UMPOLUNG AMIDE SYNTHESIS: APPLICATIONS IN ENANTIOSELECTIVE PEPTIDE SYNTHESIS

By

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To my family, and Aroop, for all of their love and support.

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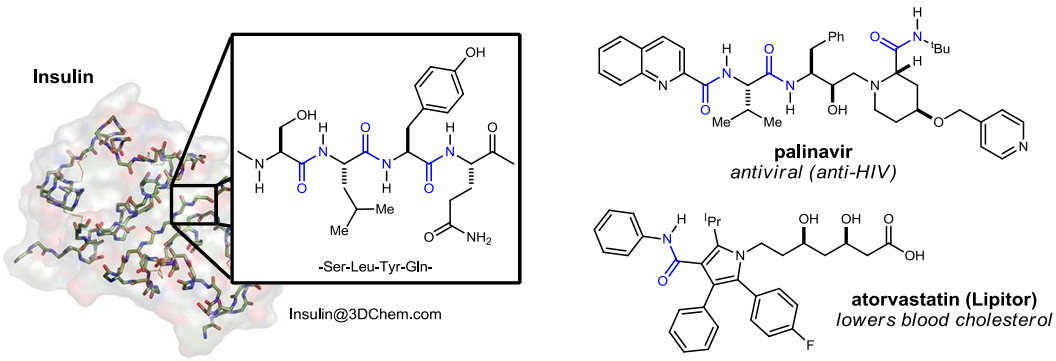
CHAPTER I

UMPOLUNG AMIDE SYNTHESIS

1.1 Introduction and Background

Amide bonds, which serve as the essential linkage between amino acids, are widely found in peptides and proteins as well as in pharmacologically active natural products and small molecule therapeutics (Figure 1). Of the top 200 drugs sold in 2007, 10% were proteins and another 8% were peptides.[1] Because of the important roles amide bonds play, their synthesis is an extremely important scientific tool. Nature constructs these essential bonds through the simple condensation of amines and carboxylic acids. Most synthetic methods in use today also utilize dehydrative approaches, with the help of coupling reagents. While this strategy works extremely well for most couplings, there are still areas of amide and peptide synthesis which can be improved.

Figure 1. Examples of protein and peptide therapeutics**.**



[1] www.arizona.edu/njardarson/group/Top200PharmaceuticalProductsbyWorldwideSalesin2009.pdf
[2] Jones, J. *Amino Acid and Peptide Synthesis,* Oxford Science Publications: Oxford, 1992.

1.1.1 Methods of Amide Coupling

Amide bond formation, which in its simplest form consists of the condensation of a carboxylic acid and an amine, [2] is one of the oldest known chemical transformations (Scheme 1). While this transformation occurs quite readily in nature with the help of enzymes, it does not occur quite so readily on the bench-top. The energy required to remove a single equivalent of water is surprisingly high, and it is for this reason that chemists have had to devise highly innovative synthetic methods for amide synthesis. One of the earliest advances,[3] and arguably the most widely used, was the development of carbodiimide coupling reagents, such as dicyclohexyl carbodiimide (DCC, **1**) (Figure 2). Over the years, this reagent class has grown to include chloroformates, uronium salts (HATU, **2**), phosphonium salts (PyBOP, **3**) and acid halogenating reagents (TFFH, **4**), among many others,[4] all which have been developed to further increase the efficiency of amide coupling.

Scheme 1. Condensation of a carboxylic acid and an amine.

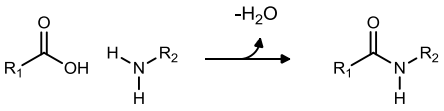
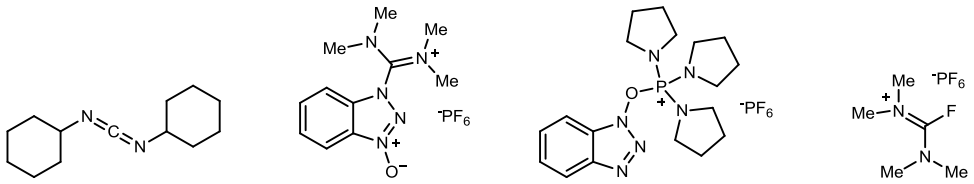


Figure 2. Common coupling reagents.

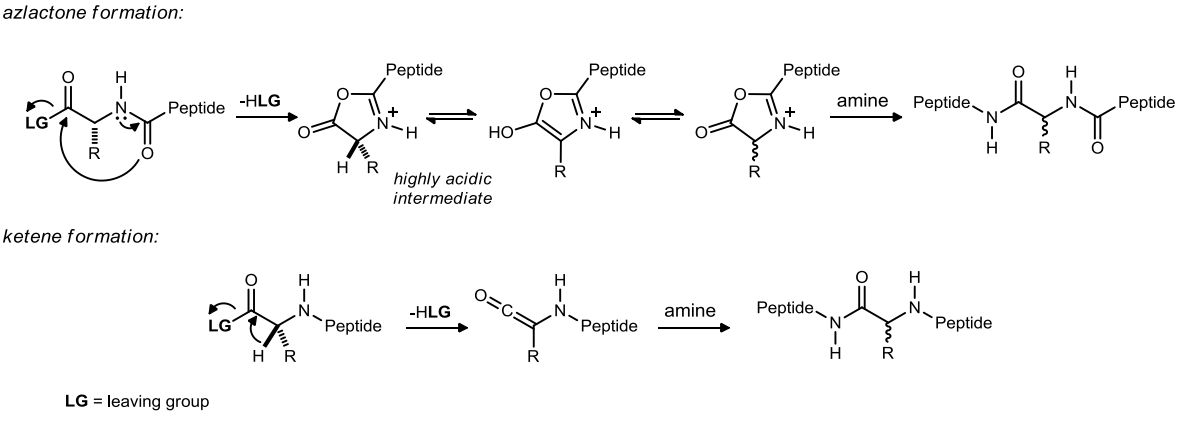


1 DCC **2** HATU **3** PyBOP **4** TFFH

[2] Jones, J. *Amino Acid and Peptide Synthesis*, Oxford Science Publications: Oxford, 1992.
[3] Sheehan, J. C. Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067.
[4] For recent reviews, see: Han, S. Y.; Kim, Y. A. *Tetrahedron* **2004**, *60*, 2447. Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827. Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606.

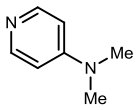
While these coupling reagents work extremely well for most simple amide couplings, their strong foundation is oftentimes weakened upon moving to larger or more complex substrates. For example, the coupling of disubstituted amines or large peptides frequently results in low conversion. A second, and perhaps more daunting, challenge of peptide coupling is suppressing the racemization which can occur at the α-carbon of the activated carboxylic acid. This racemization, which occurs due to azlactone or ketene formation (Scheme 2),[5] is especially prevalent when coupling peptidic carboxylic acid fragments, and even more so when coupling acidic amino acids such as aryl glycines. The addition of rate enhancers and/or racemization suppressants, such as dimethylaminopyridine (DMAP, **5**) or hydroxybenzotriazole (HOBT, **6**), can help to lessen the degree of racemization observed; however, they cannot completely eliminate this undesired process (Figure 3).[4]

Scheme 2. Racemization at the α-carbon of activated carboxylic acids.

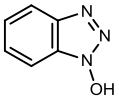


[5] Benoiton, N. L. *Chemistry of Peptide Synthesis*; Taylor and Francis Group: Boca Raton, Florida, 2006.

Figure 3. Rate-enhancers and racemization suppressants.



5
DMAP



6
HOBT

Regardless of these difficulties, the use of peptide coupling reagents has prevailed over the years as the preferred method of amide synthesis. The application of these reagents to solid phase synthesis, in which reagent excess can be used to drive the condensation to completion, has made the synthesis and purification of peptides much faster.[6] Recently, alternatives to conventional amide synthesis have emerged as chemists try to address these practical challenges.[7] As seen in Scheme 3, these novel approaches include native chemical ligation,[8] Staudinger ligation,[9] hydrative amide synthesis through alkyne-azide coupling,[10] oxidative amidation of alcohols,[11] aldehydes,[12] or alkynes,[13] and ketoacid-hydroxylamine ligation,[14] among others.[15]

---

[6] a) Atherton, E.; Sheppard, R. C. *Solid phase peptide synthesis: a practical approach*; IRL Press at Oxford University Press: Oxford, England; New York, 1989. b) Fields, G. B. *Solid phase peptide synthesis;* Academic Press: San Diego, 1997. c) Dorwald, F. Z. *Organic synthesis on solid phase: supports, linkers, reactions;* Wiley-VCH: Weinheim; Chichester, 2000. d) Sewald, N.; Jakubke, H. -D. *Peptides: chemistry and biology;* Wiley-VCH: Weinheim, 2002.

[7] Bode, J. W. *Curr. Opin. Drug Discover Dev.* **2006,** *9*, 765.

[8] Dawson, P. E.; Muir, T. W.; Clarklewis, I.; Kent, S. B. H. *Science* **1994**, *266*, 776.

[9] a) Saxon, E.; Armstrong, J. I.; Bertozzi, C. R. *Org. Lett.* **2000**, *2*, 2141. b) Saxon, E.; Bertozzi, C. R. *Science* **2000**, *287*, 2007. c) Nilsson, B. L.; Kiessling, L. L.; Raines, R. T. *Org. Lett.* **2000**, *2*, 1939. For a recent review, see: Kohn, M.; Breinbauer, R. *Angew. Chem. Int. Ed.* **2004**, *43*, 3106.

[10] a) Cho, S. H.; Yoo, E. J.; Bae, L.; Chang, C. *J. Am. Chem. Soc.* **2005**, *127*, 16046. b) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2006**, *45*, 3154.

[11] a) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790. b) Nordstrom, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672.

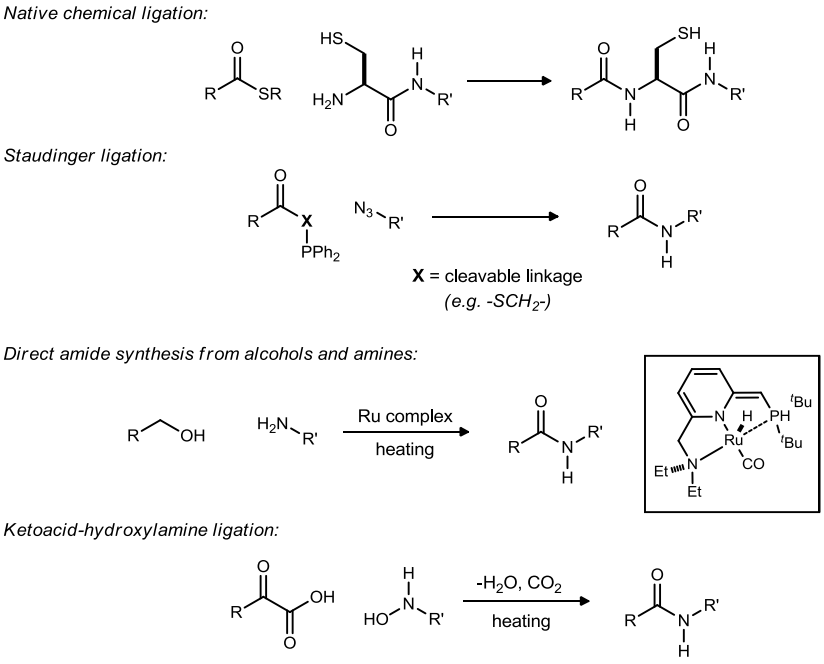
[12] a) Yoo, W. J.; Li, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 13064. b) Gao, J.; Wang, G.-W. *J. Org. Chem.* **2008**, *73*, 2955.

[13] Chan, W. K.; Ho, C. M.; Wong, M. K.; Che, C. M. *J. Am. Chem. Soc.* **2006**, *128*, 14796.

[14] Bode, J. W.; Fox, R. M.; Baucom, K. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 1248.

[15] a) Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 5446. b) Li, X.; Yuan, Y.; Kan, C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 13225. c) Wang. P.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *123*, asap.

Scheme 3. Recent novel approaches to amide synthesis



1.1.2 Enduring Obstacles in Peptide Synthesis

Though these advances in the area of amide coupling have made the synthesis of complex peptides and other amide-containing natural products possible, there is still room in this field for improvement. The most common peptide coupling reagents in use today, in addition to being expensive, and in some cases toxic or shock-sensitive, have very high molecular weights and are usually used in superstoichiometric amounts, especially in solid phase synthesis. This, coupled with the fact that one also may need to use an additional racemization-suppressant additive, means that a significant amount of chemical waste is produced, all to simply remove one equivalent of water. In 2005, the ACS Green Chemistry Initiative Pharmaceutical Roundtable voted "amide coupling avoiding poor atom economy reagents" the number one key green chemistry research

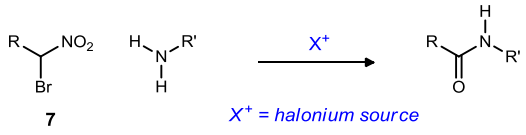
area which needed improvement.[16] Some of the recently developed methods look to solve this problem by taking steps to make amide coupling a greener reaction.[11a,14] However, while these advances have been promising, the use of metal catalysts, or the complicated synthesis of specialized starting materials make these reactions not as green as they first appear.

Additionally, most, if not all, methods of amide coupling proceed through some sort of activated ester intermediate, in which the carbon destined to become the carbonyl carbon of the amide bond is electrophilic. This means that in all of these cases, racemization at the α-stereocenter of this coupling partner is still an obstacle, especially in more demanding coupling reactions, because azlactone and ketene formation are still possible.

1.2 Umpolung Amide Synthesis

Previously in our lab, a novel amide coupling reaction was discovered in which an α-bromo nitroalkane (**7**) could be coupled to an amine in the presence of an electrophilic halonium source to form the amide (Scheme 4).[17]

Scheme 4. Halonium promoted coupling of α-bromo nitroalkanes and amines.



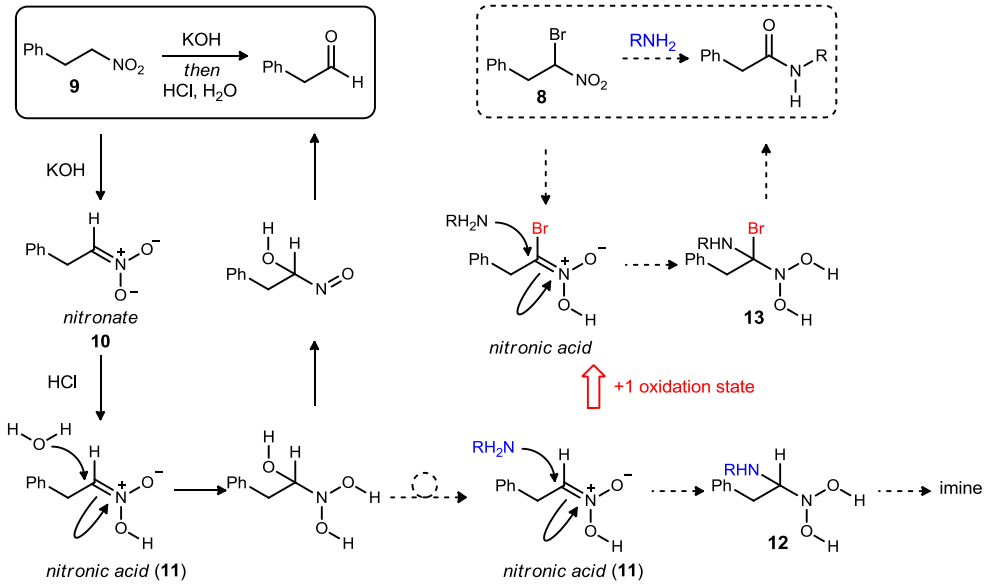
7

[16] Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zang, T. Y. *Green Chemistry* **2007**, *9*, 411.
[17] Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, *465*, 1027.

1.2.1 Reaction Discovery and Development

Studies of this carbon-nitrogen bond forming reaction began with the hypothesis that an α-bromo nitroalkane (**8**), in the presence of an amine, might provide the proper oxidation state for conversion to the amide in much the same way nitroalkanes (**9**) are converted to aldehydes via the Nef reaction (Scheme 5).[18]

Scheme 5. Nef reaction and proposed aza-Nef reaction.

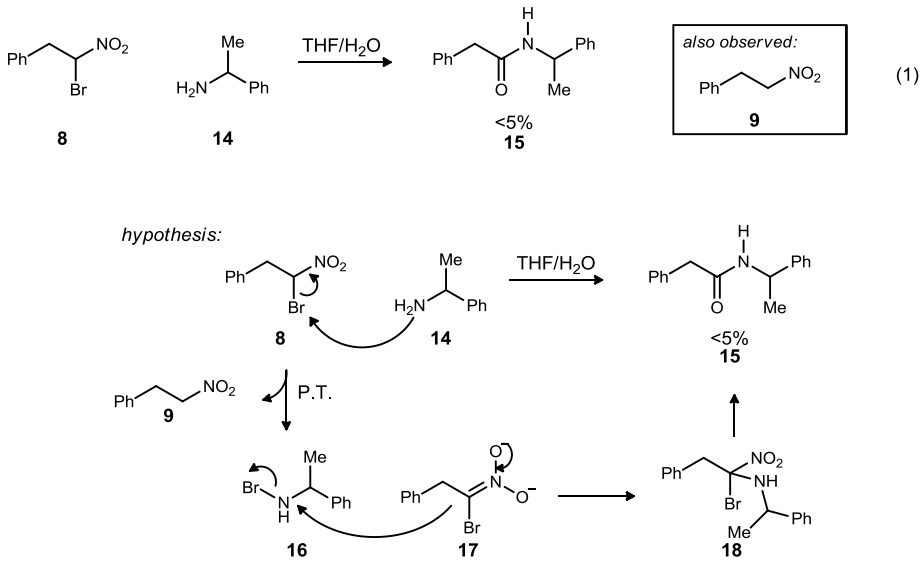


The Nef reaction involves a two-step sequence which begins with nitronate (**10**) formation under basic conditions (KOH), followed by acid hydrolysis (aq. HCl). In order to adapt this reaction to amide formation - an 'aza-Nef' - two things must be done. First, instead of hydrolyzing the nitronic acid intermediate (**11**), an amine could trap this intermediate, forming a tetrahedral intermediate (**12**) which would normally lead to imine formation. If, however, an α-bromo nitroalkane was used in place of a nitroalkane, the oxidation state of the putative tetrahedral intermediate (**13**) would allow for production of

[18] Nef, J. U. *Liebigs Ann. Chem.* **1984**, *280*, 263. For recent reviews on the Nef reaction, see: a) Ballini, R; Petrini, M. *Tetrahedron* **2004**, *60*, 1017. b) Pinnick, H. W. *Org. React.* **1990**, *38*, 655.

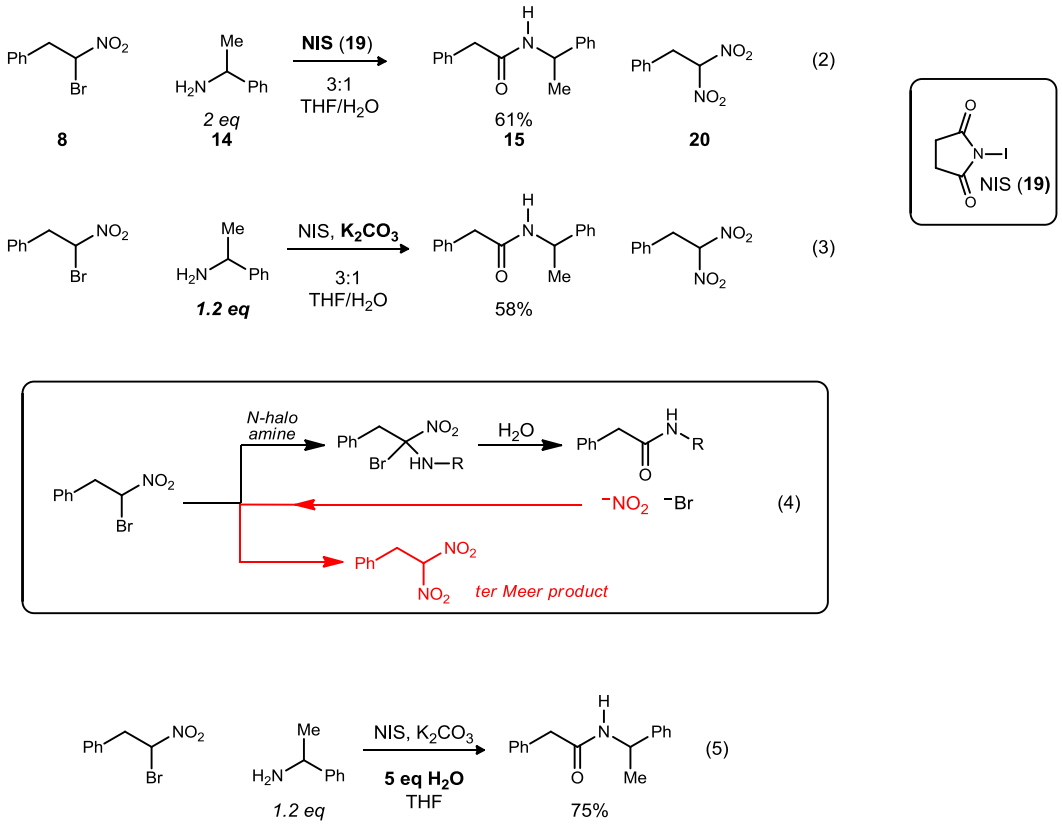
the amide bond. In order to test this, α-bromo nitroalkane **8** was stirred with two equivalents of amine **14**. After 10 days at room temperature, a trace amount of the amide product **15** could be detected (Scheme 6, eq 1).

Scheme 6. Preliminary investigations.



However, alongside this small amount of product, the debrominated nitroalkane **9** could be seen. This led to the hypothesis that an *N*-haloamine (**16**) might be forming, through bromonium transfer from **8** to **14**. The remaining α-bromo nitroalkane, once deprotonated to the nitronate (**17**), could then conceivably undergo electrophilic amination, forming a tetrahedral intermediate (**18**) which would lead to the desired amide (Scheme 6). Because of the perceived need to form the *N*-haloamine in this proposed reaction pathway, a stoichiometric amount of an external halogenating reagent, *N*-iodo succinimide (NIS, **19**), was added. Gratifyingly, the yield of the desired amide product increased to 61% (Scheme 7, eq 2). The addition of an external base, K_2CO_3, allowed the amount of amine to be reduced to 1.2 equivalents (Scheme 7, eq 3).

Scheme 7. Optimization of the amide coupling of α-bromo nitroalkanes and amines.



