture results, but the isolated yield of the amide was further improved to 70% (Table 1, entry 5). Although water could not be rigorously excluded from the reaction mixture with confidence, owing to the hydrophilic nature of the amine, we

found that the desired amide could be isolated under nominally dry conditions at the expense of lower conversion and a more complex crude reaction mixture (Table 1, entry 6). We have determined that 5 equivalents of (added) water will deliver the amide product in good yield. Lowering the reaction temperature to 0 °C provided a modest improvement to the overall yield without significantly lengthening the time to completion (Table 1, entry 7).

A standard experimental protocol was developed in order to ascertain an initial scope for the reaction, with a near equimolar amount of donor and acceptor established as an important characteristic. These conditions included NIS (1 equivalent), potassium carbonate (2 equivalents), water (5 equivalents), amine (1.2 equivalents) and α-bromo nitroalkane **1** (1 equivalent), operating at ice water temperature for a standard reaction time. Although not optimized for any single example so as to provide a standard benchmark, these conditions provided a promising level of generality. The α-bromo nitroalkane component was first examined using α-methyl benzyl amine as a representative acceptor (Table 2). Nitroalkane donors carrying aliphatic and aromatic chains are readily employed using this method (Table 2, entries 1–4), and amides bearing electrophilic halides (Table 2, entry 5) or an acid labile acetal/leaving group at the β-position (Table 2, entry 6) can be prepared without complication. At an extreme of donor steric congestion, α-bromo nitroalkane **1g** was converted smoothly to amide **4g** in 54% yield (Table 2, entry 7). Lactonization-prone carbinol **1h** and its homolog **1i** produced amides **4h** and **4i** in 48% and 70% isolated yield (Table 2, entries 8–9) using these standard conditions, and the terminal methyl ester **1j** led to amide **4j** in 70% yield (Table 2, entry 10).

The amine component was similarly examined (Table 3) using α-bromo nitroalkane 1a as a constant. Simple monosubstituted amines bearing aliphatic and aromatic substituents performed well, delivering the desired amide in good isolated yields (most >70%). Particular attention was paid to common functional groups that might be desirable in more complex amide preparation, such as allyl and propargyl amines (Table 3, entries 2–3). Furthermore, an unprotected 1,4-amino alcohol formed the corresponding amide chemoselectively in 71% yield (Table 3, entry 4). Amide formation using glycine methyl ester provided a promising indication that applications in peptide synthesis might be possible (Table 3, entry 5). α-Amido nitriles are present in some pharmaceuticals,[32], [33] and this functionality is readily accessed using the key reaction as well (Table 3, entry 6). Amines with increasing steric hindrance provided comparable levels of efficiency (Table 3, entries 7–8), including *tert*-butyl amine (Table 3, entry 9). One limitation at present is the use of aniline, as no coupling product could be retrieved using the standard reaction protocol (Table 3, entry 10). Beyond aniline, however, there appear to be relatively few apparent limitations. Diethyl amine was evaluated as a representative disubstituted amine, as these are often more difficult substrates for dehydrative amide synthesis. The standard reaction protocol provided the desired tertiary amide **5** in 50% yield (Figure 2, eq 1). Finally, we explored the potential of α-bromo nitroalkane donors in peptide synthesis by coupling of dipeptide **6** with donor **1a** and retrieved amide **7** in 72% isolated yield (Figure 2, eq 2).

