

Umpolung reactivity in amide and peptide synthesis

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The amide bond is one of nature's most common functional and structural elements, as the backbones of all natural peptides and proteins are composed of amide bonds. Amides are also present in many therapeutic small molecules. The construction of amide bonds using available methods relies principally on dehydrative approaches, although oxidative and radical-based methods are representative alternatives. In nearly every example, carbon and nitrogen bear electrophilic and nucleophilic character, respectively, during the carbon–nitrogen bond-forming step. Here we show that activation of amines and nitroalkanes with an electrophilic iodine source can lead directly to amide products. Preliminary observations support a mechanism in which the polarities of the two reactants are reversed (German, *umpolung*) during carbon–nitrogen 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.

Great structural diversity in protein synthesis is achieved in nature 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 amines¹. 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 before coupling. In addition to solid phase peptide synthesis^{2,3}, which often uses reagent excess to drive the condensation to completion, alternatives to conventional amide synthesis have emerged recently to address these practical challenges, including highly innovative approaches⁴. Among these, Staudinger ligation^{5–9}, native chemical ligation¹⁰, hydrative amide synthesis through alkyne–azide coupling^{11,12}, oxidative amidation of alcohols^{13,14}, aldehydes^{15,16} or alkynes¹⁷, and ketoacid–hydroxylamine ligation¹⁸ are of contemporary importance¹⁹.

In this Article, we describe a new route to the preparation of amides and peptides that offers not only the advantage of convenience, but also a strategic divergence from traditional approaches. This amide synthesis uses 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^{20–24}. Unlike traditional amide bond-forming reactions, which engage a nucleophilic amine with an electrophilic active ester derivative, this amide synthesis uses an α -halo nitroalkane as an acyl donor for a variety of common amines. A halonium ion source (for example, *N*-iodo succinimide, NIS) is used to activate the amine, and

base is used 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*)^{25–27} from conventional variants (Fig. 1).

Formation of the C–N bond

Our study of the basic bond-forming reaction began with the hypothesis that an α -bromo nitroalkane (for example, **1a** in Fig. 2) might provide the proper oxidation state for coupling to an amine. This design was guided by the knowledge that the non-brominated 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 (H₂SO₄, H₂O)^{28,29}. The inclusion of water (3:1 THF:H₂O = 93 equiv.) was based on the perceived need to hydrolyse 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,

Condensative amide synthesis (conventional approach)

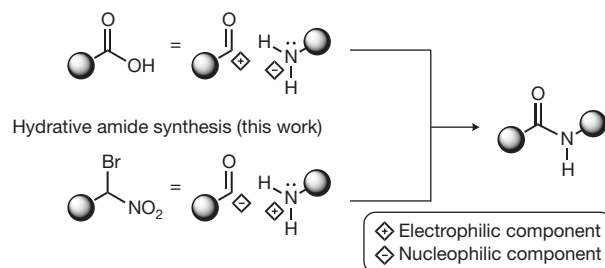


Figure 1 | Comparison of component polarization in conventional condensative amide synthesis and α -bromo nitroalkane–amine coupling.

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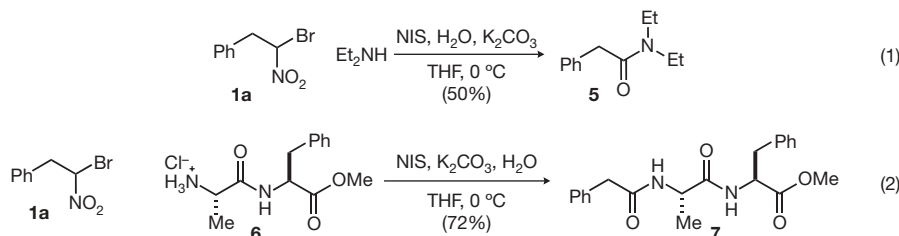


Figure 2 | Amide and peptide synthesis. Ph, phenyl; NIS, *N*-iodo succinimide; THF, tetrahydrofuran.

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 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 (compare entries 3 and 4, Table 1). When the amount of water was reduced further to 5 equiv., 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 equiv. 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 equiv.), potassium carbonate (2 equiv.), water (5 equiv.), amine (1.2 equiv.) and α -bromo nitroalkane **1** (1 equiv.), 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 used in 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 homologue **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%).