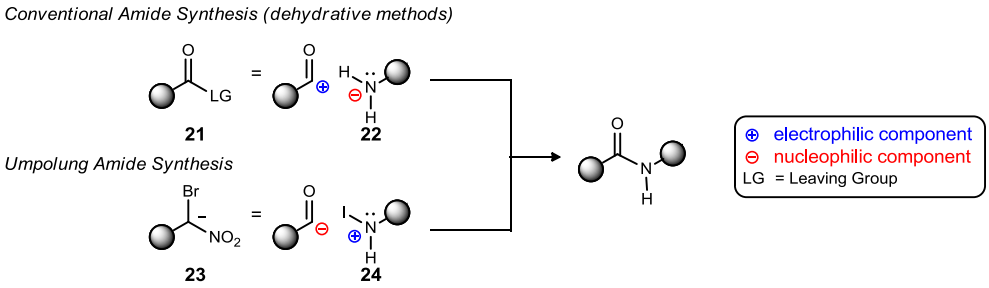
When a large excess of water (Scheme 7, eq 2 and 3) is used in these reactions, a significant amount of the dinitroalkane **20** is observed. This side product most likely is produced due to a competing ter Meer reaction[19,20] (Scheme 7, eq 4) of the α-bromo nitroalkane **8** and nitrite, presumably produced as a byproduct in the amide coupling reaction. While the exact mechanism of this transformation has not been extensively studied,[21] it is known that basic aqueous conditions are needed to deprotonate the α-halo nitroalkane and solvate the nitrite. By limiting the amount of added water (Scheme 7, eq

[19] E. ter Meer, *Justus Liebigs Ann. Chem.* **1876**, *181*, 1.
[20] For applications in the synthesis of dinitroalkanes, see: a) Feuer, H.; Colwell, C. E.; Leston, G.; Nielson, A. T. *J. Org. Chem.* **1962**, *27*, 3598. b) Hamel, E. E.; Dehn, J. S.; Love, J. A.; Scigliano, J. J.; Swift, A. H. *Ind. Eng. Chem. Prod. Res. Dev.* **1962**, *1*, 108.
[21] For a summary, see: Todres, Z.V. *Ion-Radical Organic Chemistry: Principles and Applications*, CRC Press Taylor & Francis Group: Boca Raton, Florida, 2008, 243.

5), and therefore the amount of solvated nitrite, the yield of the coupling can be increased to 75%, and production of the dinitro side product (**20**) can be minimized.

The need for an added halogenating reagent, NIS, in this reaction strongly suggested it was proceeding through the proposed *N*-haloamine-nitronate coupling (Scheme 6). The mechanism of this amide coupling is fundamentally novel, in that the polarities of the reactants in the key C-N bond forming step are reversed (umpolung)[22] from those normally seen in amide coupling reactions. Instead of an electrophilic activated acid (**21**), or similar substrates, which will be attacked by a nucleophilic amine (**22**), this mechanism utilizes a nucleophilic carboxylic acid surrogate (**23**) which attacks an electrophilically activated *N*-haloamine (**24**) (Scheme 8). This umpolung mechanism offers certain advantages over conventional amide coupling; specifically, racemization at the α-carbon of the carboxylic acid is mechanistically prohibited due to the now nucleophilic character of the acyl donor carbon.

Scheme 8. Reversed reactant polarities in umpolung amide coupling.



These umpolung amide coupling conditions were then applied to other amines and α-bromo nitroalkane substrates, including sterically demanding and peptidic ones, with a promising level of generality (isolated yields of 48-81%). The only limitation at

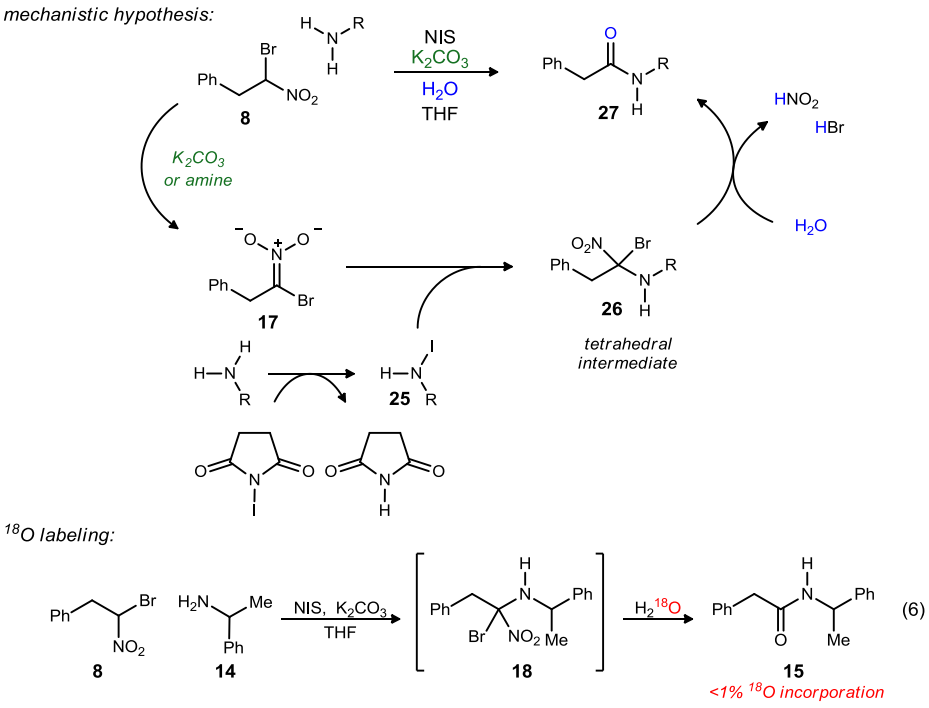
[22] a) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975,** *40*, 231. b) Grobel, B. T.; Seebach, D. *Synthesis* **1977**, 357. c) Seebach, D. *Angew. Chem. Int. Ed.* **1979**, *18*, 239.

this time seems to be the use of aromatic amines, as aniline did not produce any of the desired amide product.[17]

1.2.2. Mechanistic Studies

In the proposed mechanistic pathway of this coupling (Scheme 9), it was assumed that the addition of water to tetrahedral intermediate **26**, and subsequent loss of HNO_2 and HBr, resulted in the amide. If this were the case, the use of ^{18}O labeled water should result in ^{18}O incorporation into the carbonyl of the amide bond. However, when this reaction was performed, less than 1% ^{18}O incorporation was observed (eq 6).[23] This suggested that the oxygen of the amide was coming from some other source.

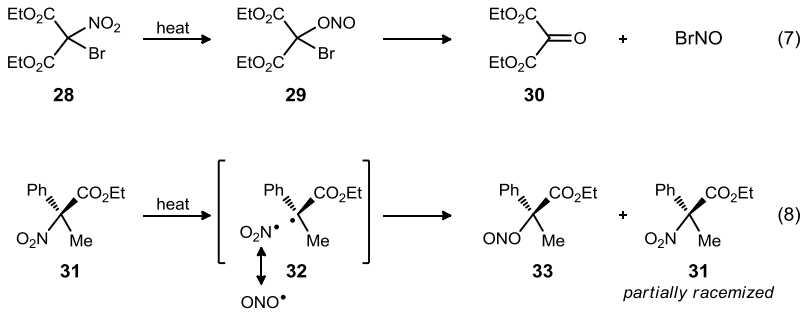
Scheme 9. Original mechanistic hypothesis and ^{18}O labeling study.



[23] Shen, B.; Johnston, J. N. Ph.D. Dissertation 2010, Department of Chemistry, Vanderbilt University.

Another possible source of oxygen in this reaction system is the nitro group. The rearrangement of bromonitromalonate **28** to the corresponding nitrite **29**, followed by elimination of nitrosyl bromide to afford ketone **30** was reported in 1904 (Scheme 10, eq 7).[24] Years later, a similar rearrangement was reported by Schollkopf and co-workers.[25] They observed that, under thermal conditions, substituted nitroacetate **31** partially rearranged to the corresponding nitrite (**33**). Additionally, the recovered unreacted starting material had partially racemized (eq 8). Based on this, the authors proposed that the nitro-nitrite rearrangement occurred via a radical pair intermediate (**32**), formed from homolytic cleavage of the C-N bond. Recombination of this radical pair could then either form the new C-O bond of the nitrite, or could reform the C-N bond of the starting material, due to the ambident character of the nitro radical. This would then explain the observed racemization of the starting nitroacetate.

Scheme 10. Examples of the nitro-nitrite rearrangement.

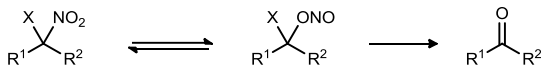


These two examples, as well as others which involve the conversion of *gem*-halo nitro functionalities into carbonyl groups,[26] bear commonality in that a tertiary *gem*-halo

[24] Willstatter, R.; Hottenroth, V. *Chem. Ber.* **1904**, *37*, 1775.
[25] Hochstein, W.; Schollkopf, U. *Justus Liebigs Ann. Chem.* **1978**, 1823.
[26] Selected examples: a) Nguyen, N. V.; Baum, K. *Tetrahedron Lett.* **1992**, *33*, 2949. b) Ketari, R.; Foucanud, A. *J. Org. Chem.* **1981**, *46*, 4498. c) Hartshorn, M. P.; Ing, H. T.; Richards, K. E.; Thompson, R. S.; Vaughan, J. *Aust. J. Chem.* **1982**, *35*, 221. d) Hartshorn, M. P. Ing, H. T.; Richards, K. E.; Sutton, K. H.; Vaughan, J. *Aust. J. Chem.* **1982**, *35*, 1635. e) Chanbers, M. V.; Harshorn, M. P.; Robinson, W. R.;

nitro is needed for the transformation to occur. Additionally, at least one of the substituents on the tertiary carbon must be a radical stabilizing group, such as an ester or alkoxy group (Scheme 11). These observations are consistent with the radical pair intermediate proposed by Schollkopf.

Scheme 11. Summary of nitro-nitrite rearrangement of *gem*-halo nitro compounds.



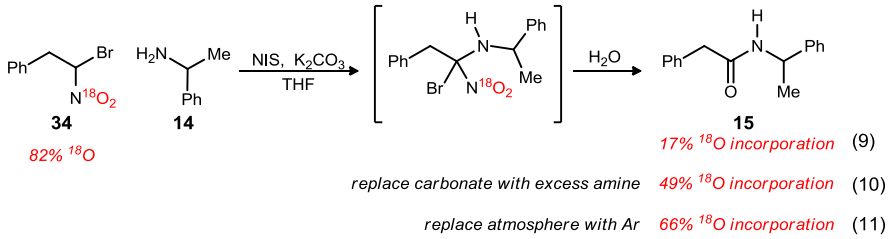
R^1 = radical stabilizing group
X = F, Cl, Br, CN

In order to test whether or not a similar nitro-nitrite rearrangement was occurring to give the amide from the *gem*-bromo nitro tetrahedral intermediate, ^{18}O labeled α-bromo nitroalkane was prepared (82% ^{18}O) and coupled to amine **14** (Scheme 12, eq 9). A small amount of ^{18}O label (17%) was observed in the amide, suggesting that the nitro-nitrite rearrangement was occurring, but was not the only pathway in operation. The only other possible sources of oxygen in the reaction, carbonate and molecular oxygen, were identified and removed from the reaction conditions. When carbonate was replaced by excess amine, the amount of ^{18}O label incorporated into the amide increased to 49% (Scheme 12, eq 10), and when the reaction was degassed and done under argon, it increased to 66% (Scheme 12, eq 11).[27]

Vaughan, J. *Aust. J. Chem.* **1985**, *38*, 133. f) Hartshorn, M. P.; Robinson, W. T.; Wright, G. J.; Cheng, L. Y. *Aust. J. Chem.* **1989**, *42*, 1569. g) Baum, K.; Archibald, T. G.; Tzeng, D.; Gilardi, R.; Flippen-Anderson, J. L.; George, C. *J. Org. Chem.* **1991**, *56*, 537.

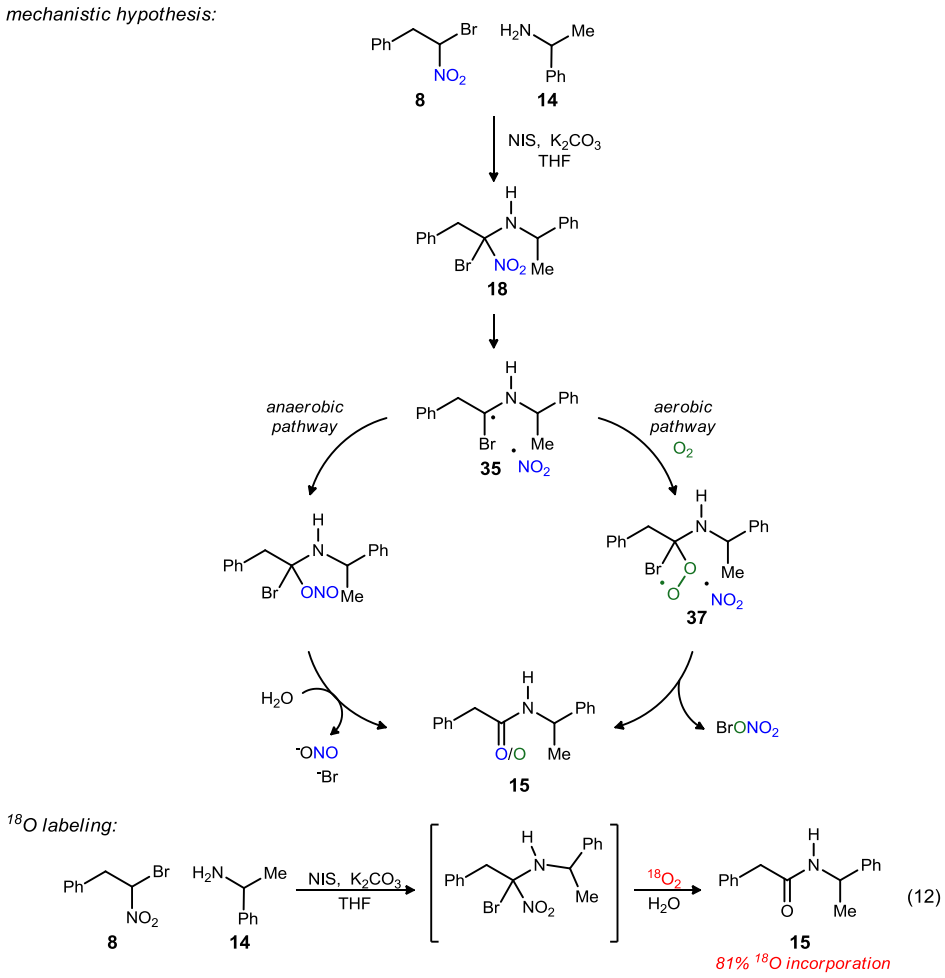
[27] Shackleford, J. P.; Shen, B.; Johnston, J. N. *Proc. Natl. Acad. Sci.* **2012**, *0*, 0.

Scheme 12. Additional ^{18}O labeling experiments.



This suggested that the possibility of two different reaction pathways leading from the tetrahedral intermediate (**18**) to the amide product (**15**): one anaerobic and one aerobic (Scheme 13). The aerobic pathway would still proceed through homolytic cleavage to a radical pair intermediate. However, instead of recombining with the nitro radical, the tertiary carbon radical (**35**) reacts with molecular oxygen to form oxygen radical **37**; it is this intermediate which leads to amide formation. This hypothesis was confirmed when the coupling was done under an atmosphere of $^{18}O_2$, and 81% ^{18}O label was incorporated into the product (Scheme 13, eq 12). This high level of ^{18}O, in addition to validating this reaction pathway, suggested that the aerobic pathway is much faster than the anaerobic one, a fact that can also be seen experimentally. When performed under argon, the reaction takes two days to reach full conversion; under an oxygen atmosphere it is done within two hours.[27]

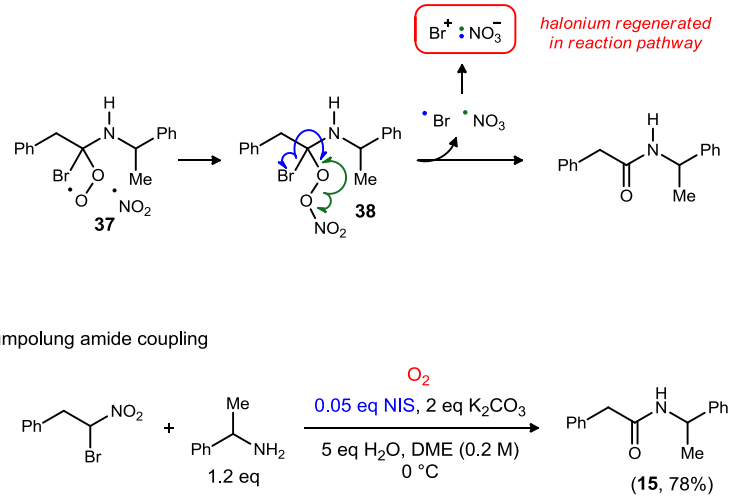
Scheme 13. Proposed anaerobic and aerobic reaction pathways.



It was also apparent that under aerobic conditions there was the opportunity for regeneration of an equivalent of halonium, in the transformation from radical **37** to amide **15**. The nitro radical would likely combine with radical **37**, forming intermediate **38** Homolytic cleavage of both the Br-C bond, as well as the O-O bond would result in amide **15**, while releasing $Br^{\bullet}$ and $NO_3^{\bullet}$. A redox reaction between these two radicals should then give Br^{+} and NO_3^{-} (Scheme 14). This hypothesis was confirmed when, under

an atmosphere of O_2, only 0.05 equivalents of NIS resulted in full conversion and high yield of **15** (Scheme 14, eq 13).[28]

Scheme 14. Regeneration of halonium catalyst.



1.2.3 Investigation of Halonium Reagent Effects

While the mechanism of amide formation from the tetrahedral intermediate was being studied, we also wished to investigate the electrophilic amination of the α-bromo nitroalkane which would lead to this intermediate. As discussed previously, it is proposed that this amination occurs via the *N*-haloamine, an intermediate that, though uncommon, is known to electrophilically aminate carbon nucleophiles.

Electrophilic Amination with N-Haloamines

Though *N*-haloamines[29] have been extensively utilized in the Hoffman-Loffler-Freytag reaction,[30] their use as electrophilic amination reagents is relatively limited.[31]

[28] Shen, B.; Johnston, J. N. *unpublished results.*
[29] For a review, see: Kovacic, P.; Lowery, M. K.; Field, K. W. *Chem. Rev.* **1970,** *70*, 639.

Coleman and co-workers reported that monochloroammonia and monobromoammonia reacted with Grignard reagents to give monosubstituted amines (**39**) in moderate to good yield (57-85% yield for NH_2Cl and 29-63% yield for NH_2Br, Scheme 15, eq 14).[32] This reaction occurs in an S_N2 fashion, with Cl^- or Br^- acting as the leaving group. However, because of the electronegativity of the nitrogen atom, *N*-haloamines can act as ambident electrophiles. Because of this, a competing side reaction can occur in which an S_N2 substitution occurs at the halogen, with NH_2^- acting as the leaving group, producing the alkyl halide (**40**) and ammonia (eq 15).

The Coleman group later used *N*-chloro alkyl amines in the amination of Grignard reagents. However, the isolated yields of the disubstituted amines (**41**) were low, apparently due to this ambident reactivity; the major products isolated were the de-halogenated primary amines (**42**) (Scheme 15, eq 16).[33] Recently, *N*-chloro alkyl amines were used, with aryl Grignard reagents, to prepare tertiary anilines (**43**) in moderate to good yields (33-73%) (Scheme 15, eq 17).[34]

---

[30] For reviews, see: a) Wolff, M. E.; *Chem. Rev.* **1963**, *63*, 55. b) Neale, R. S. *Synthesis* **1971**, 1. c) Majetich, G.; Wheless, K. *Tetrahedron* **1995**, *51*, 7095.

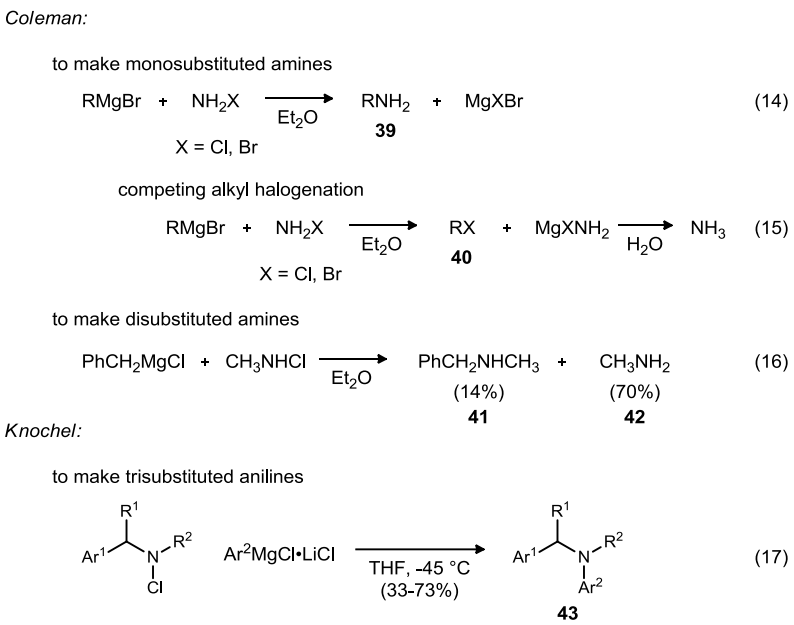
[31] For reviews on electrophilic amination, see: a) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947. b) Dembech, P.; Seconi, G.; Ricci, A. *Chem. Eur. J.* **2000**, *6*, 1281. c) Watson, I. D. G.; Yudin, A. K. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 906. d) Erdik, E. *Tetrahedron* **2004**, *60*, 8747.

[32] a) Coleman, G. H.; Hauser, C. R. *J. Am. Chem. Soc.* **1928**, *50*, 1193. b) Coleman, G. H.; Yager, C. B. *J. Am. Chem. Soc.* **1929**, *51*, 567.

[33] Coleman, G. H. *J. Am. Chem. Soc.* **1933**, *55*, 3001.

[34] Sinha, P.; Knochel, P. *Synlett* **2006**, 3304.

Scheme 15. Examples of *N*-haloamines in the electrophilic amination of Grignard reagents.

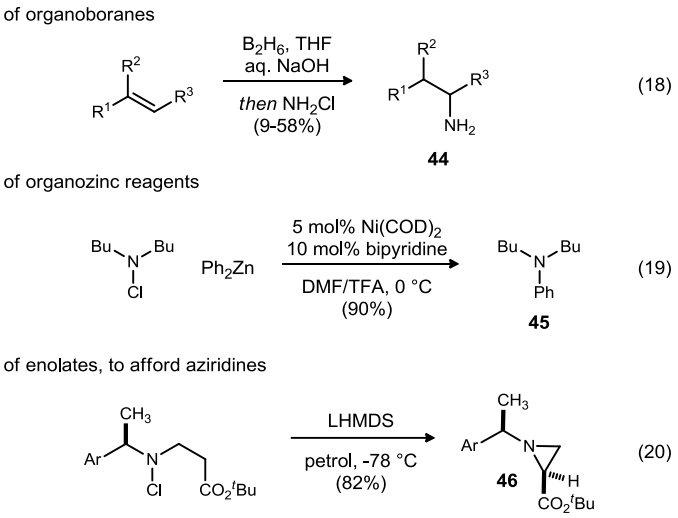


Organoboranes, generated from the hydroboration of alkenes, are also reported to react with monochloroammonia to give monosubstituted amines (**44**) in moderate yields (Scheme 16, eq 18).[35] Organolithium[36,37] and organozinc[36] reagents have also been reported to undergo electrophilic amination in the presence of *N*-haloamines, but with less success than Grignard reagents.[31] The lone exception to this is a recent report of a Ni(0) catalyzed electrophilic amination of diarylzinc reagents with *N*,*N*-dialkyl-*N*-chloroamines, which gave trisubstituted anilines (**45**) in high yields (Scheme 16, eq 19).[38] Several reports of the electrophilic amination of enolates, utilizing *N*-haloamines, have

[35] Brown, H. C.; Heydkamp, W. R.; Breuer, E.; Murphy, W. S. *J. Am. Chem. Soc.* **1964**, *86*, 3565.
[36] Coleman, G. H.; Hermanson, J. L.; Johnson, H. L. *J. Am. Chem. Soc.* **1937**, *59*, 1868.
[37] Wolf, V.; Kowitz, F. *Justus Liebigs Ann. Chem.* **1960**, *683*, 33.
[38] Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598.

been made,[39] several of which have focused on an intramolecular amination to afford nitrogen-containing heterocycles (Scheme 16, eq 20).[40]

Scheme 16. Other examples of electrophilic amination using *N*-haloamines.