These exploratory experiments are consistent with the preliminary mechanistic hypothesis outlined in Figure 3, but not a Nef reaction mechanism. NIS serves as a halogenating agent for the amine,[30], [31], [37] converting it into an electrophilic partner (**9**) for the nitronate (**8**) (or

perhaps the nitronic acid through tautomerization of **1a**). The latter is formed by proton transfer to amine, and ultimately to carbonate, which is consistent with our observation that excess amine (5 equivalents) can be used as an alternative to carbonate to drive the reaction to completion. The key carbon-nitrogen bond forming step involves an apparent nucleophilic attack by nitronate at nitrogen of the putative *N*-halo amine.[30], [31] The tetrahedral intermediate formed (**10**) is then ultimately converted to the amide product through hydrolysis, leading to our current proposal that this reaction is formally a hydrative amide synthesis from an amine.[11] Under the conditions outlined, amine *N*-dealkylation was not observed.[34], [35], [36]

A series of experiments designed to further test elements of the pathway outlined in Figure 3 and alternatives were pursued. For example, exposure of amine **2** to NIS in CDCl$_3$ (25 °C) revealed rapid consumption of both components.[37] Peaks consistent with the putative *N*-iodo amine (**9**) (or **9**-succinimide complex) could be observed spectroscopically by ^{1}H NMR and HRMS. The sample showed no significant decomposition after several hours at room temperature in CDCl$_3$. The possibility that α-bromo nitroalkane **1a** is simply a precursor to an electrophilic carbonyl intermediate, such as an aldehyde or acyl halide, was examined by a series of experiments summarized in Figure 4. Phenyl acetaldehyde would be formed as an intermediate from **1a** during a Nef-oxidative amidation sequence. When phenyl acetaldehyde was exposed to the reaction conditions, its consumption was eventually observed, but a complex mixture of products formed without evidence for formation of amide **4a** (Figure 4, eq 3). Separately, we monitored the behavior of nitroalkane **1a** in the presence of NIS/K$_2$CO$_3$, but in the absence of amine, and again observed slow conversion to a mixture of products (Figure 4, eq 4). We observed peaks (^{1}H NMR) consistent with production of an α-bromo-α-iodo nitroalkane in this experiment, but this intermediate was also ultimately consumed during the formation of the complex mixture. In order to test whether this complex mixture contains an active ester of some type (e.g. acid halide), amine was added after **1a** was consumed, but again, amide **4a** was not formed. Alternatively, we tested the potential formation of an electrophilic active ester by replacement of the amine with benzyl alcohol, but this variation failed to produce the ester product (Figure 4, eq 5). The involvement of atmospheric oxygen was also considered, but little difference was observed among the 1) typical reaction setup and variants that were 2) degassed, or 3) run with an oxygen atmosphere.

The studies described above establish a preliminary scope in the context of simple intermolecular α-bromo nitroalkane couplings with amines, and provide a new framework for amide synthesis under mild, near pH-neutral conditions with a heterogeneous base. We next focused on the generation of chiral nonracemic α-bromo nitroalkane donors that would deliver amides of protected α-amino acids directly from this amide synthesis protocol. Aryl glycine derivatives are subunits of naturally occurring small molecules[38] and the vancomycin class of antibiotics provides particularly prominent examples. These aryl glycine-derived peptides constitute an amide subclass that is difficult to prepare using conventional amide synthesis (particularly via dehydrative methods) due to base-promoted epimerization of the active ester intermediate. Furthermore, the preparation of chiral nonracemic aryl glycine carboxylic acids is synthetically intensive.[38]

We prepared the required α-bromo nitroalkane substrate in straightforward fashion from commercially available bromo nitromethane and imine **11** using chiral proton catalyst **12**.[39], [40], [41], [42], [43] The addition product (**13**) that resulted was retrieved as a 1:1 mixture of diastereomers, each with 98% ee and homochiral at the benzylic carbon (Figure 5, eq 6). α-Bromo nitroalkane **13** was then coupled to both *rac*-amine **2** and (*R*)-**2** (96% ee) using our standard reaction protocol, delivering **14** in 76% yield in each case (Figure 5, eq 7). The use of racemic amine allowed a careful analysis of the diastereomeric ratio in the example derived from (*R*)-**2** (96% ee) to determine that it is >98:2 as expected. This is significant as aryl glycines often undergo some degree of epimerization when active ester intermediates are used in couplings with amines. Moreover, the absence of epimerization here is consistent with the mechanism proposed in Figure 3. This behavior could be further generalized as a component of peptide synthesis. Dipeptide **9** (Ala-Phe-OMe) delivered tripeptide **15** in 72% yield using α-bromo nitroalkane **13** (Figure 5, eq 8). Coupling of aryl glycine donor **13** to the canonical amino acids, using a uniform protocol for all examples, provided a promising level of generality as shown in Table 4. Of particular note is the efficient coupling of sterically hindered members, including proline (Table 4, entry 15), and the use of unprotected side chains for serine and threonine (Table 4, entries 6–7).