Table 2 | Scope of the α -bromo nitroalkane donor

Entry	Product	ID	Yield* (%)
1		b	71
2		c	76
3		a	75
4		d	70
5		e	81
6		f	72
7		g	54
8		h	48
9		i	70
10		j	70

Table 1 | Development of an α -halo nitroalkane based amide synthesis

Entry	NIS (equiv.)	H ₂ O (equiv.)	K ₂ CO ₃ (equiv.)	Yield*
1†	0	93	0	<5
2†	0	93	2	<5
3†	1.2	93	0	61
4‡	1.0	93	2	58
5‡	1.0	5	2	70
6‡	1.0	0	2	55
7‡§	1.0	5	2	75

Reactions used 1 equiv. of α -bromo nitroalkane (0.2 M in THF) and *rac*-**2**, with amine added as the final reagent at 25 °C. NIS, *N*-iodo succinimide; THF, tetrahydrofuran; Ph, phenyl; Me, methyl.

* Isolated yields.

† 2 equiv. of amine used.

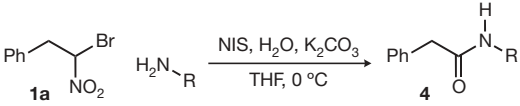
‡ 1.2 equiv. of amine used.

§ Reaction temperature 0 °C.

NIS (1 equiv.), K₂CO₃ (2 equiv.), amine (1.2 equiv.), H₂O (5 equiv.), and nitroalkane (1 equiv., 0.2 M in THF) were stirred for a standard 2-day reaction time before workup. See Supplementary Information for details.

* Isolated yield.

Table 3 | Scope of the amine acceptor

			
Entry	Product	ID	Yield* (%)
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†		i	60
10		j	0

Reaction conditions as Table 2. Bn, benzyl.

* Isolated yield.

† 1.8 equiv. of *t*-BuNH₂.

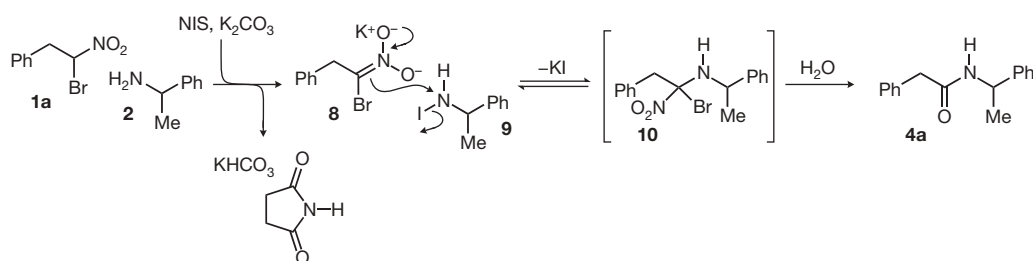
Particular attention was paid to common functional groups that might be desirable in more complex amide preparation, such as allyl and propargyl amines (Table 3, entries 2, 3). Furthermore, an unprotected 1,4-amino alcohol formed the corresponding amide chemoselectively in 71% yield (Table 3, entry 4). 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 also readily accessed using the key reaction (Table 3, entry 6). Amines with increasing steric hindrance provided comparable levels of efficiency (Table 3, entries 7, 8), including *t*-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 (Fig. 2, equation (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 (Fig. 2, equation (2)).

Possible mechanisms

These exploratory experiments are consistent with the preliminary mechanistic hypothesis outlined in Fig. 3, but not with a Nef reaction mechanism. NIS serves as a halogenating agent for the amine^{30,31}, 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 equiv.) 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 amine¹¹. Under the conditions outlined, amine *N*-dealkylation was not observed^{34–36}.