N-Haloamines in Umpolung Amide Synthesis

Although it was known that the use of NIS as a halonium source afforded the amide product **15** in good yields, it is one of the most expensive halogenating reagents with a price of $879 per mole of I^+. Therefore, the efficacy of other halonium ions (Br^+ and Cl^+) and halogenating reagents in this umpolung amide coupling was explored; not only to understand more about this interesting mechanism, but also with the hope of finding a cheaper halonium source.

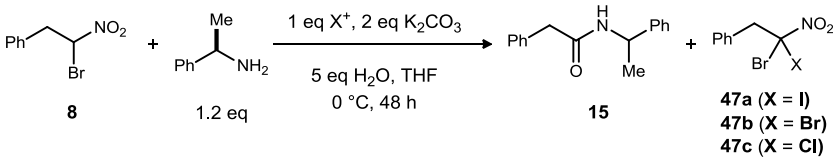
To start, the reactivities of *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS) were compared to that of NIS. As seen in Table 1, both NBS (entry 2) and NCS

[39] a) Yamada, S. I.; Shioiri, T.; Oguri, T. *J. Chem. Soc., Chem. Comm.* **1972**, 623. b) Oguri, T.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1975,** *23*, 167.
[40] a) Clemo, G. R.; Hoggarth, M. *J. Chem. Soc.* **1954**, 95. b) Grieco, P. A.; Dai, Y. *J. Am. Chem. Soc.* **1998**, *120*, 5128. c) Bew, S. P.; Hughes, D. L.; Palmer, N. J.; Savic, V.; Soapi, K. M.; Wilson, M. A. *Chem. Commun.* **2006**, 4338. d) Makosza, M.; Bobryk, K.; Krajewski, D. *Heterocycles* **2008**, *76*, 1511.

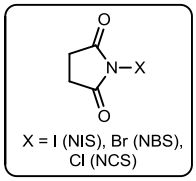
(entry 3) gave much lower preliminary yields of the amide (25% and 21%, respectively) than NIS (entry 1). In the case of NBS, this appeared to be an issue of reactivity, as the reaction only went to 50% conversion. Additionally, a build-up of the dibromo nitroalkane (**47b**), produced from the halogenation of **7**, was observed. This compound has been isolated and resubjected to reaction conditions, resulting in production of the amide product, though at a very slow rate, proving it is a competent intermediate in this reaction.[23]

The reaction which utilized NCS did not have these same problems; conversion of the α-bromo nitroalkane **7** was high, and none of the dihalo nitroalkane was observed. However, the crude ^{1}H NMR analysis showed a much messier reaction, with a significant amount of unreacted amine remaining. This suggests that decomposition of the α-bromo nitroalkane may be occurring when this reagent is used.

Table 1. Comparison of NIS, NBS and NCS in umpolung amide coupling.



entry	X^+ source	% conv	**15:47**	% yield
1	NIS	100	1:0	72
2	NBS	50	3:4	25
3	NCS	100	1:0	21

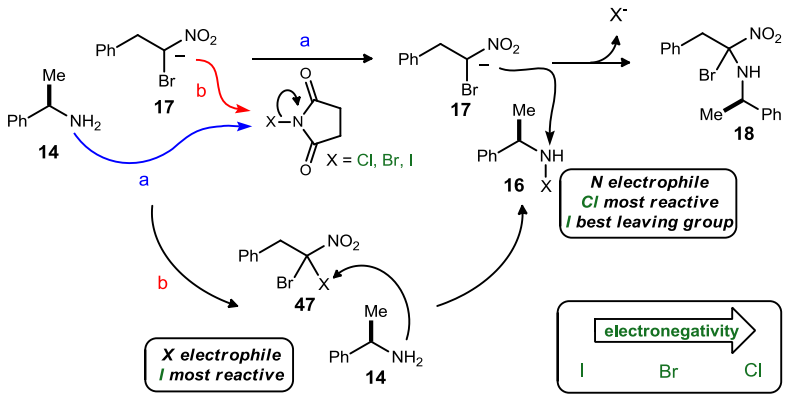


The fact that build-up of dibromo nitroalkane **47** readily occurs when a brominating reagent is used, but the α-chloro-α-bromo and α-iodo-α-bromo nitroalkanes (**47a, 47c**) are rarely seen, can be understood by looking at the electronegativities of each halogen (Scheme 17). The dihalo intermediates are produced when nitronate **17** is

halogenated before amine **14** (pathway b). If this happens, iodonium, the least electronegative halogen, will transfer fastest from **47a** to **14**; hence the α-iodo-α-bromo nitroalkane (**47**) is a transient intermediate only observed if the reaction is stopped at a very early stage. Bromonium and chloronium transfer would be much slower, which would explain why the dibromo nitroalkane is observed to such a great extent under these reaction conditions. The absence of a significant amount of the α-chloro-α-bromo nitroalkane in the reaction mixture could be due to the decomposition of this intermediate, which would explain the high conversion but low yield of amide product.

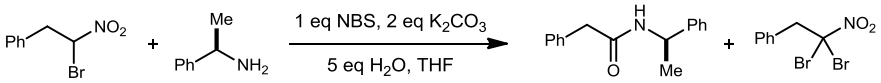
Once the nitronate **17** and *N*-haloamine **16** have formed, electrophilic amination occurs. In this step, chlorine would be the most reactive of the halogens, as it would polarize the halogen-nitrogen bond to the greatest extent, making the nitrogen more electrophilic. This trend in electrophilic amination can be seen in the literature; *N*-chloroamines, when reacted with Grignard reagents, exhibit the highest reactivity, while *N*-bromoamines are seen to be less reactive.[31] Though *N*-iodoamines have rarely been used in electrophilic amination, their success in this reaction can be explained by the fact that iodonium, as the largest halogen, would be the best leaving group in the S_N2-type amination (Scheme 17).

Scheme 17. Halogen reactivity.



Though NBS initially gave a low yield of the amide, the reaction seemed promising in that no decomposition was observed, only low conversion. Therefore, attempts were made to increase conversion to the amide, and push the equilibrium of the reaction past the dibromo resting state. This was initially done by increasing the amount of amine used. As seen in Table 2, increasing the equivalents of amine from 1.2 to 2 increased the conversion to 78%, and the yield to 38% (entry 2). Additionally, less of the dibromo nitroalkane **47b** was observed. By increasing the equivalents of amine to 5, and raising the reaction to room temperature, full conversion of both the starting α-bromo nitroalkane **7** and dibromo nitroalkane **47b** was achieved, giving a 68% yield of the amide.

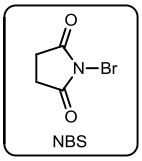
Table 2. Pushing the equilibrium past the dibromo nitroalkane intermediate.



8 **15** **47b**

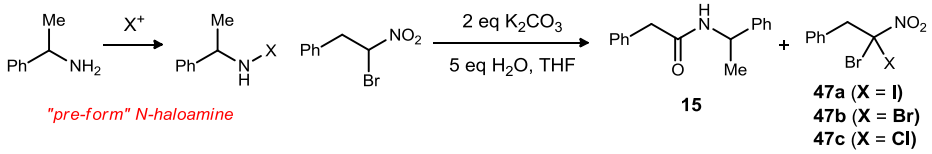
entry	eq. of amine	temp	% conv[a]	**15:47b**	% yield
1	1.2	0 °C	65	3:4	19
2	2	0 °C	78	2:1	38
3	5	0 °C	74	1:0	47
4	5	rt	100	1:0	68

a) determined by crude NMR analysis after reactions were diluted with CH_2Cl_2, dried over $MgSO_4$ and condensed



It was hypothesized that a second possible way to achieve full conversion, without resorting to excess amine, would be to avoid production of the dihalo intermediate all together by pre-mixing the halogenating reagent and amine before adding the α-bromo nitroalkane or base. It was hoped that by doing this, the *N*-haloamine would have a chance to form before the α-bromo nitroalkane could become halogenated. This method of addition was utilized, with NIS, NBS and NCS, to assess how, if at all, it would affect their reactivity. For NIS and NCS, the yields remained unchanged from the standard order of addition (Table 3, entries 1 and 3) respectively. However, an increase in conversion and yield could be seen with NBS (Table 3, entry 2), and notably no dibromo nitroalkane was observed.

Table 3. Avoiding the dihalo nitroalkane by "preforming" the *N*-haloamine.



entry	X^+ source	% conv[a]	**15:47**	% yield
1	NIS	100	1:0	64
2	NBS	71	1:0	56
3	NCS	100	1:0	24

a) determined by crude NMR analysis after reactions were diluted with CH_2Cl_2, dried over $MgSO_4$ and condensed

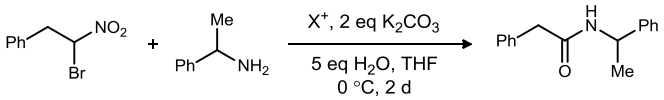
After having studied the basic differences in reactivity observed between Cl^+, Br^+ and I^+, a more extensive screen of halogenating reagents was performed, with a focus on the price per mole of halonium for each of the reagents. As seen in Table 4, the absence of a halonium source resulted in a 3% yield of amide **15**, with some of the de-brominated starting material also observed (entry 1). At this time, it was found that by switching the solvent from THF to DME, chlorinating reagents gave cleaner reaction mixtures and higher yields (entries 2-5, 22-54%), with trichlorocyanuric acid (TCCA) giving the highest yield (entry 4, 55%). This reagent, which is commonly used to chlorinate swimming pools,[41] is also the cheapest of the halogenating reagents screened.

While the new order of addition in which the amine and halogenating reagent are pre-mixed was used and the reactions allowed to stir for an extended period (4 d), conversions and yields of the brominating reagents were still relatively low (Table 4, entries 6-9, 28%-54%). However, *N*-bromophthalimide gave a promising yield of 54%, which could most likely be increased by using several equivalents of amine. Other iodonium sources were looked at, specifically I_2 and ICl; gratifyingly, it was found that

[41] Barros, J. C. *Synlett* **2005**, 2115.

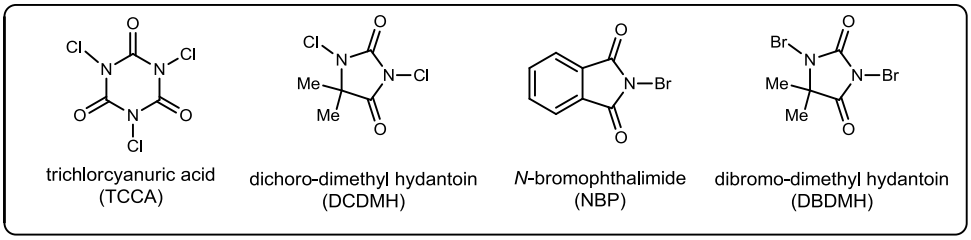
I_2, a readily available and less expensive source of iodonium, gave a yield comparable to that of NIS (Table 4, entry 10, 70%).

Table 4. Full halogenating reagent screen.



	entry	X^+ source	eq	% yield	price/mol ($)
	1	none	--	3	–
Cl^+	**2**[a,b]	$Ca(OCl)_2$[c]	1.5	22	7
Cl^+	**3**[a,b]	NCS	1.0	40	20
Cl^+	**4**[a]	TCCA	0.33	55	4
Cl^+	**5**[a]	DCDMH	0.5	53	10
Br^+	**6**[d]	Br_2	1.0	40	25
Br^+	**7**[d]	NBS	1.0	42	34
Br^+	**8**[d]	NBP	1.0	54	585
Br^+	**9**[d]	DBDMH	0.5	28	10
I^+	**10**	I_2	1.0	70	60
I^+	**11**	ICl	1.0	43	97
I^+	**12**	NIS	1.0	72	879

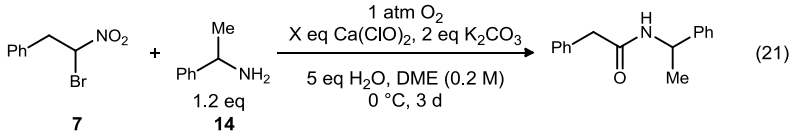
order of addition: amine, X^+ source, K_2CO_3 and H_2O added; brought to 0 °C; α-BN added *a*) done in DME *b*) reaction let stir 3 d *c*) 65% available Cl^+ *d*) reaction let stir 4 d



Since it had been discovered that this reaction could be carried out with catalytic amounts of halonium,[28] we decided to try to use sub-stoichiometric amounts of several chloronium sources which had previously given us low yields and messy reaction mixtures. It was thought that if undesirable side reactions or decomposition pathways were occurring when the concentration of chloronium was high, perhaps by keeping the chloronium concentration low, and relying on the inherent catalytic turnover seen with

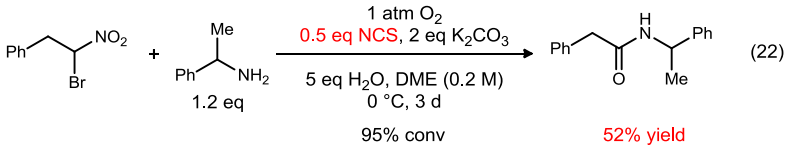
this coupling, these could be avoided. Therefore, decreasing equivalents of $Ca(OCl)_2$ were used to couple **7** and **14** (Scheme 18, entries 1-4). It was found that by using only 0.2 eq of $Ca(OCl)_2$, the yield of this reaction could be increased to 58% (entry 4). It was also found that by using only half an equivalent of NCS in this reaction, the yield could be increased from 40% (Table 4, entry 3) to 52% (Scheme 18, eq 22).

Scheme 18. Coupling under catalytic conditions with Cl^+: improved yields.



(21)

entry	$Ca(ClO)_2$ eq	% conv	% yield
1	1.0	67	22
2	0.6	75	38
3	0.5	83	42
4	0.2	95	58



(22)

In conclusion, a better understanding of the reactivities of the *N*-iodoamine, *N*-bromoamine and *N*-chloroamine was gained by examining the effectiveness of NIS, NBS, and NCS in the umpolung amide coupling of **7** and **14**. Additionally, several less expensive halogenating reagents were identified which could be used in place of NIS, including TCCA, NBP and I_2, though only I_2 gave yields comparable to NIS. $Ca(OCl)_2$ can also be used, under catalytic conditions, to give moderate yields of the amide.

CHAPTER II

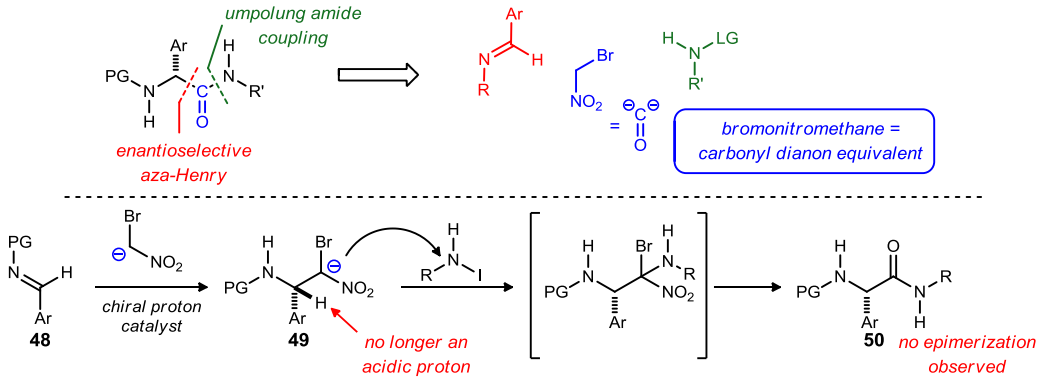
APPLICATIONS IN ENANTIOSELECTIVE PEPTIDE SYNTHESIS

2.1 Introduction and Background

Arylglycines are an important class of non proteinogenic amino acids, as they are found in many complex, naturally occurring peptide antibiotics. Somewhat difficult to synthesize and couple due to the ease with which they racemize, these amino acids have received significant attention since the discovery of vancomycin (**51**),[42] a potent glycopeptide antibiotic used as a last defense against resistant strains of bacteria. The discovery of the umpolung amide coupling of α-bromo nitroalkanes and activated amines presents a unique opportunity for the synthesis of arylglycine-containing compounds (**50**). Aryl α-bromo nitroalkanes (**49**), arylglycine precursors, can be enantioselectively synthesized via the aza-Henry addition of bromonitromethane to aryl imines (**48**, Scheme 19), in the presence of a chiral proton catalyst.[28] These enantioenriched α-bromo nitroalkanes can then be coupled using umpolung amide synthesis with no detectable racemization at the acidic α-carbon of the aryl glycine.

[42] McCormick, M.H.; Stark, W.M.; Pittenger, G.E.; Pittenger, R.C.; McGuire, G.M. *Antibiot. Annu.* **1955**, 606.

Scheme 19. Arylglycine synthesis via an enantioselective aza-Henry and umpolung amide synthesis.

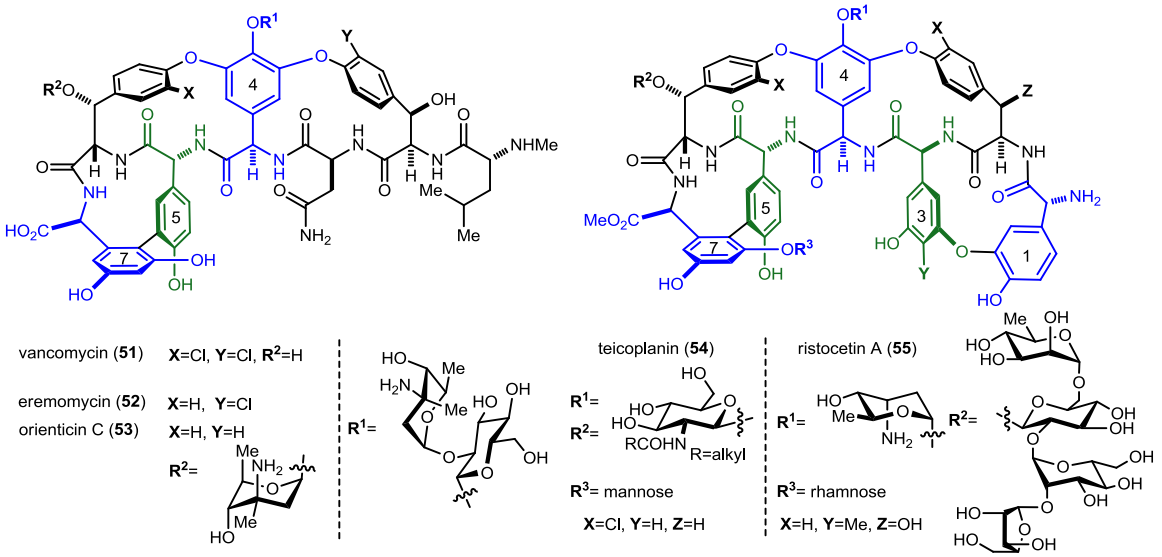


2.1.1 Methods of Enantioselective Arylglycine Synthesis

The asymmetric synthesis of arylglycines has historically been a very daunting task for synthetic chemists.[43] Due to the electron withdrawing nature of the aryl ring, the acidity of the α-proton is quite high. Therefore, racemization at this stereocenter can readily occur, especially under basic conditions. In the past 10 to 15 years, however, there have been a number of highly innovative approaches to the asymmetric synthesis of these compounds. Many of these methods came about in the midst of intense synthetic focus on vancomycin (**51**), a heptapeptide containing three arylglycine residues, and its family members.

[43] Williams, R.M.; Hendrix, J.A. *Chem. Rev.* **1992**, *92*, 889.

Figure 4. Aryl glycine containing natural products: vancomycin family of antibiotics.



Towards the Synthesis of Vancomycin

The Vancomycin class of glycopeptide antibiotics, seen in Figure 4, includes vancomycin, isolated in 1956 from *Streptomyces orientalis*, eremomycin (**52**), orienticin C (**53**), teicoplanin (**54**) and ristocetin A (**55**). These compounds are known to inhibit bacterial cell wall biosynthesis,[44] and are therefore potent antibiotics. Vancomycin is clinically used to treat severe staphylococcal and pseudomembranous colitis infections.[45] In addition to these important biological activities, the interesting structure of vancomycin[46] has made it a synthetically desirable target. The western portions of all five structures are very similar, being composed of three cross-linked arylglycine residues. Teicoplanin[47] and ristocetin's[48] structures incorporate two additional cross-linked

[44] (a) Nieto, M.; Perkins, H. R. *Biochem. J.* **1971**, *123*, 789. (b) Nieto, M. ; Perkins, H. R. *Biochem. J.* **1971**, *124*, 845.
[45] (a) Williams, D. H.; Rajananda, D.; Williamson, M. P.; Bojeson, G. *Top. Antibiot. Chem.* **1980**, *5*, 119.
[46] (a) Williamson, M. P.; Williams, D. H. *J. Am. Chem. Soc.* **1981**, *103*, 6580. (b) Harris, C. M.; Kopecka, H.; Harris, T. M. *J. Am. Chem. Soc.* **1983**, *105*, 6915.
[47] Cavelleri, B.; Ferrari, P.; Malabarba, A.; Magni, A.; Pallanza, R.; Gallo, G. G. *J. Antibiot.* **1987**, *40*, 49.
[48] Harris, C. M.; Fesik, S. W.; Thomas, A. M.; Kannan, R.; Harris, T. M. *J. Org. Chem.* **1986**, *51*, 1509.

arylglycines in their eastern sections. The total synthesis of these compounds is challenging for several reasons, one being the issue of atropisomerism associated with the fused aryl rings, the other being the ease with which the arylglycine residues can epimerize.

In 1998, Evans[49] and Nicolaou[50] simultaneously reported independent syntheses of the aglycon of vancomycin, in back to back articles in the same journal. Prior to that, however, Evans reported the synthesis of orienticin C (bis-deschlorovancomycin).[51] The arylglycine residues required for his synthesis of both orienticin C and vancomycin were constructed using a chiral auxillary directed asymmetric enolate azidation reaction, which had been previously developed in his lab.[52] Enolate formation occurs upon treatment of **56** with KHMDS. Azidation, directed by the chiral auxillary, occurs on the least hindered face, giving **57** in moderate dr. In most cases, however, the diastereomers are separable, giving aryl glycine **58**, after hydrogenation and saponification, in high enantiomeric excess (ee). Evans used this methodology to synthesize arylglycines 5 (**59**) and 7 (**60**) in 98% and 96% ee, respectively, while arylglycine 4 was derived from commercially available D-4-hydroxyphenylglycine (Figure 2). Derivatives of these three arylglycine residues were then used to complete the syntheses of **51** and **53**.