In addition to the practical advantages associated with the use of an enantioselective, organocatalytic addition reaction to prepare the acyl donor equivalent and the mild conditions employed in the amide synthesis, this approach provides a conceptually new approach to enantioselective peptide construction (Figure 6). Bromo nitromethane constitutes the amide carbonyl carbon in the final product, and serves as the lynchpin of the synthesis while providing a carbonyl dianion synthetic equivalent. This reactivity is *umpolung*[25] to traditional condensative amide synthesis.[44]

In summary, we have discovered a nonconventional amide synthesis via iodonium-promoted nitroalkane-amine coupling. The conditions are only mildly basic and have been shown to accommodate a range of nitroalkanes and amines. At the levels of strategy and mechanism, this amide synthesis appears to reverse the reactive polarity of acyl and amine subunits relative to traditional condensative approaches, providing a nucleophilic acyl donor and an electrophilic amine acceptor. This new approach led to the development of an aryl glycine amide synthesis without epimerization or extensive protection/deprotection schemes. And the first use of commercially available bromo nitromethane in stereoselective peptide synthesis establishes a practical alternative in peptide synthesis to the longstanding reliance on the carboxylic acid feedstock. This strategic shift may ultimately enable the efficient fully chemical synthesis of chiral, nonracemic peptides using a combination of entirely enantioselective methods and nitroalkane-amine couplings as demonstrated in eq 8.

Methods Summary

Reactions were carried out in glass vials or round-bottomed flasks. Commercially available reagents were purchased and used as received unless otherwise noted. Products were characterized by nuclear magnetic resonance (NMR), infrared spectroscopy (IR), and high resolution mass spectrometry (HRMS). The enantiomeric excess of chiral, non-racemic aza-Henry adduct **13** was determined by chiral high-performance liquid chromatography

(HPLC) by comparison to an assay developed using racemic **13**. For complete experimental details, including procedures and full characterization (optical rotation, melting point, IR, ^{1}H and ^{13}C NMR, and HRMS) of all new compounds, see the Supplementary Information.

Methods

General Procedure for Amide Synthesis Using an Amine (Free Base): The amine (1.2 equiv) was added dropwise to a solution of α-bromo nitroalkane (1.0 equiv, 0.2 M) and NIS (1.0 equiv) in THF and H$_2$O (5.0 equiv) at 0 °C, followed by K$_2$CO$_3$ (2.0 equiv). The reaction mixture was stirred at 0 °C for 2 d. The resulting mixture was diluted with dichloromethane, dried with MgSO$_4$ and then filtered through Celite. The filtrate was concentrated and subjected to purification by flash column chromatography on silica gel.

General Procedure for Amide Synthesis Using an Ammonium Salt: K$_2$CO$_3$ (3.2 equiv) was added to a suspension of the ammonium salt (1.2 equiv) and the α-bromo nitroalkane (1.0 equiv, 0.2 M) in THF and H$_2$O (5.0 equiv) at 0 °C, followed by NIS (1.0 equiv). The reaction mixture was stirred at 0 °C for 2 d. The resulting mixture was diluted with dichloromethane, dried with MgSO$_4$ and then filtered through Celite. The filtrate was concentrated and subjected to purification by flash column chromatography on silica gel.