A series of experiments designed to further test elements of the pathway outlined in Fig. 3 and alternatives were pursued. For example, exposure of amine **2** to NIS in CDCl₃ (25 °C) revealed rapid consumption of both components³⁷. Peaks consistent with the putative *N*-iodo amine (**9**) (or **9**-succinimide complex) could be observed spectroscopically by ¹H NMR and high-resolution mass spectrometry (HRMS). The sample showed no significant decomposition after several hours at room temperature in CDCl₃. 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 Fig. 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** (Fig. 4, equation (3)). Separately, we monitored the behaviour of nitroalkane **1a** in the presence of NIS/K₂CO₃, but in the absence of amine, and again observed slow conversion to a mixture of products (Fig. 4, equation (4)). We observed peaks (¹H 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 (for example, acid halide), amine was added after **1a** was consumed, but again, amide **4a** was not formed. We also 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 (Fig. 4, equation (5)). The involvement of atmospheric oxygen was also considered, but little difference was observed among

**Figure 3 | Mechanistic hypothesis for amide synthesis from an α -bromo nitroalkane and amine.**

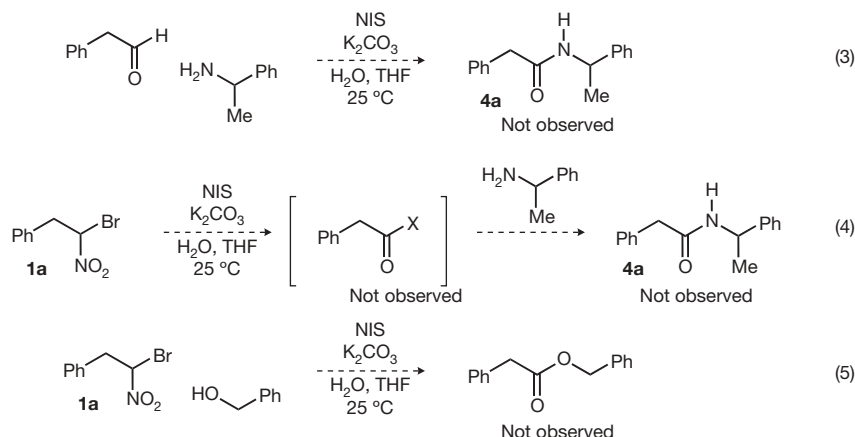


Figure 4 | Experiments designed to probe intermediacy of possible carbonyl electrophiles.

the typical reaction set-up and variants that were degassed, or run with an oxygen atmosphere.

Use of chiral donors

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 non-racemic 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 molecules³⁸ 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) owing to base-promoted epimerization of the active ester intermediate. Furthermore, the preparation of chiral non-racemic aryl glycine carboxylic acids is synthetically intensive³⁸.

We prepared the required α -bromo nitroalkane substrate in straightforward fashion from commercially available bromo nitromethane and imine **11** using chiral proton catalyst **12**^{39–44}. The addition product (**13**) that resulted was retrieved as a 1:1 mixture of diastereomers, each with 98% enantiomeric excess (e.e.) and homo-chiral at the benzylic carbon (Fig. 5, equation (6)). α -Bromo nitroalkane **13** was then coupled to both *rac*-amine **2** and (*R*)-**2** (96% e.e.) using our standard reaction protocol, delivering **14** in 76% yield in each case (Fig. 5, equation (7)). The use of racemic amine allowed

a careful analysis of the diastereomeric ratio in the example derived from (*R*)-**2** (96% e.e.) 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 Fig. 3. This behaviour 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** (Fig. 5, equation (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 (Fig. 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*^{25–27} to traditional condensative amide synthesis⁴⁵.

Conclusion

We have discovered a non-conventional amide synthesis via iodonium-promoted nitroalkane–amine coupling. The conditions are