---

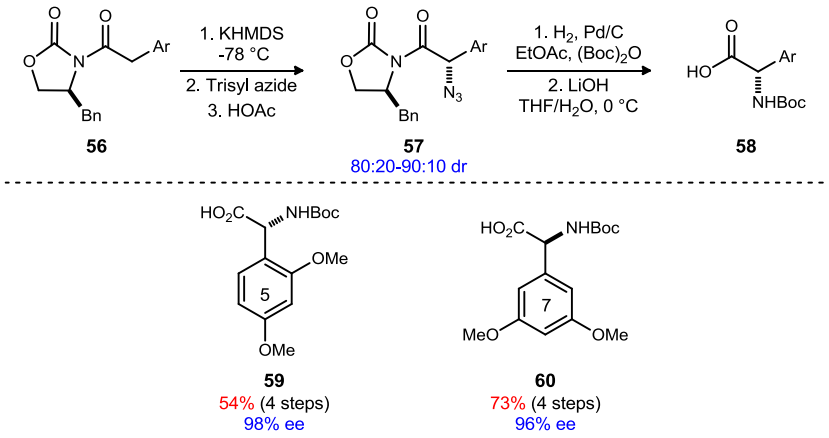
[49] (a) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem. Int. Ed.* **1998**, *37*, 2700.(b) Evans, D. A.; Dinsmore, C. J.; Watson, P. S.; Wood, M. R.; Richardson, T. I.; Trotter, B. W.; Katz, J. L. *Angew. Chem. Int. Ed.* **1998**, *37*, 2704.

[50] (a) Nicolaou, K. C.; Natarajan, S.; Li, H.; Jain, N. F.; Hughes, R.; Solomon, M. E.; Ramanjulu, J. M.; Boddy, C. N. C.; Takayanagi, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 2708.(b) Nicolaou, K. C.; Jain, N. F.; Natarajan, S.; Hughes, R. ; Solomon, M. E.; Li, H.; Ramanjulu, J. M.; Takayanagi, M.; Koumbis, A. E.; Bando, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 2714.(c) Nicolaou, K. C.; Takayanagi, M.; Jain, N. F.; Natarajan, S.; Koumbis, A. E.; Bando, T.; Ramanjulu, J. M. *Angew. Chem. Int. Ed.* **1998**, *37*, 2717.

[51] (a) Evans, D. A.; Watson, P. S. *Tet. Lett.* **1996**, *37*, 3251. (b) Evans, D. A.; Barrow, J. C.; Watson, P. S.; Ratz, A. M.; Dinsmore, C. J.; Evrard, D. A.; DeVries, K. M.; Ellman, J. A.; Rychnovsky, S. D.; Lacour, J. *J. Am. Chem. Soc.* **1997**, *119*, 3419.

[52] (a) Evans, D. A.; Evrard, D. A.; Rychnovsky, S. D.; Fruh, T.; Wittingham, W. G.; DeVries, K. M. *Tet. Lett.* **1992**, *33*, 1189.(b) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.(c) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151.

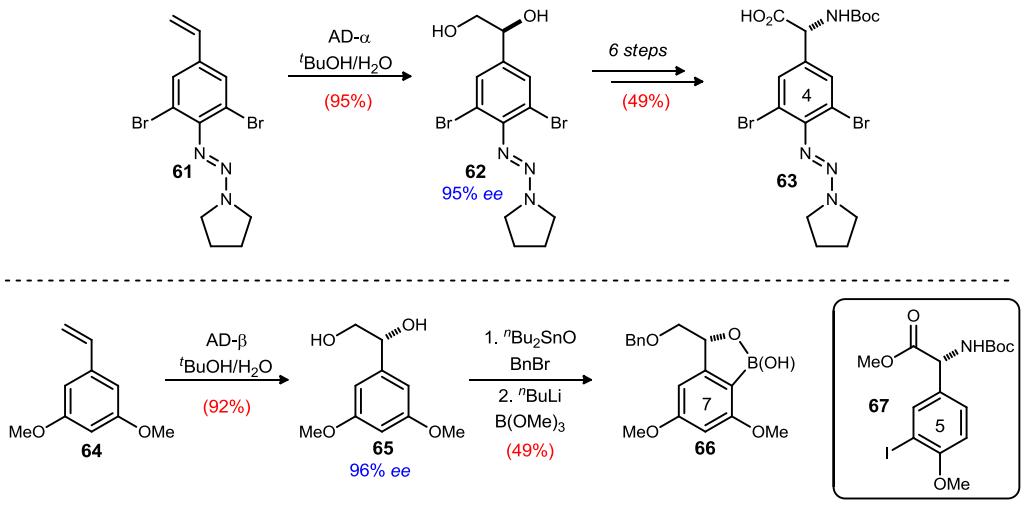
Scheme 20. Evans' chiral auxillary directed synthesis of aryl glycines.



Nicolaou, on the other hand, synthesized the required arylglycine residues via a Sharpless asymmetric dihydroxylation[53] of the appropriate styrene derivative. The dihydroxylation of **61** and **64** gave diols **62** and **65**, respectively, both in high ee and yield. Diol **62** was then transformed, in 6 steps that included a Mitsunobu azide substitution[54] and subsequent Staudinger reduction,[55] to arylglycine **63** in 49% yield. Diol **64** required less synthetic transformations before being incorporated into the natural product, as Nicolaou brought this piece (**66**) in via a Suzuki coupling with aryl iodide **67** (synthesized in 4 steps from D-4-hydroxyphenylglycine). A subsequent Mitsunobu reaction gave the azide, which was reduced to the amine only just before coupling with amino acid fragment **67** (Scheme 21).

[53] Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2484.
[54] Lal, B.; Pramanik, B.; Manha, M. S.; Bose, A. K. *Tet. Lett.* **1977**, 1977.
[55] Staudinger, H.; Meyer, J. *Hel. Chem. Acta.* **1919**, *2*, 635.

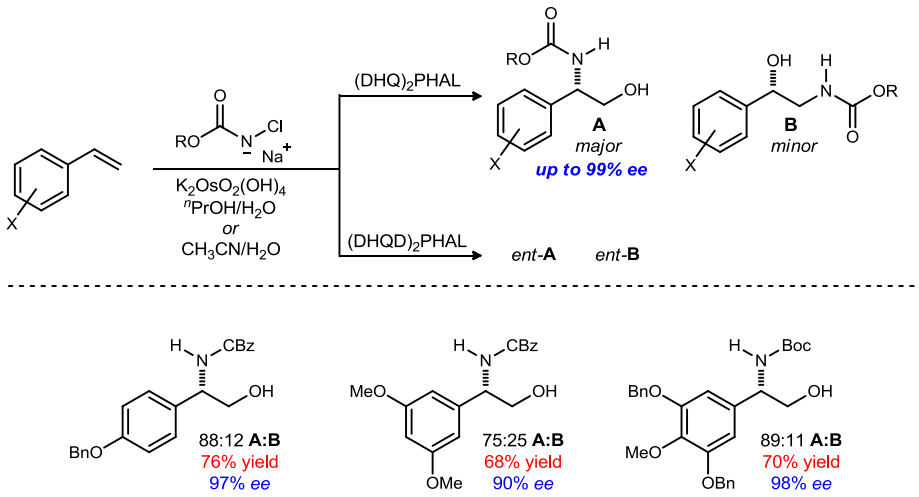
Scheme 21. Nicolaou's use of Sharpless asymmetric dihydroxylation in the synthesis of Vancomycin.



The same year Evans' and Nicolaou's syntheses of vancomycin were published, Sharpless reported the asymmetric aminohydroxylation of styrenes,[56] giving the *N*-carbamate protected arylglycinols (**A**), one oxidation step away from arylglycines, in high ee. The regioselectivity of this reaction proved troubling, with some of the undesired regioisomer (**B**) always observed (Scheme 22). Regardless of this minor drawback, Sharpless asymmetric aminohydroxylation became the method of choice for the asymmetric construction of arylglycine residues in subsequent syntheses of peptide antibiotics.[57]

[56] Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207.
[57] *Vancomycin*: (a) Crowley, B. M.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 2885. *Teicoplanin*: (b) Evans, D. A.; Katz, J. L.; Peterson, G. S. *J. Am. Chem. Soc.* **2001**, *123*, 12411. *Ristocetin*: (c) Crowley, B. M.; Mori, Y.; McComas, C. C.; Tang, D.; Boger, D. L. *J. Am. Chem. Soc.* **2004**, *126*, 4310.(d) McComas, C. C.; Crowley, B. M.; Hwang, I.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2933. *Chloropeptin/ Complestatin*: (e) Elder, A. M.; Rich, D. H. *Org. Lett.* **1999**, *1*, 1443. *Feglymycin*: (f) Dettner, F.; Hanchen, A.; Schols, D.; Toti, L.; Nuber, A.; Sussmuth, R. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 1856.

Scheme 22. Sharpless asymmetric aminohydroxylation.

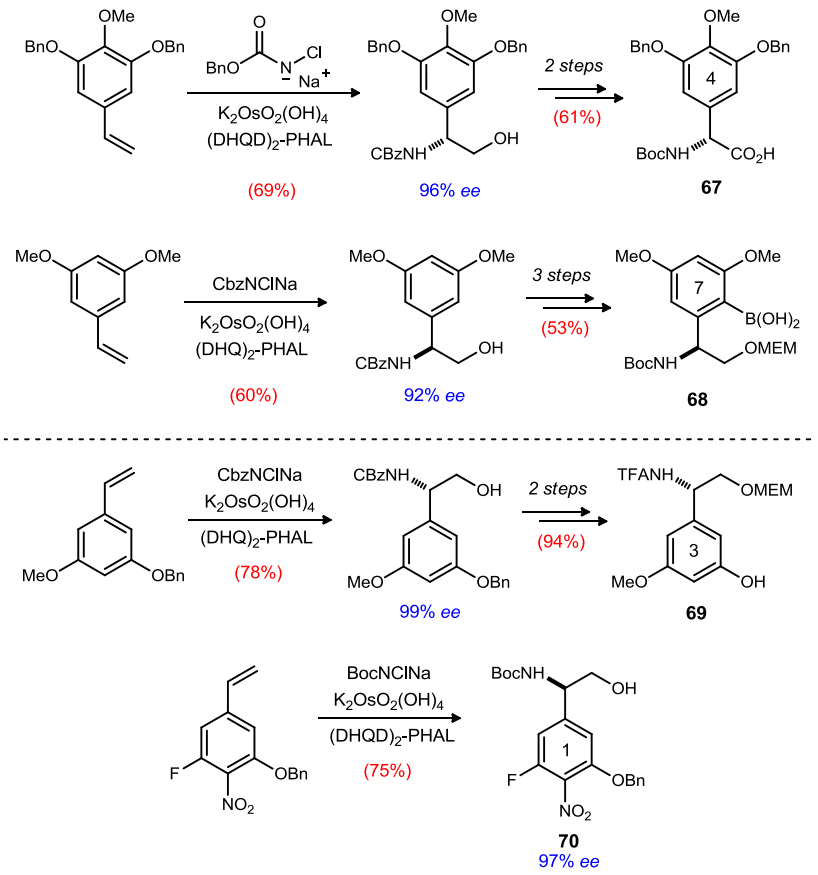


For example, in Boger's synthesis of vancomycin,[58] a Sharpless asymmetric aminohydroxylation protocol is utilized in the construction of arylglycines 4 (**67**) and 7 (**68**), in excellent enantioselectivity and good overall yields. Boger used this same procedure to make arylglycines 3 (**69**) and 1 (**70**), required in the synthesis of teicoplanin[59] (Scheme 23). While the enantioselective step of these syntheses is slightly lower yielding, the advantage in this method is that fewer synthetic steps are then required to obtain the desired arylglycine derivative.

[58] Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004.

[59] (a) Boger, D. L.; Kim, S. H.; Miyazaki, S.; Strittmatter, H.; Weng, J. H.; Mori, Y.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc.* **2000**, *122*, 7416.(b) Boger, D. L.; Kim, S. H.; Mori, Y.; Weng, J. H.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 1862.(c) Boger, D. L.; Weng, J. H.; Miyazaki, S.; McAtee, J. J.; Castle, S. L.; Kim, S. H.; Mori, Y.; Rogel, O.; Strittmatter, H.; Jin, Q. *J. Am. Chem. Soc.* **2000**, *122*, 10047.(d) Boger, D. L. *Med. Res. Rev.* **2001**, *21*, 356.

Scheme 23. Boger's application of Sharpless asymmetric aminohydroxylation.



Recent Approaches

Although asymmetric aminohydroxylation is still primarily used[60] in the total syntheses of aryl glycine containing natural products, there have been a number of new methodologies reported in this area in recent years. In addition to chiral auxillary directed enolate azidations and aminations,[61] aminohydroxylations,[62] and asymmetric versions of

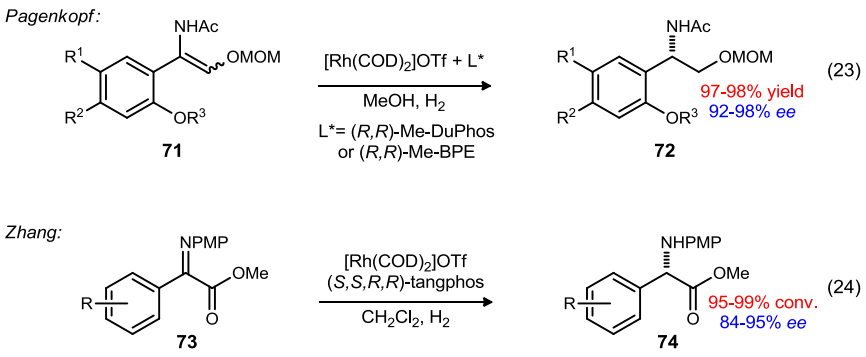
[60] With the exception of Pearson, who uses Evans' chiral auxillary directed enolate azidation in his efforts towards Ristocetin A: Pearson, A. J.; Ciurea, D. V.; Velankar, A. *Tet. Lett.* **2008**, *49*, 1922, *and references therein.*

[61] (a) Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452. (b) Kim, H. Y.; Jung, J.; Kim, S. H.; Ahn, K. H.; Kim, S. G. *Tetrahedron: Asymmetry* **2006**, *17*, 1111.(c) Anakabe, E.; Vicario, J. L.; Badia, D.; Carrillo, L.; Yoldi, V. *Eur. J. Org. Chem* **2001**, 4343.

[62] O'Brien, P.; Osborne, S. A.; Parker, D. D. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2519.

the Strecker reaction,[63] a classic method of amino acid synthesis which involves the addition of cyanide to an imine, arylglycines can now be assembled through a variety of novel asymmetric methodologies.[64] In 2004, Pagenkopf reported the asymmetric hydrogenation of aryl enamides (**71**), in the presence of a chiral rhodium catalyst, giving the corresponding arylglycinols (**72**) in excellent yield and ee (Scheme 24, eq 23).[65] Several years later, Zhang reported the asymmetric hydrogenation of imino esters (**73**), utilizing a similar rhodium catalyst, which led directly to arylglycines (**74**) in excellent conversion and good to excellent ee[66] (eq 24).

Scheme 24. Asymmetric hydrogenation of enamides and imino esters.

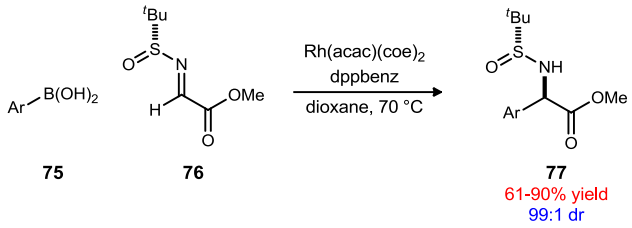


Asymmetric imine additions can also be used to construct arylglycines. In 2006, Ellman reported[67] the rhodium catalyzed addition of arylboronic acids (**75**) to chiral, non-racemic sulfinyl imino esters (**76**), giving the *N*-sulfinyl arylglycines (**77**) in good yield

[63] (a) Strecker, A. *Annalen der Chemie und Pharmazie* **1850**, *75*, 27.(b) Banphavichit, V.; Mansawat, W.; Bhanthumnavin, W.; Vilaivan, T. *Tetrahedron* **2009**, *65*, 5849, a*nd references therein.*
[64] Mellin-Morliere, C.; Aitken, D. J.; Bull, S. D.; Davies, S. G.; Husson, H. P. *Tetrahedron: Asymmetry* **2001**, *12*, 149.
[65] Pagenkopf, B. L.; Le, J. C. D. *J. Org. Chem.* **2004**, *69*, 4177.
[66] Shang, G.; Yang, Q.; Zhang, X. *Angew. Chem. Int. Ed.* **2006**, *45*, 6360.
[67] Beenen, M. A.; Weix, D. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 6304.

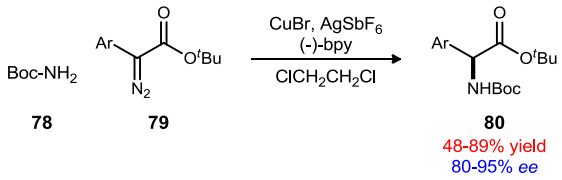
and excellent d.r. (Scheme 25). An organocatalytic version of this reaction was reported several years later.[68]

Scheme 25. Asymmetric addition of arylboronic acids to imino esters.



One of the more recent developments in this field is the asymmetric N-H insertion reaction between α-diazo esters and carbamates.[69] Reported by Fu in 2007, the enantioselective insertion of diazo **79** into the N-H bond of Boc carbamate (**78**), catalyzed by a chiral copper/bipyridine catalyst, gives direct acess to *N*-Boc protected arylglycines (**80**) in good yield and relatively high ee (Scheme 26).

Scheme 26. Asymmetric N-H insertion reactions.



Although these methods are highly innovative and offer advantages over traditional methods of arylglycine synthesis, namely in that they allow access to arylglycines in fewer steps and greater overall yield, they have largely not been applied in the total synthesis of arylglycine containing natural products. This may be due, in part, to the fact that access to enantioenriched arylglycines is only one of the challenges

[68] Dai, H.; Yang, M.; Lu, X. *Adv. Synth. Catal.* **2008**, *350*, 249
[69] Lee, E. C.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 12067.

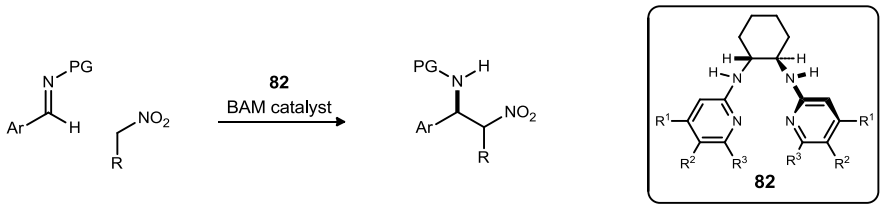
associated with the synthesis of these peptides, the other being the coupling of these sensitive amino acids while avoiding epimerization.

2.2 Enantioselective Synthesis of Arylglycine-Containing Peptides

2.1.2 Enantioselective Synthesis of Chiral α-Bromo Nitroalkanes

In recent years the development of asymmetric Henry reactions,[70] aza-Henry reactions[71] and Michael additions to nitroalkenes[72] has occurred at a very rapid pace, resulting in a diverse population of chiral, enantioenriched nitroalkanes.[73] In the Johnston lab, much work has been done on the development of the enantioselective addition of nitroalkanes to aryl imines (Scheme 81), using chiral bis-amidine (BAM) proton catalysts (**82**).[74]

Scheme 27. Chiral proton catalyzed aza-Henry addition of nitroalkanes to imines.



It order to use this chemistry to produce compounds which could then be coupled using umpolung amide synthesis, bromonitromethane could conceivably be added to *N*-

[70] For recent reviews, see: a) Palomo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 5442. b) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315. c) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2516.

[71] See Chapter 3 for a review and discussion.

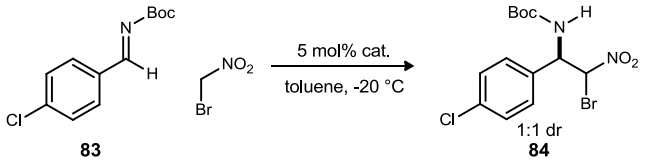
[72] For recent reviews, see: a) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171. b) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. c) Chistoffers, J.; Koripelly, G.; Rosiak, A.; Rossle, M. *Synthesis* **2007**, 1279. d) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.

[73] Ono, N. *The Nitro Group in Organic Synthesis.* Wiley-VCB: New York, New York, 2001.

[74] For discussion of this work, see Chapter 3. a) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418. b) Wilt, J. C.; Pink, M.; Johnston, J. N.; *Chem. Commun.* **2008**, *130*, 5866. c) Singh, A.; Johnston, J. N.; *J. Am. Chem. Soc.* **2008**, *130*, 5866. d) Shen, B.; Johnston, J. N. *Org. Lett.* **2008**, *10*, 4397. e) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466. f) Davis, T. A.; Wilt, J. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2010**, *132*, 2280.

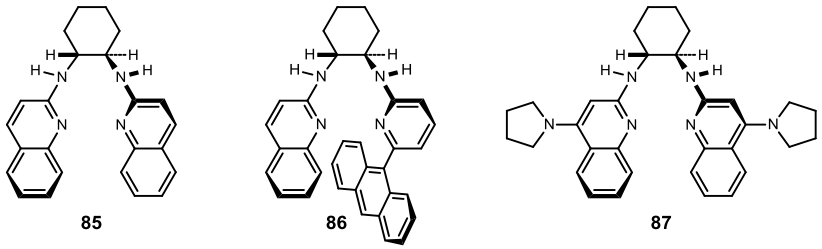
Boc-imines (**83**) to give the *N*-Boc α-bromo nitroalkanes (**84**). Therefore, we first tested the asymmetric addition of bromonitromethane to *N*-Boc aryl imine **83**, using various chiral proton catalysts.[75] While H,Quin-BAM·HOTf (**85**·HOTf) provided the adduct **84** in only 83% ee (Table 5, entry 1), H,Quin(^{6}(^{9}Anth)^{2}Pyr)-BAM·HOTf (**86**·HOTf, entry 2), as well as PBAM·HOTf (**87**·HOTf, entry 3) and the free base PBAM (**87**, entry 4), all gratifyingly afforded the adduct in high yield (87-98%) and excellent ee (94-99%), with PBAM giving the best results (94% yield, 99% ee). The isolated product from these reactions was a 1:1 mixture of diastereomers, all with conserved stereochemistry at the benzylic carbon. The lack of defined stereochemistry at the α-bromo nitro carbon is insignificant, as any stereochemistry at that carbon will be lost in the subsequent umpolung amide coupling step.

Table 5. Catalyst screen for the addition of bromonitromethane to *N*-Boc imines.