Enantioselective aza-Henry Reaction Using Bromo Nitromethane: A solution of imine **11** (1.0 equiv, 0.3 M) and H, Quin(6(9Anth)2Pyr)-BAM·HOTf (**12**, 5 mol%) in toluene was cooled to −20 °C and treated with bromonitromethane (1.2 equiv). The reaction mixture was stirred at −20 °C for 2 d, and then concentrated and subjected directly to purification by flash column chromatography on silica gel to give the α-bromo nitroalkane adduct.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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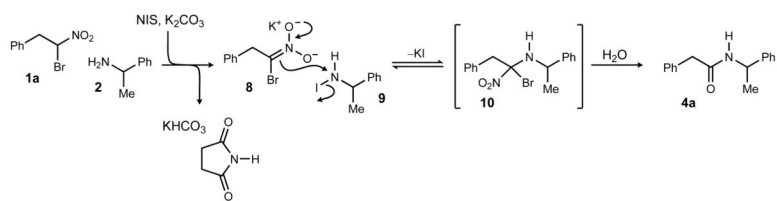
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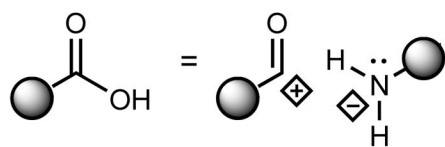
Hydrative Amide Synthesis (this work)
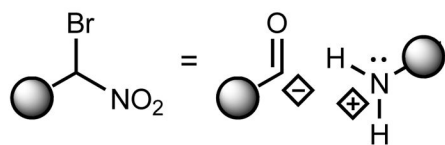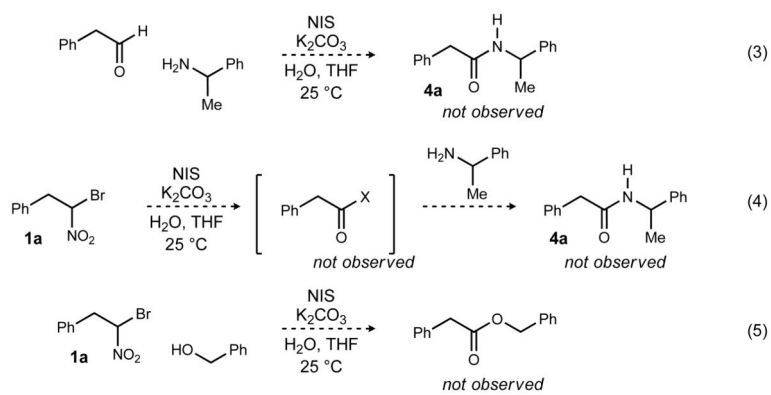
Figure 1.
Comparison of Component Polarization in Conventional Condensative Amide Synthesis and α-Bromo Nitroalkane-Amine Coupling
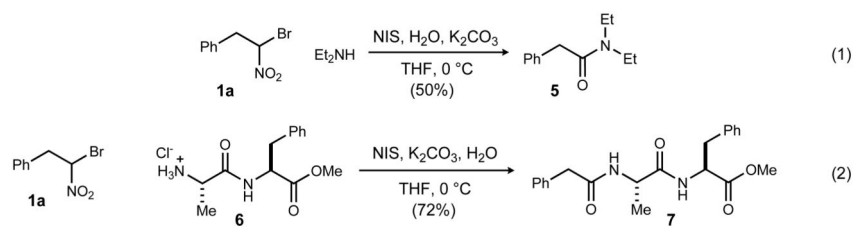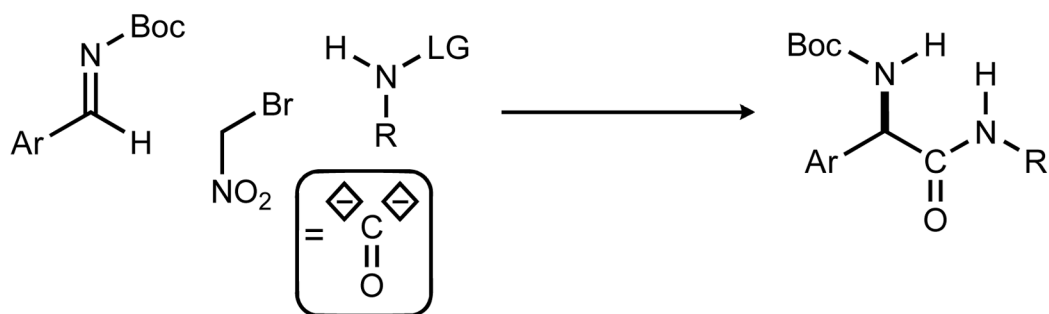
Figure 2.
Amide and Peptide Synthesis