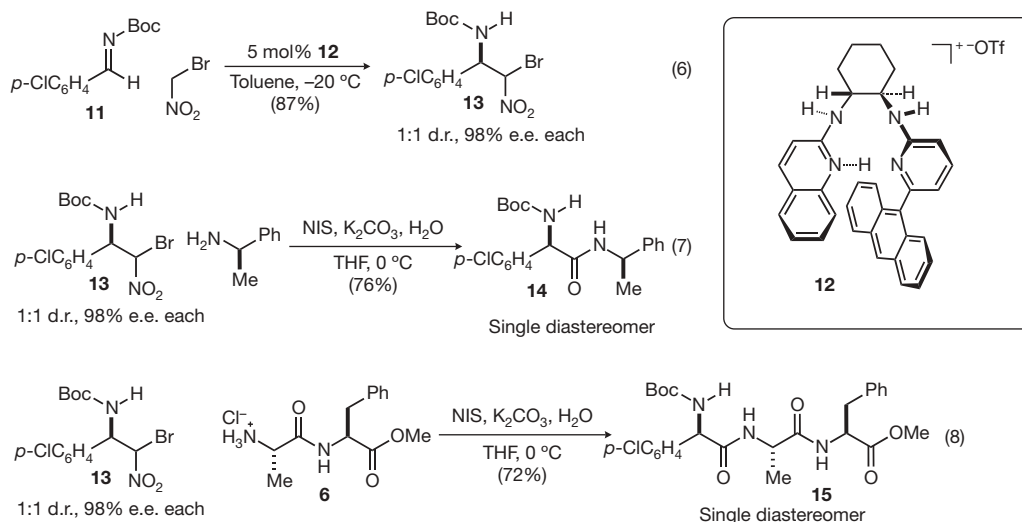


Figure 5 | Stereoselective peptide synthesis. Boc, *t*-butoxy carbonyl; e.e., enantiomeric excess; d.r., diastereomeric ratio. **12**, H₂Quin(⁶(⁹Anth)²Pyr)-BAM·H⁺·OTf.

Table 4 | Aryl glycine couplings to the canonical amino acids

Entry	Amino acid	Product	Yield* (%)	Entry	Amino acid	Product	Yield* (%)
1	glycine		79	11	L-asparagine		52
2	L-alanine		63	12	L-glutamic acid		57
3	L-valine		70	13	L-glutamine		59
4	L-leucine		81	14	L-lysine		55
5	L-isoleucine		66	15	L-proline		67
6	L-serine		64†	16	L-cysteine		52
7	L-threonine		45	17	L-methionine		43
8	L-phenylalanine		64	18	L-arginine		44
9	L-tyrosine		64	19	L-histidine		41
10	L-aspartic acid		64	20	L-tryptophan		44

Reaction conditions as Table 2. Boc, t-butoxy carbonyl; Tr, trityl (triphenylmethyl); Cbz, carboxybenzyl.

* Yields correspond to isolated, analytically pure materials, but have not been optimized for each case.

† Stirred at 25 °C for 5 h.

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 approach led to the development of an aryl glycine

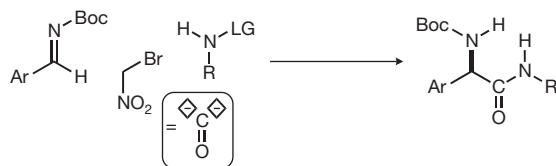
α -Halo nitroalkane peptide synthesis

Figure 6 | Enantioselective peptide synthesis. Shown is a carbonyl dianion synthon approach. Ar, aromatic ring substituent; LG, leaving group; R, alkyl substituent.

amide synthesis without epimerization or extensive protection/deprotection schemes. In addition, the first use of commercially available bromo nitromethane in stereoselective peptide synthesis establishes a practical alternative in peptide synthesis to the long-standing reliance on the carboxylic acid feedstock. This strategic shift may ultimately enable the efficient fully chemical synthesis of chiral, non-racemic peptides using a combination of entirely enantioselective methods and nitroalkane-amine couplings, as demonstrated in equation (8) (Fig. 5).

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 NMR, infrared spectroscopy (IR), and HRMS. The enantiomeric excess of chiral, non-racemic aza-Henry adduct **13** was determined by chiral high-performance liquid chromatography by comparison to an assay developed using racemic **13**. For complete experimental details, including procedures and full characterization (optical rotation, melting point, IR, ^1H and ^{13}C NMR, and HRMS) of all new compounds, see Supplementary Information.

Full Methods and any associated references are available in the online version of the paper at www.nature.com/nature.

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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 H₂O (5.0 equiv.) at 0 °C, followed by K₂CO₃ (2.0 equiv.). The reaction mixture was stirred at 0 °C for 2 d. The resulting mixture was diluted with dichloromethane, dried with MgSO₄ 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. K₂CO₃ (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 H₂O (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 MgSO₄ 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 bromonitromethane. A solution of imine **11** (1.0 equiv., 0.3 M) and **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.