83 **84**

entry	catalyst	%ee	yield
1	**85**•HOTf	83/83	87
2	**86**•HOTf	98/98	87
3	**87**•HOTf	94/94	98
4	**87**	99/99	94

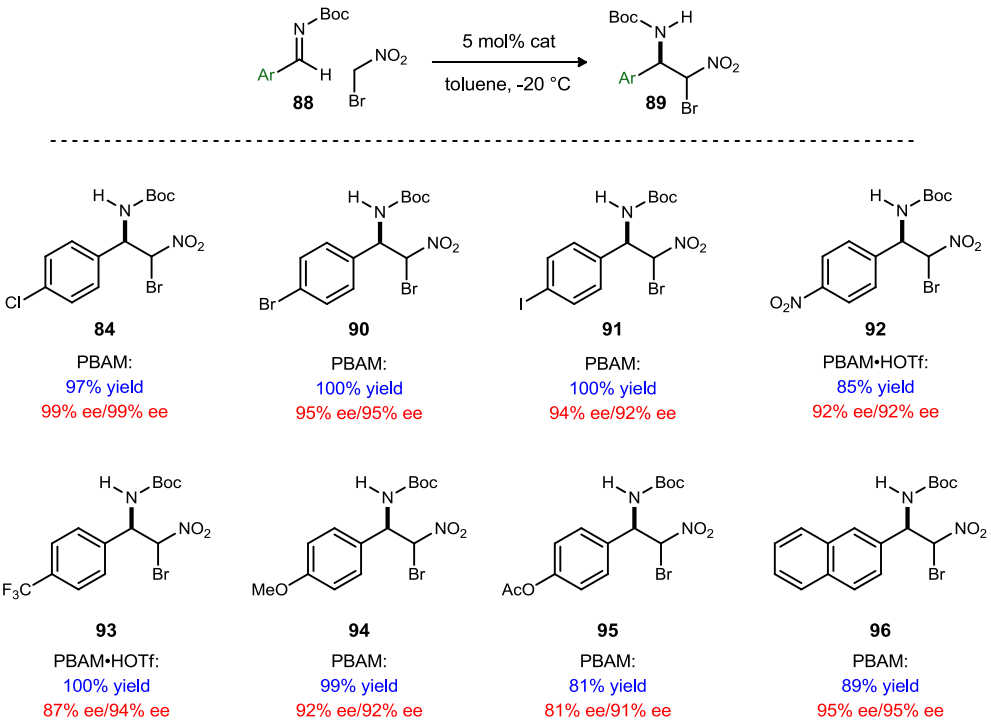


85 **86** **87**

[75] With Bo Shen.

Following the success of adding bromonitromethane to the ^{p}Cl-*N*-Boc imine, we next turned to applying these conditions to a variety of imine substrates. For this substrate screen, PBAM·HOTf (**87**·HOTf) and the free base PBAM (**87**), the two catalysts which had given us the best results previously, were used. In most cases the free base of PBAM gave slightly better yields and higher ee's than its protonated form, though in some cases PBAM·HOTf gave better results. As seen in Scheme 28, the results of this screen were very encouraging. Electron neutral (**96**), electron withdrawing (**84**, **90**, **91**, **92**, and **93**) and electron donating (**94** and **95**) imines all gave high yields (81-100%) and ee's (81-99%) of their corresponding α-bromo nitroalkane adducts.

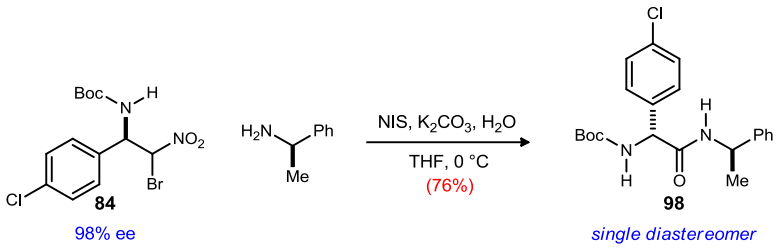
Scheme 28. Scope of bromonitromethane addition to *N*-Boc imines.



2.2.1 Coupling of Aryl α-Bromo Nitroalkanes

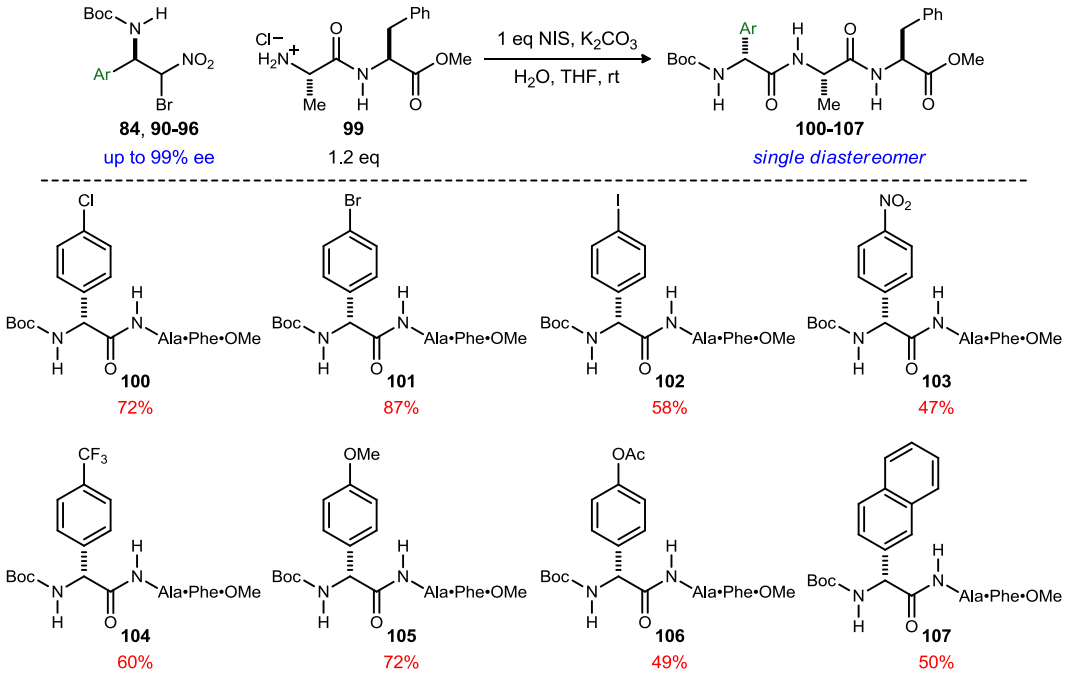
After synthesizing the α-bromo nitroalkanes (**84**, **90-96**), the next step was to couple them, using our umpolung amide coupling conditions, to give aryl glycine-containing peptides. It had previously been shown that **84** could be coupled to methyl benzylamine, in the presence of NIS, giving amide **98** in 76% yield and as a single diastereomer.[17] This was encouraging in that, as hypothesized, no epimerization was observed at the α-carbon of the phenylglycine residue (Scheme 29).

Scheme 29. Coupling of α-bromo nitroalkane **84** to α-methyl benzylamine.



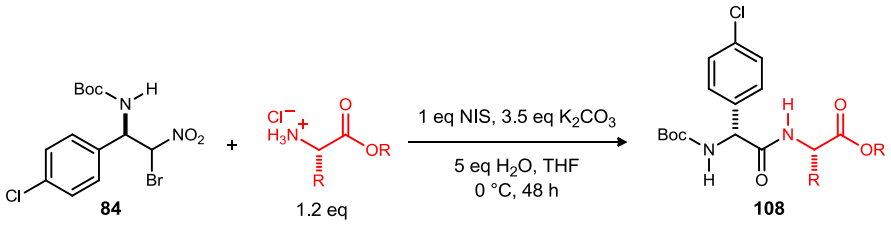
Therefore, we next wished to couple α-bromo nitroalkanes to more complicated amine substrates- specifically peptidic ones such as the Ala·Phe·OMe dipeptide. As seen in Scheme 30, α-bromo nitroalkanes **84** and **90-96** were all coupled successfully, in moderate to good yields, to the Ala·Phe·OMe dipeptide. Gratifyingly, epimerization was not observed in any of these cases.

Scheme 30. Coupling of α-bromo nitroalkanes to Ala-Phe dipeptide.



Having established that epimerization was not occurring when these aryl glycine surrogates were coupled, and that the umpolung amide coupling conditions were compatible with the Ala·Phe·OMe dipeptide, we next wanted to ascertain whether or not the various functionalities of all 20 canonical amino acids were compatible with these reaction conditions. Therefore, α-bromo nitroalkane **84** was coupled to these amino acids. We were very excited to see that, with all 20 amino acids, moderate to good yields (41-81%) of the desired dipeptides (**108a-t)** (Table 6, entries 1-20) were observed, all as single diastereomers.

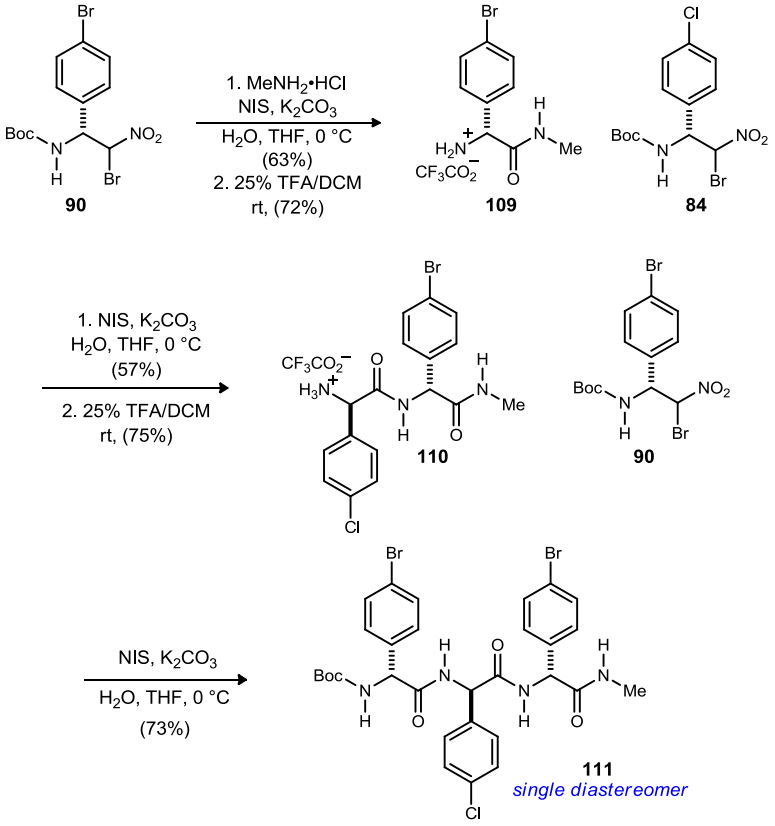
Table 6. Coupling of α-bromo nitroalkane **84** to the 20 canonical amino acids.



entry	amino acid	product	yield (%)
1	glycine	BocNH•^{p}ClPhg•Gly•OMe (**a**)	79
2	L-alanine	BocNH•^{p}ClPhg•Ala•OMe (**b**)	63
3	L-valine	BocNH•^{p}ClPhg•Val•OMe (**c**)	70
4	L-leucine	BocNH•^{p}ClPhg•Leu•OMe (**d**)	81
5	L-isoleucine	BocNH•^{p}ClPhg•Ile•OMe (**e**)	66
6	L-serine	BocNH•^{p}ClPhg•Ser•OMe (**f**)	64
7	L-threonine	BocNH•^{p}ClPhg•Thr•OMe (**g**)	45
8	L-phenylalanine	BocNH•^{p}ClPhg•Phe•OMe (**h**)	64
9	L-tyrosine	BocNH•^{p}ClPhg•Tyr(O^{t}Bu)•OMe (**i**)	64
10	L-aspartic acid	BocNH•^{p}ClPhg•Asp(OMe)•OMe (**j**)	64
11	L-asparagine	BocNH•^{p}ClPhg•Asn•O^{t}Bu (**k**)	52
12	L-glutamic acid	BocNH•^{p}ClPhg•Glu(OEt)•OEt (**l**)	57
13	L-glutamine	BocNH•^{p}ClPhg•Gln•O^{t}Bu (**m**)	59
14	L-lysine	BocNH•^{p}ClPhg•Lys(CBz)•OMe (**n**)	55
15	L-proline	BocNH•^{p}ClPhg•Pro•OMe (**o**)	67
16	L-cysteine	BocNH•^{p}ClPhg•Cys(Bn)•OMe (**p**)	52
17	L-methionine	BocNH•^{p}ClPhg•Met•OMe (**q**)	43
18	L-arginine	BocNH•^{p}ClPhg•Arg(NO$_2$)•OMe (**r**)	44
19	L-histidine	BocNH•^{p}ClPhg•His(Tr)•OMe (**s**)	41
20	L-tryptophan	BocNH•^{p}ClPhg•Trp(Boc)•O^{t}Bu (**t**)	44

Notably, serine (Table 6, entry 6) and threonine (Table 6, entry 7) were able to be successfully coupled without the need of an alcohol protecting group. However, tyrosine (Table 6, entry 9) did require protection of the free phenol; when unprotected, aryl iodination occurred to give the diiodotyrosine. Asparagine (Table 6, entry 11) and glutamine (Table 6, entry 13) also did not require protection. We were especially pleased to see that proline, the only disubstituted amino acid, was able to be coupled in 67% yield, and that the more complex amino acids, such as arginine (Table 6, entry 18), histidine (Table 6, entry 19) and tryptophan (Table 6, entry 20), produced amide product, though in slightly lower yields (41-44%). While these couplings have not been optimized, the preliminary results indicate that umpolung amide synthesis is compatible with the 20 canonical amino acids. This is quite promising as this indicates the reaction could have broad applicability in peptide synthesis.

Scheme 31. Enantioselective peptide synthesis: Iterative α-bromo nitroalkane coupling.



With the success we had incorporating single phenylglycine residues into dipeptides or tripeptides, the next logical step was to attempt to couple the α-bromo nitroalkanes in an iterative fashion. To this end, the coupling of α-bromo nitroalkane **90** to methyl amine hydrochloride, in the presence of NIS, and subsequent Boc-deprotection, afforded the *N*-methyl-^{p}Br-phenylglycine **109** in 45% yield (two steps). This compound was then coupled to α-bromo nitroalkane **84**, and the resulting dipeptide was Boc-deprotected, to give **110** in 43% yield (two steps). A third iterative coupling was then done, giving the tripeptide **111** in 73% yield (Scheme 31). Notably, this compound was isolated as a single diastereomer, and at no point during these iterative couplings was any epimerization detected. Also exciting was the fact that this sequence of reactions

represents a completely enantioselective peptide synthesis, as only achiral starting materials (*N*-Boc imines and bromonitromethane) were utilized.

In conclusion, it was demonstrated that by using a tandem enantioselective aza-Henry reaction/umpolung amide coupling, arylglycine containing peptides can be synthesized very easily and efficiently from inexpensive achiral starting materials. In addition, the umpolung amide coupling conditions have been proved to be mild enough to tolerate all functionalities found in the 20 canonical amino acids. Lastly, a completely enantioselective peptide synthesis of a tripeptide composed of three arylglycine residues was achieved through the iterative umpolung amide coupling of α-bromo nitroalkanes.

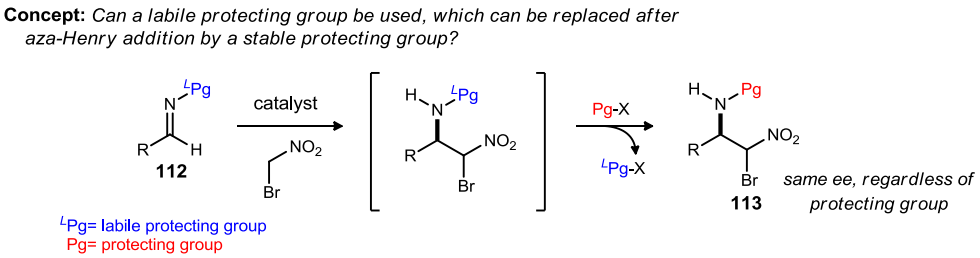
CHAPTER III

ENANTIOSELECTIVE AZA-HENRY ADDITION TO SILYL IMINES: ACCESS TO MULTIPLE PROTECTING GROUPS

3.1 Introduction and Background

While the tandem reaction sequence discussed in the previous chapter was able to provide us arylglycine containing peptides in two short steps from the Boc imine, the fact that only Boc-protected aryl glycine residues could be produced using this method was seen as a limitation. While the Boc-protecting group is used in peptide synthesis, it is not the most widely used and requires harshly acidic deprotection conditions.[5] Therefore, we decided to pursue methods of incorporating other protecting groups into this chemistry. Through these efforts, a novel methodology has been developed which allows access to the most commonly used protecting groups in peptide synthesis.

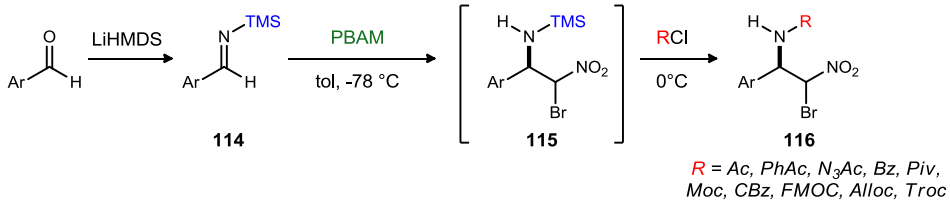
Figure 5. Concept behind aza-Henry additions to silyl imines.



The concept behind the development of this reaction, seen in Figure 5, was to add bromonitromethane to an imine protected by a labile protecting group (**112**), which could then be replaced, *in situ* after aza-Henry addition, by a more stable protecting group. The main advantage in this would be that, because the enantioselective addition would always

occur to the same ^{L}Pg-imine (**112**), the resulting ee of the variously protected α-bromo nitroalkanes (**113**) should be the same regardless of the protecting group introduced.

Scheme 32: Enantioselective aza-Henry addition to silyl imines: Access to multiple protecting groups.



This concept was realized by the addition of bromonitromethane to TMS-imines (**114**). The resulting TMS-amine (**115**), which was stable enough to not undergo retro aza-Henry in solution but not stable enough to be isolated, can then be acylated by a variety of acid chlorides or chloroformates, giving the enantioenriched α-bromo nitroalkanes (**116**). Using this method we are able to access the acetate (Ac), phenylacetate (PhAc), azidoacetate (N_3Ac), benzoyl (Bz), pivaloyl (Piv), methoxy carbonyl (Moc), carbobenzyloxy (Cbz), fluorenylmethyloxy carbonyl (Fmoc), trichloroethyloxy carbonyl (Troc) and allyloxy carbonyl (Alloc) protected arylglycine amino acids surrogates (Scheme 32).

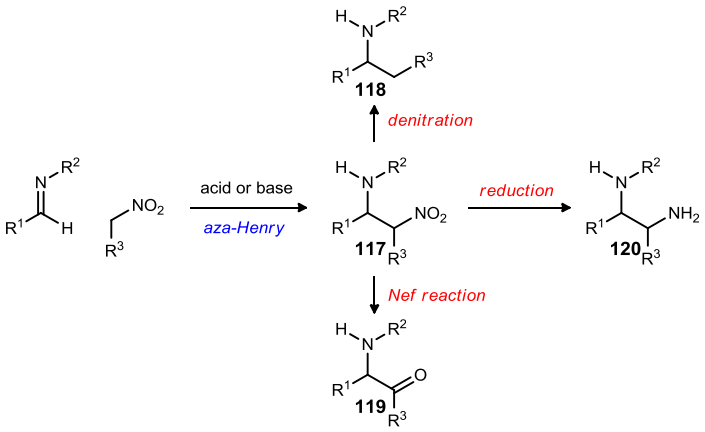
3.1.1 The Enantioselective aza-Henry Reaction

The aza-Henry reaction, also known as the nitro-Mannich, involves the nucleophilic addition of nitroalkenes to imines.[76] This addition usually requires the presence of an acid or a base, to either activate the amine or generate the nitronate. The nitroamine (**117**) generated in this reaction is useful in that it can be transformed into a

[76] For recent reviews, see: a) Westermann, B. *Angew. Chem. Int. Ed.* **2003,** *42*, 151. b) Marques-Lopez, E.; Merino, P.; Tejero, T.; Herrara, R. P. *Eur. J. Org. Chem.* **2009**, 2401.

variety of synthetically useful compounds such as vicinal diamines (**120**), α-amino carbonyl compounds (**119**) or protected secondary amines (**118**) (Scheme 33).

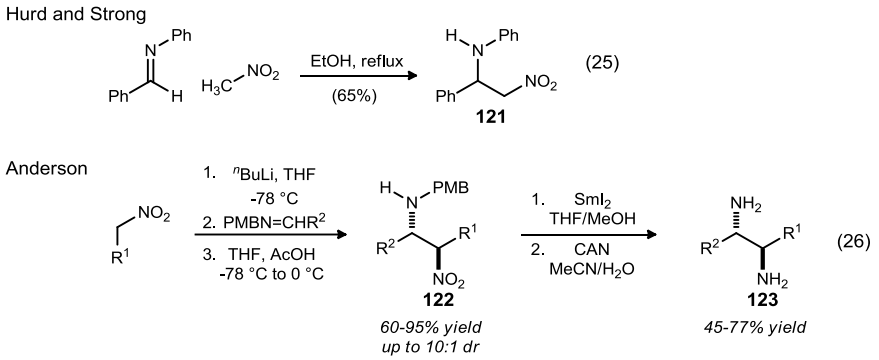
Scheme 33. The aza-Henry reaction.



The first aza-Henry reaction was reported in 1950, by Hurd and Strong.[77] They reported the condensation of nitromethane with *N*-benzylidene aniline, in refluxing ethanol, to afford *N*-(2-nitro-1-phenylethyl)aniline (**121**) in 65% yield (Scheme 34, eq 25). Utility for the aza-Henry reaction was found in 1998 when Anderson and coworkers used this reaction in the synthesis of vicinal diamines (**123**).[78] By reacting deprotonated nitroalkanes with PMB imines, they were able to produce β-nitro amines (**122**) in high yields and up to 10:1 dr. (Scheme 34, eq 26).

[77] Hurd, C. D.; Strong, J. S. *J. Am. Chem. Soc.* **1950**, *72*, 4813.
[78] Adams, H.; Anderson, J. C.; Peace, S.; Pennell, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932.

Scheme 34. Early examples of the aza-Henry reaction.



The following year, the same group reported that this reaction could be catalyzed by $Sc(OTf)_3$ with improved yields and diastereoselectivity.[79] Soon after, Qian discovered $Yb(O^iPr)_3$ could also catalyze the aza-Henry addition of nitromethane with sulfonylimines, giving the desired β-nitroamines in 81-100% yield.[80] Since then, there has been much work done on the development of an enantioselective version of the aza-Henry reaction.