Figure 3.
Mechanistic Hypothesis for Amide Synthesis from an α-Bromo Nitroalkane and Amine

Figure 4.
Experiments Designed to Probe Intermediacy of Possible Carbonyl Electrophiles [Ph = phenyl, NIS = *N*-iodo succinimide, THF = tetrahydrofuran]
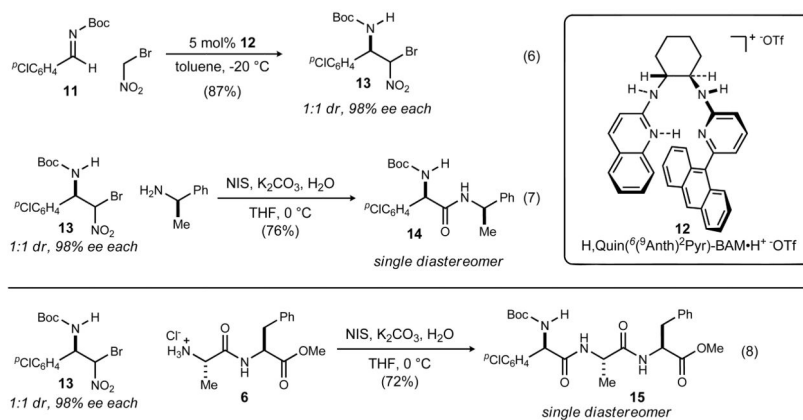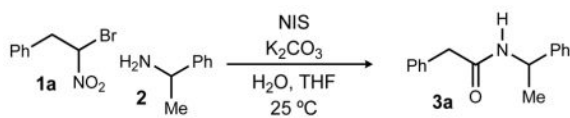
Figure 5.
Stereoselective Peptide Synthesis [Boc = tert-butoxy carbonyl, Ph = phenyl, NIS = *N*-iodo succinimide, THF = tetrahydrofuran]

α-halo nitroalkane peptide synthesis

Figure 6.
Enantioselective Peptide Synthesis: A Carbonyl Dianion Synthon Approach

Table 1

Development of an α-Halo Nitroalkane Based Amide Synthesis[a]

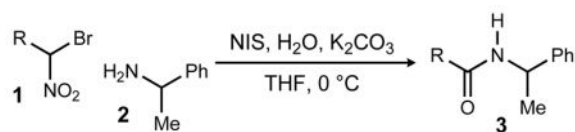| entry	NIS (equiv)	H_2O equiv	K_2CO_3 (equiv)	yield (%)[b]
1[c]	0	93	0	<5
2[c]	0	93	2	<5
3[c]	1.2	93	0	61
4[d]	1.0	93	2	58
5[d]	1.0	5	2	70
6[d]	1.0	0	2	55
7[d,e]	1.0	5	2	75

[a]Reactions employed 1 equivalent of α-bromo nitroalkane (0.2 M in THF) and *rac*-2, with amine added as the final reagent at 25 °C.

[b]Isolated yields.

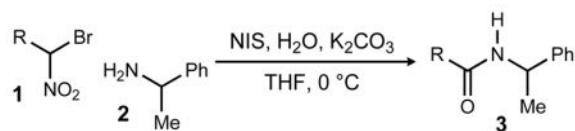[c]2 Equivalents of amine used.

[d]1.2 Equivalents of amine used.