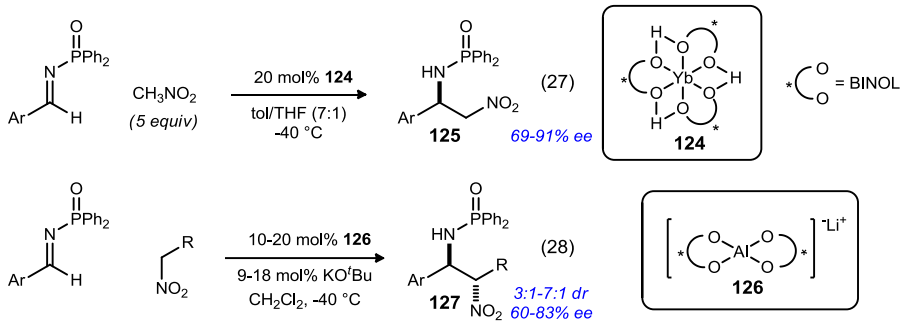
Metal Catalyzed Enantioselective aza-Henry Reactions

The first report of a catalytic enantioselective aza-Henry reaction was by Shibasaki in 1999.[81] He used a heterobimetallic complex (**124**), formed by mixing Yb, K, and BINOL in a 1:1:3 ratio, to catalyze the addition of nitromethane to *N*-phosphinoylimines. The resulting aza-Henry adducts (**125**) were obtained in up to 91% ee (Scheme 35, eq 27). By moving to an AlLi[(*R*)-binaphthoxide]$_2$ catalyst (**126**), they were then able to extend the scope of this reaction to include substituted nitroalkanes, which

[79] Anderson, J. C.; Peace, S.; Pih, S. *Synlett* **2000**, *42*, 4673.
[80] Qian, C. T.; Gao, F. F.; Chen, R. F. *Tetrahedron Lett.* **2001**, *42*, 4637.
[81] Yamada, K; Harwood, S. J.; Groger, H.; Shibasaki, M. *ANgew. Chem. Int. Ed.* **1999**, *38*, 3504.

gave good diastereoselectivity (3:1 to 7:1, favoring the *anti* diastereomer **127**) but slightly lower enantioselectivity (60-83% ee) (Scheme 35, eq 28).[82]

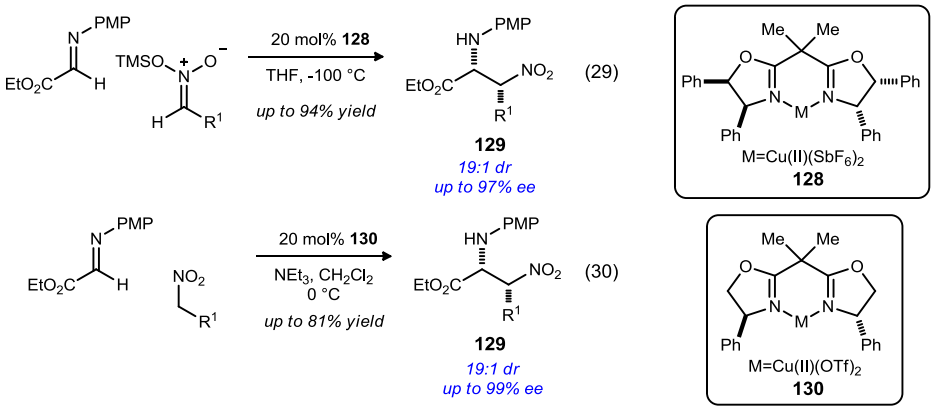
Scheme 35. Shibasaki's work on the first catalytic enantioselective aza-Henry reaction.



Shortly thereafter, Jørgensen reported the catalytic asymmetric aza-Henry addition of silyl nitronates to α-imino esters, in the presence of chiral copper(II)-bisoxazoline complex **128**, giving **129** in excellent enantio- and diastereoselectivity (Scheme 36, eq 29).[83] Shortly after, the same group reported the direct aza-Henry addition of nitroalkanes, in which an external base was added, generating the nitronate *in situ*, and allowing them to obtain equally good results (Scheme 36, eq 30).[84]

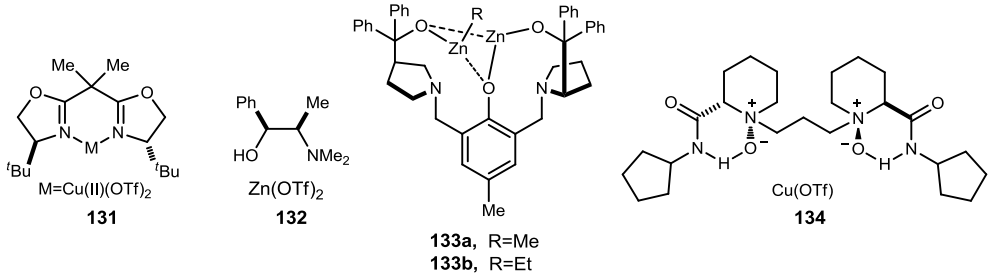
[82] a) Yamada, K.; Moll, G.; Shibasaki, M. *Synlett* **2001**, 980. b) Shibasaki, M.; Kanai, M. *Chem. Pharm. Bull.* **2001**, *49*, 511.
[83] Knudsen, K. R,; Rsgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843.
[84] Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2001,** *40,* 2992.

Scheme 36. Jørgensen's enantioselective aza-Henry addition of silyl nitronates and nitroalkanes to imines.



Since Shibasaki's and Jørgensen's pioneering work in this area, several other metal catalysts have been developed for the asymmetric aza-Henry reaction. Seen in Figure 6, these include the ^{t}Bu-BOX-Cu(OTf)$_2$ complex (**131**),[85] an (-)-*N*-methylephedrine-Zn(OTf)$_2$ combination (**132**),[86] a dinuclear zinc catalyst (**133**),[87] and an *N*,*N*'-dioxide-Cu(OTf) complex (**134**).[88]

Figure 6. Metal catalysts for the enantioselective aza-Henry reaction.



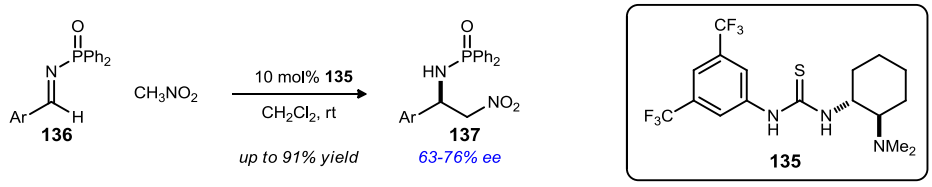
Organocatalytic Enantioselective aza-Henry Reactions

Recently, much progress has also been made in the area of organocatalytic aza-Henry additions. These reactions offer an advantage over metal catalyzed reactions in

[85] Anderson, J. C.; Howell, G. P.; Lawrence, R. M.; Wilson, C. S. *J. Org. Chem.* **2005**, *70*, 5665.
[86] Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; Lopex, R. *Angew. Chem, Int. Ed.* **2006**, *45*, 117.
[87] a) Gao, F. F.; Zhu, J.; Tang, Y.; Deng, M. Z.; Qian, C. T. *Chirality* **2006**, *18*, 741. b) Trost, B. M.; Lupton, D. W. *Org. Lett.* **2007**, *9*, 2023.
[88] Zhou, H.; Peng, D.; Qin, B.; Hou, Z. R.; Liu, X. H.; Feng, X. M. *J. Org. Chem.* **2007**, *72*, 10302.

that they are environmentally friendly; only a proton is needed to catalyze the reaction, and in most cases the catalysts can be recovered and recycled. In 2004, Takemoto demonstrated that, in the presence of their chiral thiourea catalyst (**135**), the addition of nitromethane to phosphinoylimines (**136)** gives the β-nitroamines (**137**) in up to 76% ee and 91% yield (Scheme 37).[89] They proposed that the thiourea catalyst was acting in a bifunctional manner by first deprotonating the nitroalkane and subsequently activating the imine through hydrogen bonding. By using *N*-Boc aryl imines, Takemoto later extended this reaction to include a broader scope of imines and nitroalkanes with high enantio- and diastereoselectivity.[90]

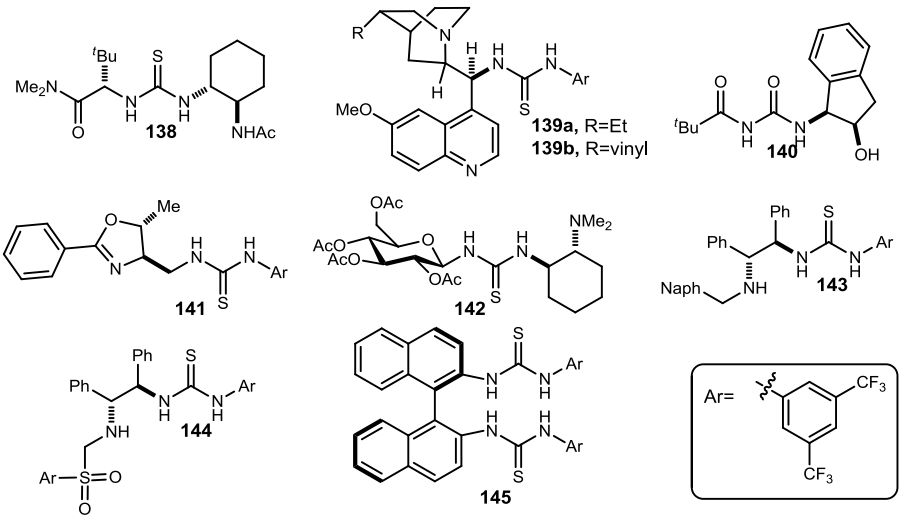
Scheme 37. Takemoto's enantioselective, thiourea-catalyzed aza-Henry reaction.



Since then, various other chiral urea and thiourea catalysts have been reported to catalyze the enantio- and diastereoselective aza-Henry reaction, including those developed by Jacobsen (**138**),[91] Schaus (**139a**),[92] Ricci (**139b**),[93] Ellman (**140**),[94] Chang (**141**),[95] Zhou (**142**),[96] Chen (**143**),[97] Wang (**144**),[98] and Wulff (**145**)[99] (Figure 7).

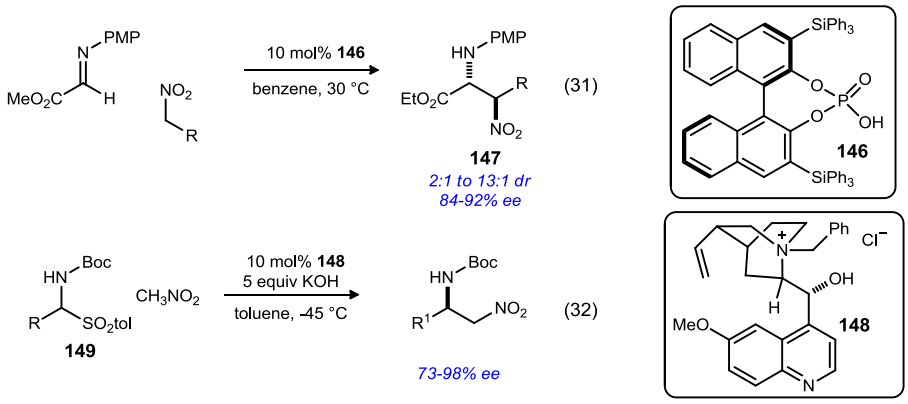
[89] Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625.
[90] Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2006**, *12*, 466.
[91] Yoon, T. P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *12*, 466.
[92] Bode, C. M.; Ting, A,; Schaus, S. E. *Tetrahedron* **2006**, *62*, 11499.
[93] Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A.; Sgarzani, V. *Tetrahedron* **2006**, *62*, 375.
[94] Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110.
[95] Chang, Y. W.; Wang, J. J.; Dang, J. N.; Xue, Y. X. *Synlett* **2007**, 2283.
[96] Wang, C.; Zhou, Z.; Tang, C. *Org. Lett.* **2008,** *10*, 1707.
[97] Han, B.; Liu, Q. –P.; Li, R.; Tian, X.; Xiong, X. –F.; Deng, J. –G.; Chen, Y. –C. *Chem. Eur. J.* **2008**, *14*, 8094.
[98] Wang, C. J.; Dong, X. Q.; Zhang, Z. H.; Xue, Z. Y.; Teng, H. L. *J. Am. Chem. Soc.* **2008**, *130*, 8606.
[99] Rampalakos, C.; Wulff, W. D. *Adv. Synth. Catal.* **2008**, *350*, 1785.

Figure 7. Chiral urea and thiourea catalysts used in the enantioselective aza-Henry reaction.



Other developments in this area include the chiral phosphoric acid **146** catalyzed asymmetric addition of nitroalkanes to α-iminoesters to provide β-nitro-α-amino esters (**147**) (Scheme 38, eq 31),[100] as well as the use of the more stable α-amido sulfones (**149**), which can eliminate to the imine *in situ* (Scheme 38, eq 32).[101]

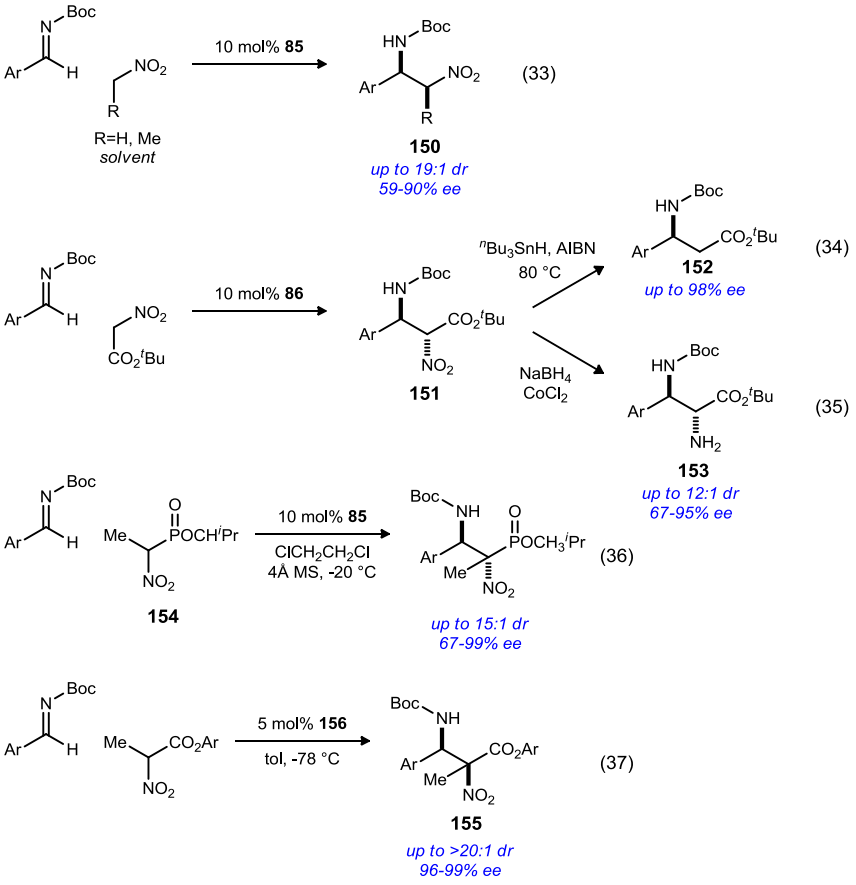
Scheme 38. Recent developments in the enantioselective aza-Henry reaction.



[100] Rueping, M.; Antonchick, A. P. *Org. Lett.* **2008**, *10*, 1731.
[101] a) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7975. b) Palomo, C.; Oiarbide, M.; Laso, A.; Lopez, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622.

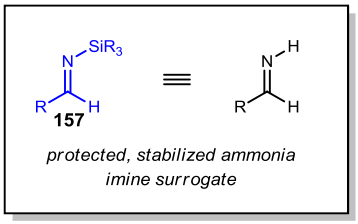
In 2004, simultaneous with Takemoto's report of the thiourea-catalyzed aza-Henry reaction, the Johnston group reported the development of a novel "chiral proton" catalyst. A protonated chiral bisamidine (H,Quin-BAM·HOTf **85**), it catalyzed the addition of nitroalkanes to *N*-Boc imines, giving the aza-Henry adducts (**150**) in high enantiomeric excess and d.r. (Scheme 39, eq 33).[74a] It was found that the chiral proton was important in catalyzing this reaction, as the unprotonated catalyst resulted in a very slow addition rate. Further work in this area has extended the chiral proton catalyzed aza-Henry addition to nitroacetic acid additions, using the unsymmetrical catalyst **86** (Scheme 39, eq 34, 35).[74d,e] These adducts (**151**) are useful in that they can further be transformed, through reduction or denitration, to give α,β-diamino acids (**153**) or β-amino acids (**152**), respectively. The addition of α-nitrophosphonate (**154**) to *N*-Boc imines, in high ee and d.r., could be affected by **85** (Scheme 39, eq 36);[74b] however, the more reactive methoxy-substituted unsymmetrical BAM catalyst **156** was needed for the addition of α-nitroacetate, to generate the quaternary center of the resulting adduct (**155**) in excellent ee and dr.[74c] In general, it has been found that increasing the Brønsted basicity of these BAM catalysts, through quinoline substitution, increases their reactivity in an orthogonal manner; this can be seen in the enhanced reactivity of ^{4}Pyrrolidine-Quin-BAM·HOTf (PBAM, **87**).[74e]

Scheme 39. Johnston's chiral proton catalyzed aza-Henry reaction.



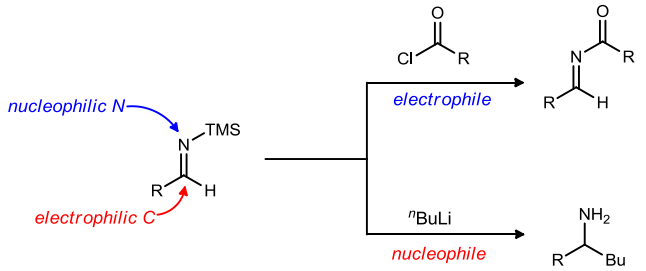
3.1.2 Reactivity of N-Silyl Imines

Figure 8. *N*-Silyl imines as stabilized ammonia imine surrogates.



Easily prepared from amines and aldehydes or ketones, imines are a highly useful synthetic tool which have been widely used to introduce amines into compounds, often with concomitant carbon-carbon bond formation.[102] With many imines, the *N*-substituent is simply acting as a protecting group, stabilizing the imine and activating it towards nucleophilic addition. This group is then removed to reveal the unprotected amine. *N*-silyl imines (**157**) have been used to circumvent this additional deprotection step; during work-up, the *N*-silyl bond is easily hydrolyzed.[103] Therefore, these imines can essentially be thought of as stabilized, protected ammonia imine surrogates (Figure 8). They are unique in that the nitrogen of the imine is fairly nucleophilic.[104] Therefore, *N*-silyl amines can react as an electrophile or a nucleophile, and occasionally as both (Figure 7).

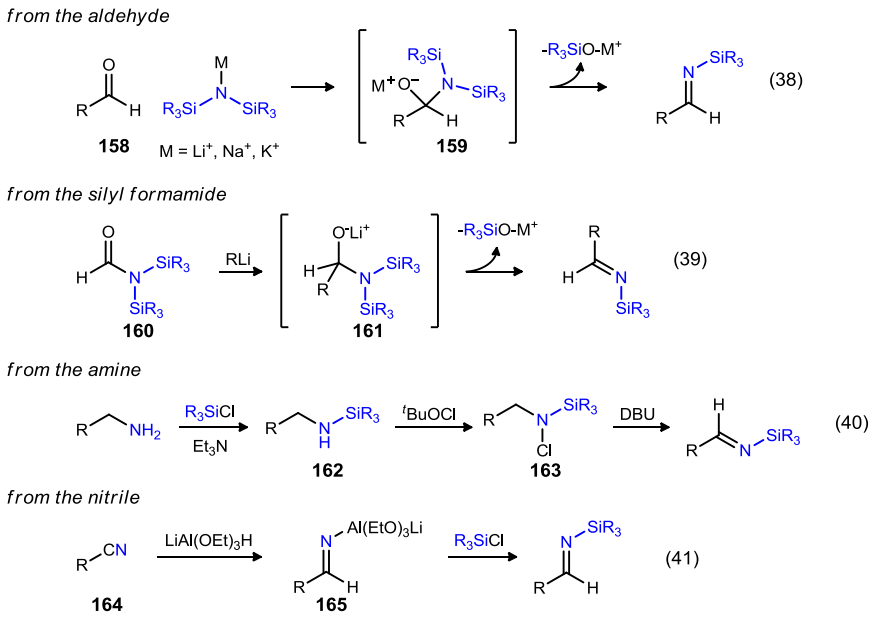
Figure 9. Nucleophilic and electrophilic character of silyl imines.



[102] Trost, B. M. Fleming, I. *Comprehensive Organic Synthesis;* Pergamon Press: Oxford, 1991.
[103] For a review, see: Panunsio, M.; Zarantonello, P. *Org. Process Res. Dev.* **1998**, *49.*
[104] Cainelli, G.; Panunzio, M.; Andreoli, P.; Martelli, G.; Spunta, G.; Giacomini, D.; Bandini, E. *Pure Appl. Chem.* **1990**, *62*, 605.

N-Silyl amines can be synthesized in a variety of ways. The most common method is through the reaction of metal silazanes and aldehydes (**158**). Silyl transfer, from the silazane to the resulting alkoxide, results in loss of the silanolate and imine formation (Scheme 40, eq 38). A similar alkoxide intermediate (**159**) can be reached *via* nucleophilic addition to *N*,*N*-disilyl formamides (**160**) (Scheme 40, eq 39). Other methods include oxidation of *N*-silyl protected amines (**162**) to afford the *N*-haloamine (**163**), which is subsequently eliminated in the presence of DBU (Scheme 40, eq 40). Lastly, reduction of nitriles (**164**) with an aluminum hydride source results in the *N*-metalloimine (**165**). Transmetalation of this compound then gives the desired *N*-silyl imine (Scheme 40, eq 41).[103]

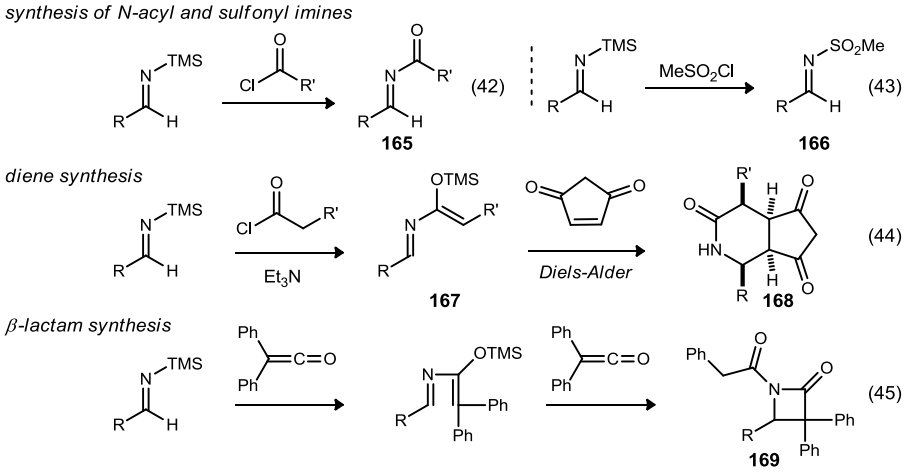
Scheme 40. Synthesis of *N*-silyl imines.



Selected examples of the nucleophilic reactivity of *N*-silyl amines can be seen in Scheme 41. *N*-silyl imines readily react with acid and sulfonyl chlorides; therefore, they

are often used as precursors to *N*-acyl (**165**)[105] or *N*-sulfonyl imines (**166**) (Scheme 41, eq 42,43).[106] Acylation of *N*-silyl imines with enolizable acid chlorides and subsequent treatment with base has been used in the synthesis of azadienes (**167**), which are used in the synthesis of nitrogen-containing heterocycles such as (**168**) (Scheme 41, eq 44).[107,108] A second method of synthesizing azadienes from *N*-silyl imines is to react them with isocyanates. In addition to [4+2] cyclizations,[109] these dienes can undergo [2+2] cycloadditions[110] to give the β-lactam (**169**) (Scheme 41, eq 45). There have also been several examples of *N*-silyl imines used as dieneophiles in Diels-Alder cycloadditions.[111]

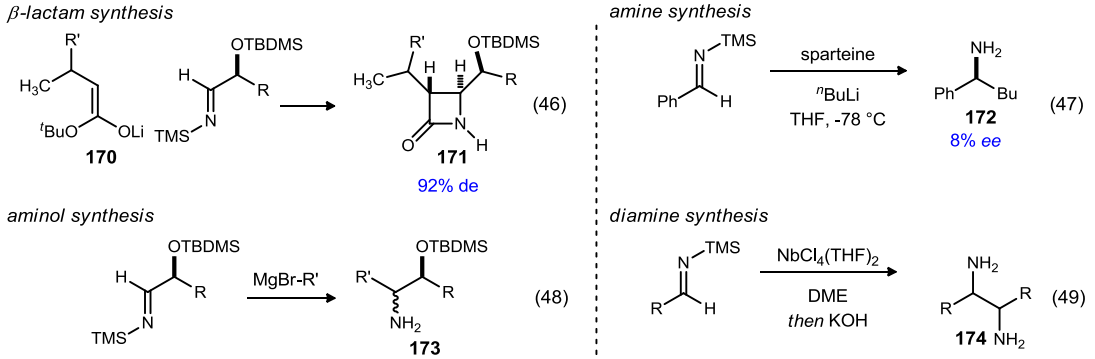
Scheme 41. Silyl imines as nucleophiles.



[105] Kupfer, R.; Meier, S.; Wurthwein, E. –U. *Synthesis*, **1984**, 688.
[106] Georg, G. I.; Harriman, G. C. B.; Peterson, S. A. *J. Org. Chem.* **1995**, *60*, 7366.
[107] Ghosez, L. *Pure Appl. Chem.* **1996**, *68*, 15.
[108] For other examples of this, see reference 77.
[109] a) Barluenga, J.; Tomas, M.; Ballesteros, A.; Lopez, A. L. *Synthesis* **1989**, 228. b) Barluenga, J.; Thomas, M.; Ballesteros, A.; Lopez, L. A. *Synthesis* **1995**, 985. c) Barluenga, J.; Tomas, M.; Ballesteros, A.; Lopez, L. A. *Synlett* **1991**, 93. d) Barluenga, J.; Tomas, M.; Ballesteros, A.; Lopez, L. A. *J. Org. Chem.* **1991**, *56*, 5680. e) Barluenga, J.; Tomas, M. Ballesteros, A.; Lopez, L. A. *J. Am. Chem. Soc., Chem. Commun.* **1989,** 1487.
[110] a) Birkofer, L.; Schramm, J. *Justus Liebigs Ann. Chem.* **1977**, 760. b) Gandini, E.; Martelli, G. Spunta, G.; Panunzio, M. *Synlett* **1996**, 1017.
[111] a) Barluenga, J.; Aznar, F.; Valdes, C.; Cabal, M. –P. *J. Org. Chem.* **1993**, *58*, 3391. b) Barluenga, J.; Aznar, F.; Valdes, C.; Martin, A. *J. An. Quim.* **1993**, 115. c) Barluenga, J.; Aznar, F.; Valdes, C.; Martin, A.; Garcia-Grenada, S.; Marin, E. *J. Am. Chem. Soc.* **1993,** *115*, 4403.

A second method of β-lactam synthesis using *N*-silyl imines involves the nucleophilic addition of an ester enolate (**170**) to the electrophilic imine carbon. Subsequent acyl substitution gives the desired β-lactam (**171**) (Scheme 42, eq 46).[112] In many instances the diastereoselectivity, or in some cases the enantioselectivity, of this condensative cyclization can be controlled to a high degree.[113] Amines (**172**)[114] and aminols (**173**)[115] can also be synthesized from *N*-silyl imines through the nucleophilic addition of aryl and alkyl lithium or Grignard reagents, in varying degrees of enantio- or diastereoselectivity (Scheme 42, eq 47,48). Diamine (**174**) synthesis, through the dimerization of *N*-silyl imines in the presence of $NbCl_4(THF)_2$, can also be achieved (Scheme 42, eq 49).[116]

Scheme 42. Silyl imines as electrophiles.



[112] a) Cainelli, G.; Panunsio, M.; Giacomini, D.; Martelli, G.; Spunta, G. *J. Am. Chem. Soc.* **1988**, *110*, 6879. b) Andreoli, P.; Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *J. Org. Chem.* **1991**, *56*, 5984. c) Bandini, E.; Cainelli, G.; Giacomini, D.; Martelli, G.; Panunzio, M.; Spunta, G. *Gazz. Chim. Ital.* **1993**, *123*, 509. d) Bandini, E.; Cainelli, G.; Giacomini, D.; Martelli, G.; Panunzio, M.; Spunta, G. *Bioorg. Med. Chem. Lett.* **1993**, *123*, 2347.

[113] For other examples, see reference 77.

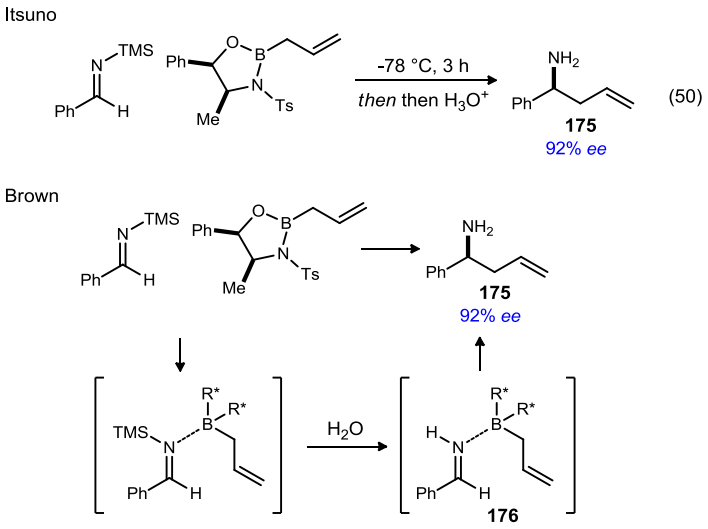
[114] a) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T.-K. *J. Org. Chem.* **1983**, *48*, 289. b) Itsuno, S.; Sasaki, M.; Kuroda, S.; Ito, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1507. c) Fraser, R. R.; Banville, J. *J. Chem. Soc., Chem. Commun.* **1979**, 47.

[115] a) Cainelli, G.; Giacomini, D.; Mezzina, E.; Panunzio, M.; Zarantonello, P. *Tetrahedron Lett.* **1991**, *32*, 2967. b) Cainelli, G.; Giacomini, D.; Panunzio, M.; Zarantonello, P. *Tetrahedron Lett.* **1992**, *33*, 7783. c) Cainelli, G.; Giacomini, D.; Walzl, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2150. d) Cainelli, G.; Giacomini, D.; Trere´, A.; Galletti, P. *Tetrahedron: Asymmetry* **1995**, *6*, 1593. e) Bongini, A.; Camerini, R.; Hofman, S.; Panunzio, M. *Tetrahedron Lett.* **1994**, *35*, 8045.

[116] a) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 6551. b) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 3152.

The enantioselective allylboration of *N*-silyl imines was reported by Itsuno, in 1997 to give homoallylamines (**175**) in good enantioselectivity (Scheme 43, eq 50).[117] However, several years later Brown, trying to repeat Itsuno's work, discovered that the allylation actually occurred during reaction work-up.[118] He later proved that upon hydrolysis or methanolysis, the *N*-silyl imine was deprotected to give the *N*-unsubstituted organoborane adduct (**176**).[119] It was through this intermediate, which could be isolated and was stable at room temperature, that the allylation occurred.

Scheme 43. Enantioselective allylboration using silyl imines.



Recent uses of *N*-silyl amines include their palladium coupling to aryl bromides to afford the *N*-aryl imines (**177**) (Scheme 44, eq 51).[120] They have also been used in the multicomponent synthesis of propargyl amides (**178**) (Scheme 44, eq 52).[121]

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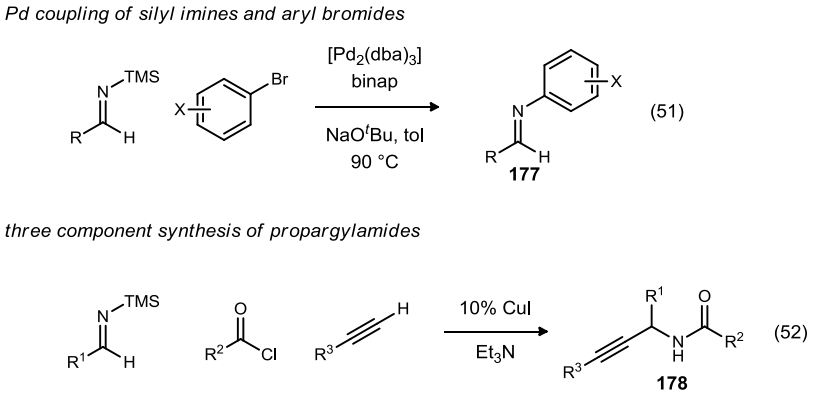
[117] a) Itsuno, S.; Watanabe, K.; Ito, K.; El-Shehawy, A. A.; Sarhan, A. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 109. b) El-Shehawy, A. A.; Abdelaal, M. Y.; Watanabe, K.; Ito, K.; Itsuno, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1731.
[118] Chen, G. –M.; Ramachandrran, P. V.; Brown, H. C. *Angew. Chem. Int. Ed.* **1999**, *38*, 825.
[119] Chen, G. –M.; Brown, H. C. *J. Am. Chem. Soc.* **2000**, *122*, 4217.
[120] Barluenga, J.; Aznar, F.; Valdes, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 343.
[121] Black, D. A.; Arndtsen, B.A. *Tetrahedron* **2005,** *61*, 11317.

Scheme 44. Recent applications of silyl imines.



3.2 Enantioselective aza-Henry Addition to N-Silyl Imines

As mentioned previously, work in this area began with the hope of incorporating an *N*-protecting group into the enantioselective aza-Henry reaction which was more widely used in peptide synthesis. Therefore, our initial aims were to simply make the *N*-fluorenylmethyloxy carbonyl (Fmoc) protected imine, and optimize the asymmetric addition of bromonitromethane to this compound. It was anticipated that incorporating different protecting groups into this chemistry would be a formidable challenge as the *N*-substituent plays a significant role in the reactivity and enantioselectivity seen in the aza-Henry reaction.

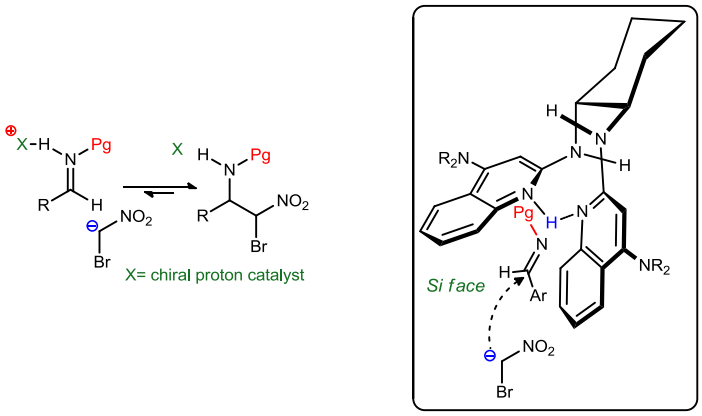
3.2.1 Reaction Discovery and Development

Importance of the Imine Protecting Group

There are several requirements a substituent must fulfill in order to be a successful *N*-protecting group in the asymmetric aza-Henry reaction. It must be able to activate the imine towards nucleophilic addition as well as stabilize the resulting adduct. It is for this reason that electron withdrawing functionalities, such as the Boc group, work

so well in this reaction. It has been seen that Boc imines react much faster than alkyl imines and due to the resonance stability they offer to the resulting adduct, the retro aza-Henry is rarely seen. The *N*-protecting group will also affect how the imine sits in the chiral pocket of the catalyst (Figure 10).[122] Therefore, the enantioselective addition of bromonitromethane would have to be optimized for each different protecting group used.

Figure 10. Importance of *N*-protecting group in the aza-Henry reaction.



It is for these reasons that use of a silyl *N*-protecting group was not initially considered; it was assumed that they would offer little by means of activation or stabilization as the N-Si bond is rather weak and not highly polarized.[123] Therefore, attention was instead turned to *N*-Fmoc-protected imines. This protecting group would offer the same advantages of a Boc protecting group, but is widely used in peptide synthesis.

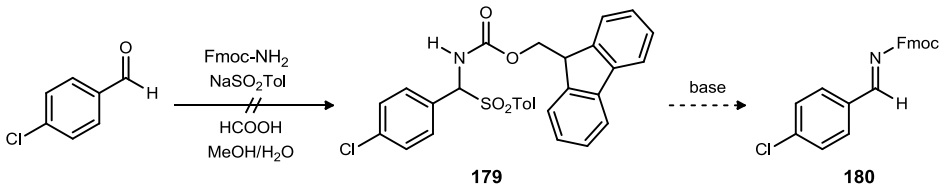
Synthesis and Coupling of N-Fmoc-α-Bromo Nitroalkane

In order to incorporate the Fmoc-protecting group into the aza-Henry reaction the *N*-Fmoc-imine must first be synthesized, a task that proved to be more difficult than expected. Attempts were made to synthesize the Fmoc-protected sulfone (**178**), as

[122] Yoder, R. A.; Nugent, B. M.; Singh, A.; Smith, T. A.; Johnston, J. N. *unpublished results.*
[123] Jensen, J. H.; Carroll, M. T.; Gordon, M. S. *Organometallics* **1991**, *10*, 2657.

subsequent treatment of this compound with base would result in elimination to the Fmoc-imine (**179**) (Scheme 45). While this transformation occurs quite readily when the Boc protecting group is employed, the Fmoc-sulfone was never able to be synthesized as the reaction returned only starting materials.

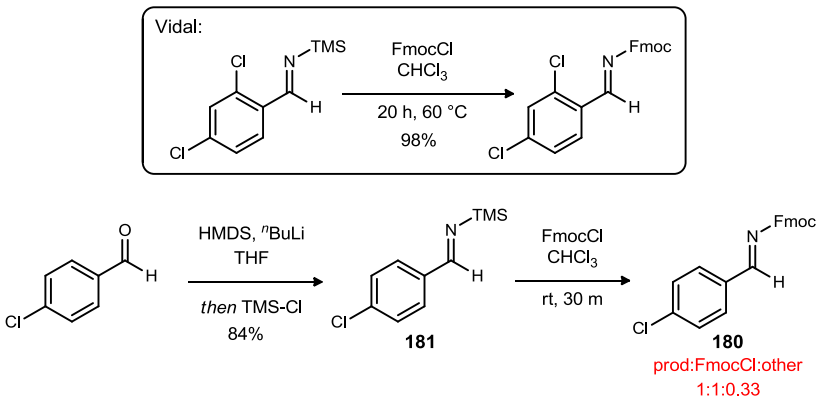
Scheme 45. Attempts to synthesize the Fmoc-protected sulfone.



After trying a variety of conditions to synthesize the Fmoc-sulfone with no success, we turned to a procedure reported by Vidal and Collet[124] in which they acylate the TMS-imine with FmocCl, forming the Fmoc-imine in high yield (Scheme 46). Therefore, TMS-imine **181** was synthesized in good yield from the corresponding aldehyde, and treated it with FmocCl. Though our substrate (**181**) was very similar to the one reported in the literature, in our hands this reaction did not go cleanly to Fmoc-imine (**180**) under a variety of conditions. It seemed as though the TMS-imine was decomposing as a 1:1 mixture of product to unreacted FmocCl was always seen, accompanied by other unidentifiable side products (Scheme 46).

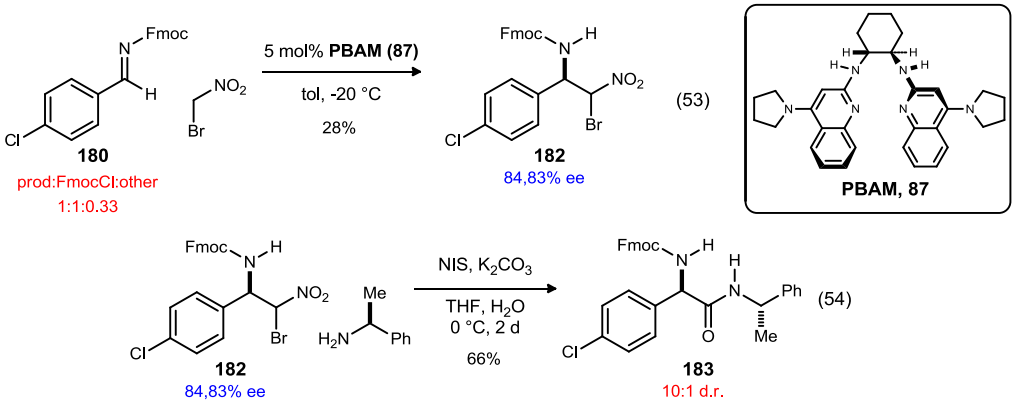
[124] Vidal, J.; Collet, A. *Chem. Eur. J.* **1997**, *3*, 1691.

Scheme 46. Synthesis of the Fmoc-imine from the TMS-imine.



Unfortunately, the Fmoc-imine (**180**) which had formed was not able to be purified, as it was extremely moisture sensitive. Therefore, this imine was taken on as a crude mixture and subjected it to asymmetric aza-Henry reaction conditions (Scheme 47, eq 53). Gratifyingly, we were able to obtain the Fmoc-α-bromo nitroalkane adduct (**182**), though in low yield (28%), as a mixture of diastereomers each with high ee (84, 83%). This adduct was then coupled with methyl benzyl amine under umpolung amide synthesis (UmAS) conditions (Scheme 47, eq 54). There was some concern about the compatibility of the Fmoc protecting group with the slightly basic UmAS conditions, as this protecting group is deprotected under basic conditions. However, these were soon laid to rest- the dipeptide **183** was obtained in 66% yield, with no detectable deprotection.

Scheme 47. Synthesis and coupling of *N*-Fmoc-α-Bromo Nitroalkane **182**.

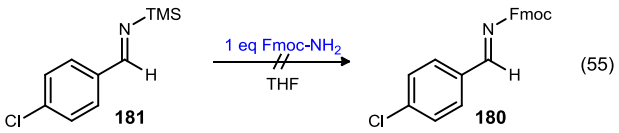


A second concern was that the Fmoc-adduct could possibly be deprotected by the basic chiral proton catalyst (PBAM, **87**, Scheme 47) used to affect the transformation. However, stirring both **182** and **183b** with a full equivalent of catalyst **87** at room temperature resulted in no detectable deprotection over the time period of the aza-Henry reaction (1 day).

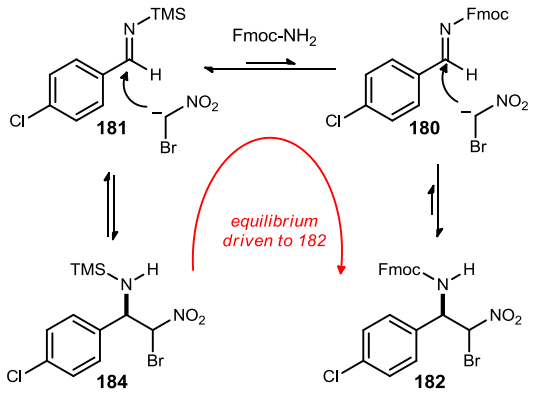
Discovery and Optimization of aza-Henry Addition to N-TMS Imines

While it was exciting that the Fmoc-α-bromo nitroalkane adduct (**182**) could be synthesized in good enantiomeric excess and successfully coupled under UmAS conditions, other routes to the Fmoc-imine (**180**) were explored in the hopes of increasing the overall yield of the Fmoc-adduct. Since TMS-imine (**181**) was on hand, a transamination between this compound and Fmoc-NH_2 was attempted. Unfortunately, only starting materials were observed in this reaction, even after stirring at room temperature for several days (Scheme 48).

Scheme 48. Attempt at *trans*-imination.



hypothesis: if small amounts of the FMOC-imine are forming, can we trap it with BNM?

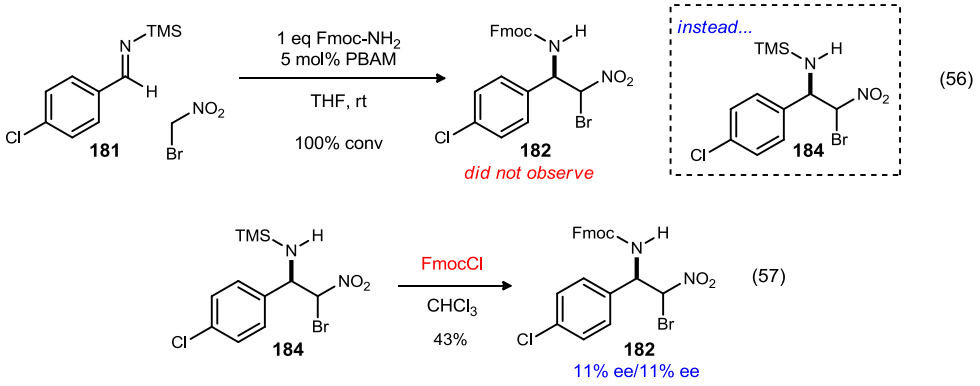


It was thought the Fmoc-imine could possibly be forming in this reaction, but only in trace amounts. The transimination reaction would be a reversible one and if the equilibrium were to lie on the side of the TMS-imine, Fmoc-imine production might not be detectable. To see if this was the case, PBAM (**87**) and bromonitromethane were added to this reaction. The hypothesis was that while bromonitromethane could add to either imine (**181** or **180**), it would be more likely to add to the Fmoc-imine (**180**). Additionally, while addition to the Fmoc-imine would be reversible, it was hypothesized that equilibrium would lie towards the addition product. In the addition to the TMS-imine (**181**), however, it was unclear whether the reaction equilibrium would favor the reactants or the product. Therefore, if any of **180** was being formed, the equilibrium should be driven by the addition to this compound, giving the Fmoc-adduct (**182**) (Scheme 48).

What was observed in this reaction was unexpected. The TMS-imine (**181**) was completely consumed, however none of the Fmoc-adduct (**182**) was observed. Instead, it

appeared that the bromonitromethane had added to the TMS-imine, giving the TMS-adduct **184** (Scheme 49, eq 56). This was confirmed when the product was treated with FmocCl and production of the Fmoc-α-bromo nitroalkane adduct (**182**) was seen (Scheme 49, eq 57). Surprisingly, the enantiomeric excess of this adduct was found to be 11% for each diastereomer. While low, this indicated that the aza-Henry addition to the TMS-imine had the potential to be an asymmetric one.

Scheme 49. Attempts to trap Fmoc-imine: First observation of aza-Henry addition to TMS-imine.

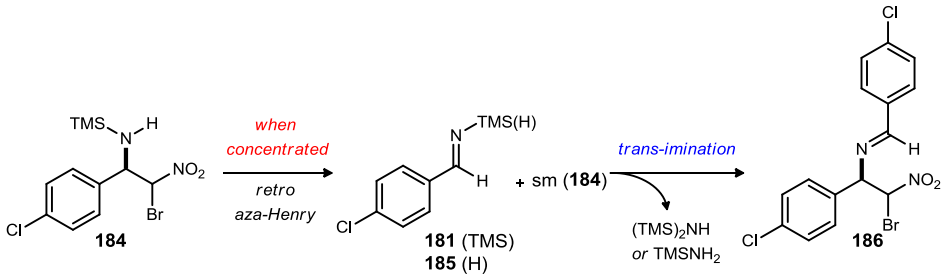


The utility of this transformation, if it was able to be optimized, was immediately clear. Any number of different acylating reagents could be used to trap the resulting TMS-amine adduct, allowing us access to a multitude of protected α-bromo nitroalkane donors. It was for this reason optimization of the aza-Henry addition of bromonitromethane to TMS-imines was pursued.

It was immediately apparent that the TMS-amine adduct could not be isolated. While it can be observed by ^{1}H and ^{13}C NMR and seems to be stable when dilute, concentration of this intermediate leads to rapid formation of imine **186**. It is thought that this occurs when some of the adduct **184** undergoes a retro aza-Henry reaction, to give

back either the TMS-imine or the unprotected imine (**185**). A transimination between **181** or **185** and remaining TMS-adduct **184** then results in the production of **186** (Scheme 50).