[e]Reaction temperature was 0 °C.

Table 2

Development of an α-Halo Nitroalkane Based Amide Preparation: Scope of the α-Bromo Nitroalkane Donor[a]

entry	product	yield (%)[b]
1	b	71
2	c	76
3	a	75
4	d	70
5	e	81
6	f	72
7	g	54
8	h	48

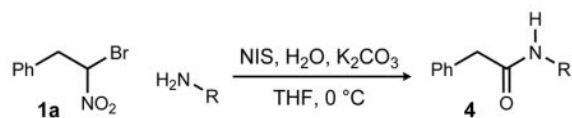| entry	product	yield (%)[b]
9	i	70
10	j	70

[a] NIS (1 equivalent), K_2CO_3 (2 equivalents), amine (1.2 equivalents), H_2O (5 equivalents), and nitroalkane (1 equivalent, 0.2 M in THF) were stirred for a standard 2 day reaction time prior to workup. See the Supporting Information for complete details.

[b] Isolated yield.

NIS = *N*-iodo succinimide, THF = tetrahydrofuran, Ph = phenyl, Me = methyl

Table 3

Development of an α-Halo Nitroalkane Based Amide Preparation: Scope of the Amine Acceptor[a]

entry	product	yield (%)[b]
1	**a**	72
2	**b**	73
3	**c**	61
4	**d**	71
5	**e**	72
6	**f**	62
7	**g**	72
8	**h**	75
9[c]	**i**	60

entry	product	yield (%)[b]
10		0
	j	

[a] NIS (1 equivalent), K_2CO_3 (2 equivalents), amine (1.2 equivalents), H_2O (5 equivalents), and nitroalkane (1 equivalent, 0.2 M in THF) were stirred for a standard 2 day reaction time prior to workup. See the Supporting Information for complete details.
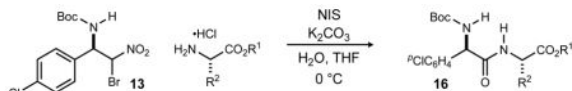
[b] Isolated yield.

[c] 1.8 Equivalents of $^tBuNH_2$.

NIS = N-iodo succinimide, THF = tetrahydrofuran, Ph = phenyl, Bn = benzyl, Me = methyl

Table 4

Aryl Glycine Couplings to the Canonical Amino Acids[a]
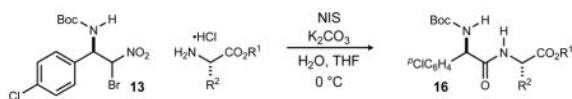
entry	amino acid	product	yield (%)
1	glycine		79
2	L-alanine		63
3	L-valine		70
4	L-leucine		81
5	L-isoleucine		66
6	L-serine		64[b]
7	L-threonine		45
8	L-phenylalanine		64

entry	amino acid	product	yield (%)
9	L-tyrosine		64
10	L-aspartic acid		64
11	L-asparagine		52
12	L-glutamic acid		57
13	L-glutamine		59
14	L-lysine		55
15	L-proline		67
16	L-cysteine		52
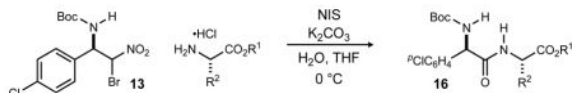
entry	amino acid	product	yield (%)
17	L-methionine		43
18	L-arginine		44
19	L-histidine		41
20	L-tryptophan		44

[a] Yields correspond to isolated, analytically pure materials, but have not been optimized for each case. Standard reaction conditions applied: NIS (1 equivalent), K_2CO_3 (3.5 equivalents), amine (1.2 equivalents), H_2O (5 equivalents), and nitroalkane (1 equivalent), 0.2 M in THF.

[b] Stirred at 25 °C for 5 hours.

[Boc = *tert*-butoxy carbonyl, Ph = phenyl, NIS = *N*-iodo succinimide, THF = tetrahydrofuran]