Scheme 50. Undesired transimination.

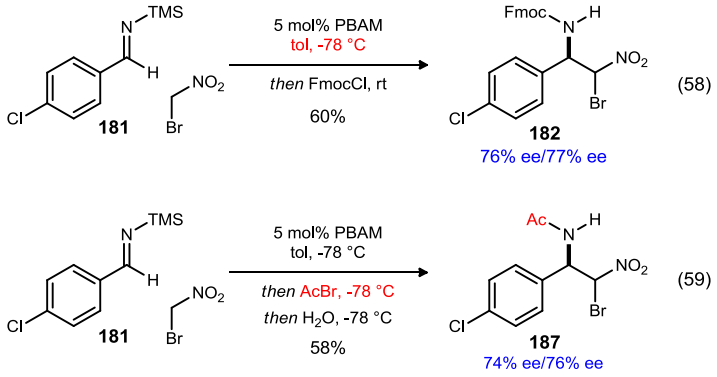


It was therefore realized the TMS-amine adduct (**184**) needed to be trapped by FmocCl *in situ*, before solvent removal. A one pot reaction in which the TMS-imine (**181**), PBAM catalyst (**87**, Scheme 47) and bromonitromethane were stirred at -78 °C in toluene for 24 hrs before addition of FmocCl was attempted (Scheme 51, eq. 58). It was exciting to see that this resulted in an increased yield (60%) and enantiomeric excess (76, 77% for each diastereomer) of the Fmoc-α-bromo nitroalkane adduct (**182**).

However, it was found that the FmocCl was not reactive towards the TMS-amine at low temperatures; the reaction had to be warmed to room temperature for acylation to occur. If the aza-Henry addition to the TMS-imine was not complete before warming the reaction, a portion of the addition could be occurring at a higher temperature which would result in lower enantioselectivity. Therefore, an acylating reagent was required which would be reactive enough to acylate the TMS-amine adduct at -78 °C. It was found that acetyl bromide could be used for this purpose. By keeping the reaction at -78 °C and quenching with water before warming to room temperature, an accurate picture of the reactivity and enantioselectivity of this reaction could be obtained. It was found that the addition to imine **181** was complete in 20 hours, as the Ac-α-bromo nitroalkane adduct

(**187**) was isolated in 58% yield and 74, 76% enantiomeric excess, which was comparable to that of the Fmoc-α-bromo nitroalkane adduct (**182**) (Scheme 51, eq 59).

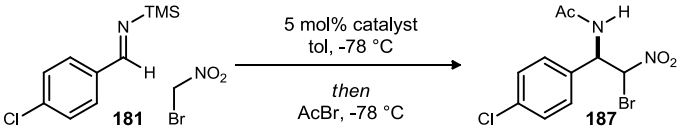
Scheme 51. Initial optimization.



A comprehensive catalyst screen was then undertaken in order to ascertain whether another catalyst might give the desired adduct in higher enantiomeric excess. Initially, the triflic acid salts of PBAM (**87**) were examined. While in other aza-Henry reactions to Boc-imines it had been observed that the protonated catalysts were more active and gave higher enantioselection than the unprotonated catalysts, the opposite was true in this chemistry. The 1:1 PBAM·HOTf salt (**87**·HOTf) gave significantly lower conversion and enantiomeric excess (Table 7, entry 2) than the free base (**87**, Table 7, entry 1). Interestingly, the 2:3 salt (**87**$_2$(HOTf)$_3$), Table 7, entry 3) performed even worse, giving results very similar to those of the unactivated H, Quin-BAM (**85**, Table 7, entry 4). This suggested that the increased Brønsted basicity of PBAM was vital to this reaction. Therefore, other PBAM derivatives (**188-191, 193-198**, Table 7, entries 5-8, 11-

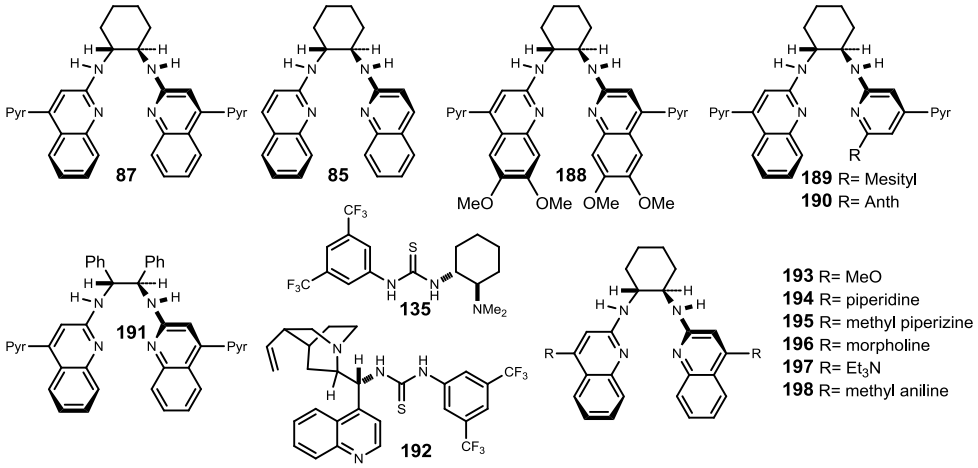
16) were utilized,[125] though none gave higher enantioselection than PBAM. Several thiourea catalysts (**135,192**)[89,126] were also used, with poor results (Table 7, entries 9-10).

Table 7. Catalyst screen.



entry	catalyst	% conv[b]	% yield	d.r.[c]	% ee
1	PBAM (**87**)	94	58	2:1	74,76
2	PBAM•HOTf 1:1	51	19	2:1	60,61
3	PBAM•HOTf 2:3	41	10	2:1	38,40
4	H-Quin-BAM (**85**)	47	18	1.5:1	33,32
5	6,7-MeO-PBAM (**188**)	94	61	1.3:1	67,68
6	Mesityl-PBAM (**189**)	86	51	1.5:1	18,18
7	Anth-PBAM (**190**)	93	47	1.7:1	35,32
8	Stilb-PBAM (**191**)	92	42	1:1	37,36
9	Takemoto Thiourea (**135**)	84	42	1.2:1	-16,-17
10	Deng Thiourea (**192**)	82	34	1:1	8,3
11	4-MeO-BAM (**193**)	70	17	2.8:1	24,23
12	4-Pipe-BAM (**194**)	67	11	2:1	29,30
13	4-Mpz-BAM (**195**)	80	40	2:1	42,43
14	4-Morpho-BAM (**196**)	54	20	1.7:1	25,26
15	4-NEt_2-BAM (**197**)	42	2	1.4:1	17,18
16	MAN-BAM (**198**)	80	31	2:1	39,41

a) Imine stirred with 1.2 equiv of bromonitromethane and 5 mol% catalyst for 16 h at -78 °C. Reactions were then quenched with excess H_2O at -78 °C after stirring with acetyl bromide for 2 h. *b*) Conversions based on aldehyde resulting from imine hydrolysis. *c*) Diastereomeric ratio based on crude ^1H NMR analysis.

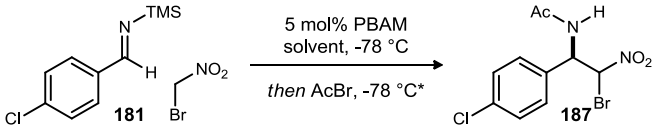


With no catalyst able to out-perform PBAM, we next turned to a solvent screen (Table 8). A number of solvents were tested, and while no solvent performed better than

[125] Singh, A.; Davis, T. A.; Dobish, M. C.; Johnston, J. N. *unpublished results.*
[126] Han, B.; Liu, Q. –P.; Li, R.; Tian, X.; Xiong, X. –R.; Deng, J. –G.; Chen, Y. –C. *Chem. Eur. J.* **2008**, *14*, 8094.

toluene, Et_2O and methyl ^{t}butylether (MTBE) (entries 3 and 4, respectively) gave comparable levels of enantioselection (Table 8, entry 1), but low isolated yields, of the adduct **187**. It should be noted that at this time a small jump in enantiomeric excess was observed under standard reaction conditions (from 74, 76% to 84, 82%). This is attributed to the handling of the TMS-imine. While silyl imines are stable at low temperatures, they are very moisture and temperature sensitive. By taking the imine into the glovebox (an inert Ar atmosphere), it could be stored and measured out under cool, anhydrous conditions which resulted in less decomposition and/or hydrolysis. Fortunately, this increase in purity of the imine seems to translate into increased enantioselectivity (Table 8, entry 1).

Table 8. Solvent screen.



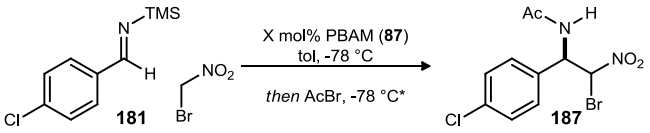
entry	solvent	% conv[b]	% yield	d.r.[c]	% ee
1	tol	100	56	1.5:1	84,82
2	DCM	97	45	1:1	20,18
3	Et_2O	98	36	1:1.3	77,78
4	MTBE	90	45	1.6:1	79,79
5	MeOH	34	7	1:1	7,8
6	THF	88	21	1:1.4	20,18
7	hexane	44	3	1:1.3	63,60

a) Imine stirred with 1.2 equiv of bromonitromethane and catalyst for 16 h at -78 °C. Reactions were then quenched with excess H_2O at -78 °C after stirring with acetyl bromide for 2 h. *b*) Conversions based on aldehyde resulting from imine hydrolysis. *c*) Diastereomeric ratio based on crude ^{1}H NMR analysis.

Since no catalysts or solvents surveyed resulted in an increase in enantioselectivity, we next decided to look at the effect catalyst loading (of PBAM, **87**) had on the enantioselectivity of the addition. It was realized that due to their increased basicity (relative to Boc-amines and imines), the TMS-amine (**184**) or imine (**181**) could

be competing with PBAM to catalyze the aza-Henry reaction. Therefore, by increasing the catalyst loading, PBAM should become a more effective catalyst. As seen in Table 9, this was proved to be the case. By increasing the loading of PBAM to 20 mol% (entry 4), the ee of the desired adduct rose to 87, 88% (for both diastereomers). Additionally, it was seen that when no catalyst was used (Table 9, entry 1), some product was observed, though in very low amounts. This suggests that even at very low temperatures, there is a small background reaction in which PBAM is not necessary.

Table 9. Catalyst loading.



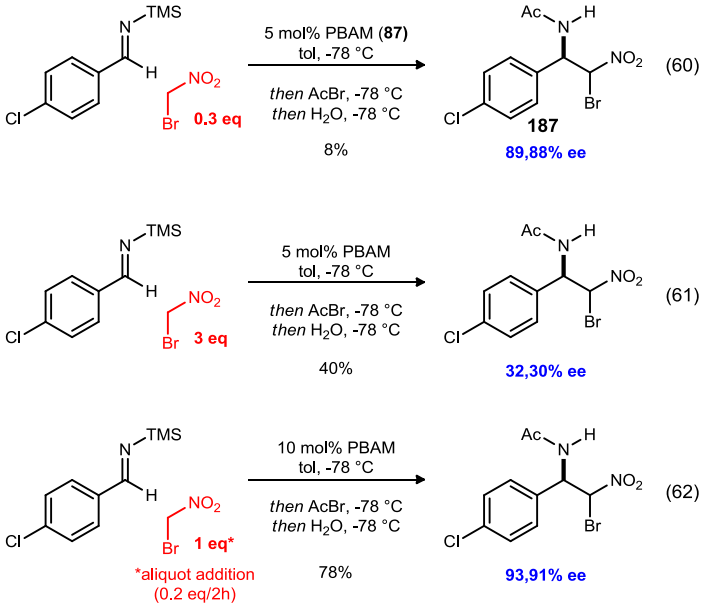
entry	X (mol%)	% conv[a]	% yield	d.r.[b]	% ee
1	0	<1	<1	3.7:1	0
2	5	100	56	1.4:1	84,82
3	10	99	42	1.4:1	84,85
4	20	99	44	1.5:1	87,88

a) Imine stirred with 1.2 equiv of bromonitromethane and catalyst for 16 h at -78 °C. Reactions were then quenched with excess H_2O at -78 °C after stirring with acetyl bromide for 2 h. *b*) Conversions based on aldehyde resulting from imine hydrolysis. *c*) Diastereomeric ratio based on crude ^1H NMR analysis.

Knowing that the TMS-amine (**184**) could be competitively catalyzing this reaction, we wished to determine if the enantioselectivity of this addition was greater towards the beginning of the reaction when the concentration of TMS-amine would be lowest. Therefore, 0.3 equivalents of bromonitromethane were added to imine **181** (Scheme 52, eq 60). After several hours, the bromonitromethane was consumed, with 30% conversion of **181**. The enantiomeric excess of this reaction was determined to be 89, 88% (for each diastereomer). Initially, this result suggested that our hypothesis was correct. However, when an excess of bromonitromethane was used (Scheme 52, eq 61) the result was a dramatic decrease in enantiomeric excess. Interestingly, these results

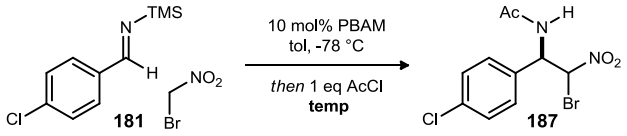
seemed to mirror the results obtained with the protonated PBAM catalysts (Table 7, entries 2 and 3). It was thought that perhaps the excess bromonitromethane was acting as an acid, protonating PBAM and decreasing its reactivity. To test this, a reaction was done in which bromonitromethane was kept at low concentration by adding it in aliquots over 8 hours. Gratifyingly, this slow addition resulted in increased enantioselection (93, 91%, both diastereomers) of the adduct **187** (Scheme 52, eq 62).

Scheme 52. Examining bromonitromethane concentration.



Satisfied with the enantioselectivity of this reaction, we next looked into optimizing the conditions of the acylation step. Up to this point, acetyl bromide had been used to acylate the TMS-amine at -78 °C. However, it was known that most acid chlorides or chloroformates would not react at such low temperatures. Therefore the acylation of TMS-amine **184** with acetyl chloride was tested at incremental temperatures. It was found that by raising the temperature of the acylation step to 0 °C, an optimal yield of 83% could be achieved (Table 10, entry 4).

Table 10. Optimization of acylation conditions.



entry	temp (°C)	% yield	d.r.[b]	%ee
1	-78	72	2:1	92,92
2	-40	58	3.6:1	91,92
3	-20	71	3.6:1	90,90
4	0	83	4:1	91,92
5	25	60	4:1	90.89

a) Bromonitromethane added in aliquots (0.2 eq/2 h) over 10 h to imine and catalyst at -78 °C. Reactions stirred overnight at -78° C before addition of acetyl chloride. Reaction then warmed to desired temperature and stirred for 24 h. *b*) Diastereomeric ratio based on crude ^{1}H NMR analysis.

3.2.2 Reaction Scope

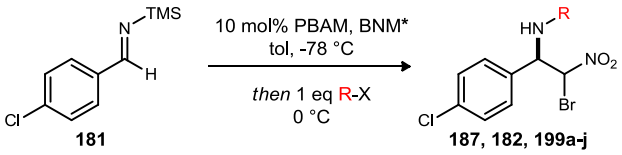
With the optimal conditions of both the asymmetric aza-Henry addition and subsequent acylation in place, the next step was to extend the scope of this reaction in regard to both the acylating reagents and TMS-imines used.

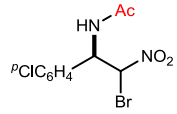
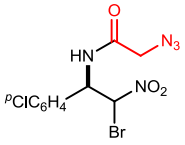
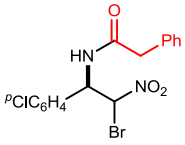
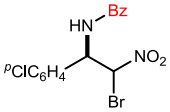
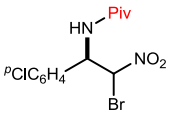
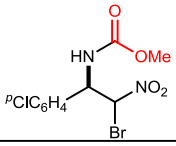
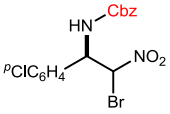
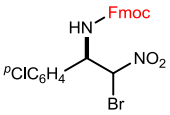
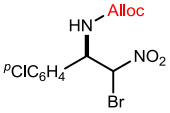
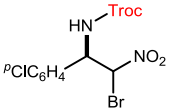
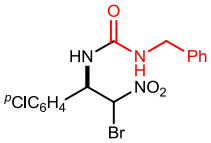
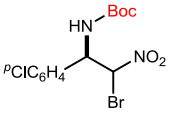
Protecting Group Scope

As seen in Table 11, a variety of different acid chlorides (entries 1-6) and chloroformates (entries 7-11) were used to trap the TMS-amine (**184**) in good yields (67-85%) and high to excellent ee (90-97%). Excitingly, using this procedure gives access to the acetate (Ac, **197**), phenylacetate (PhAc, **199a**), azidoacetate (N_3Ac, **199b**), benzoyl (Bz, **199c**), pivaloyl (Piv, **199d**), methoxy carbonyl (Moc, **199e**), carbobenzyloxy (Cbz, **199f**), fluorenylmethyloxy carbonyl (Fmoc, **182**), trichloroethyloxy carbonyl (Troc, **199g**) and allyloxy carbonyl (Alloc, **199h**) protecting groups. The use of benzyl isocyanate (Table 11, entry 12) and Boc anhydride (Table 11, entry 13) as trapping reagents gave the urea and Boc-protected adducts (**199i,j**), respectively, in good enantiomeric excess but poor yields. It seems that these substrates do not trap the TMS-amine substrate fast enough, as large amounts of the transimination side product **186**,

which results from the TMS-deprotection and retro aza-Henry reaction of **184**, were observed.

Table 11. Protecting group scope.



entry	R-X	product	yield	% ee
1	acetyl chloride		83 (**187**)	92,91
2	acetyl bromide		78 (**187**)	93,91
3	azidoacetyl chloride		82 (**a**)	91,91
4	phenylacetyl chloride		85 (**b**)	93,94
5	benzoyl chloride		70 (**c**)	94,95
6	pivaloyl chloride		67 (**d**)	96,97
7	methyl chloroformate		67 (**e**)	91,91
8	benzyl chloroformate		72 (**f**)	91,90
9	Fmoc chloride		76 (**182**)	91,91
10	allyl chloroformate		85 (**g**)	91,91
11	trichloroethyl chloroformate		83 (**h**)	92,91
12	benzyl isocyanate		33 (**i**)	92,86
13	Boc anydride		36 (**84**)	80,81

* aliqot addition over 10 h (0.2 eq every 2 h)

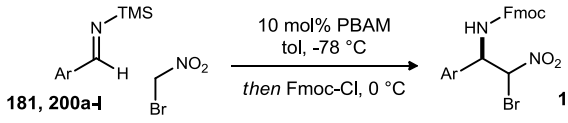
Particularly exciting was the fact that the *N*-N_3Ac-α-bromo nitroalkane (**199a**) was able to be synthesized in good yield (82%) and high enantiomeric excess (91,91%, each diastereomer) (Table 11, entry 2), as this compound could have applications in click chemistry,[127] or Staudinger ligation.[9]

[127] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.

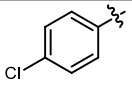
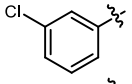
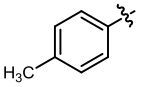
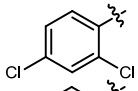
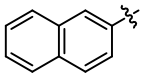
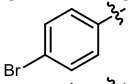
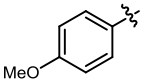
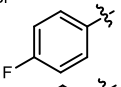
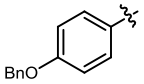
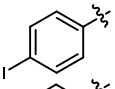
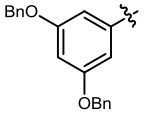
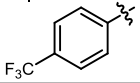
Imine Scope

The scope of the reaction as a function of the imine was next investigated. Initial results were very promising, as a variety of electron poor aryl imines worked well in this chemistry (Table 12, entries 1-7), giving the corresponding Fmoc-adducts (**182, 201a-1**) in good yields (64-83%) and high enantiomeric excess (76-91%). Also notable was the fact that *meta*- and *ortho*-substituted aromatic imines were well tolerated, with no loss in enantioselectivity (Table 12, entries 2-3)

Table 12. Imine scope.



181, 200a-l 182, 201a-l

entry	Ar	% yield	% ee[b]	entry	Ar	% yield	% ee
1		76 (**182**)	91,91	8		63 (**g**)	65,66
2		70 (**a**)	90,91	9		63 (**h**)	70,71
3		70 (**b**)	90,91	10		63 (**i**)	83,84
4		64 (**c**)	86,85	11		76 (**j**)	62,62
5		74 (**d**)	86,86	12[c]		74 (**k**)	-76,-74
6		83 (**e**)	88,88	13[d]		61 (**l**)	79,82
7		66 (**f**)	80,76				

a) Bromonitromethane added in aliqot additions over 10 h (0.2 eq every 2 h) to the imine and catalyst at -78 °C before stirring overnight. Fmoc-Cl added and reaction warmed to 0 °C before stirring for 24 h. *b*) Product isolated as 1:1 mixture of diastereomers; enantiomeric excess reported for the major, minor diastereomer. *c*) The (*S,S*)-PBAM catalyst was used. *d*) Reaction performed on 400 mg scale.

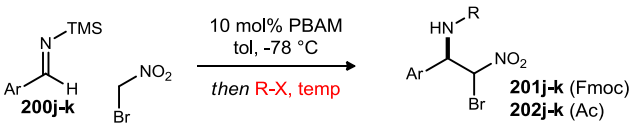
However, when electronically neutral and electron rich imines were examined, a drop in enantioselection was observed. The electronically neutral phenyl imine (**200g**) and the electron rich 4-methoxy aryl imine (**200j**) gave the lowest levels of

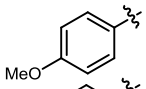
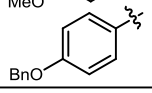
enantioselection (65, 66% and 62, 62%, Table 12, entries 8 and 11). Curiously, the enantioselection seemed to increase with bulkier electron neutral and electron rich imines, allowing for the synthesis of the 2-naphthalene (**201i**) and 3,5-dibenzyloxy (**201l**) α-bromo nitroalkanes in enantiomeric excesses comparable to those seen with electron poor substrates (83, 84% and 79, 82%, Table 12, entries 10 and 13). However, we were pleased to see the use of (*S,S*)-PBAM allowed us access to the *S*-enantiomer of the α-bromo nitroalkanes (Table 12, entry 12), and that this chemistry was amenable to scale-up (Table 12, entry 13).

Electron Rich Imines: Mechanistic Studies

In order to understand why lower levels of enantioselection were observed with electron rich substrates, we investigated these reactions further. It was hypothesized that the aza-Henry addition to electron neutral and electron poor imines might be slower, since the imines should be less reactive electrophiles. If this were the case, the reactions would not have reached full conversion before warming to room temperature. Therefore, the acetyl protected products of the ^{p}MeO and ^{p}BnO aryl aldimines **(202j**, **k**) were synthesized by quenching the reactions at -78 °C (Table 13, entries 1 and 2). While neither reaction had reached 100% completion, the conversions were higher than expected (93 and 80%, respectively). Disappointingly, the enantioselection observed in these reactions was only slightly higher in the case of the ^{p}MeO substrate (**202j**, 70, 69%), and lower in the case of the ^{p}BnO substrate (**202k**, 61, 67%).

Table 13. Imine scope: electron rich imines quenched at -78 °C.

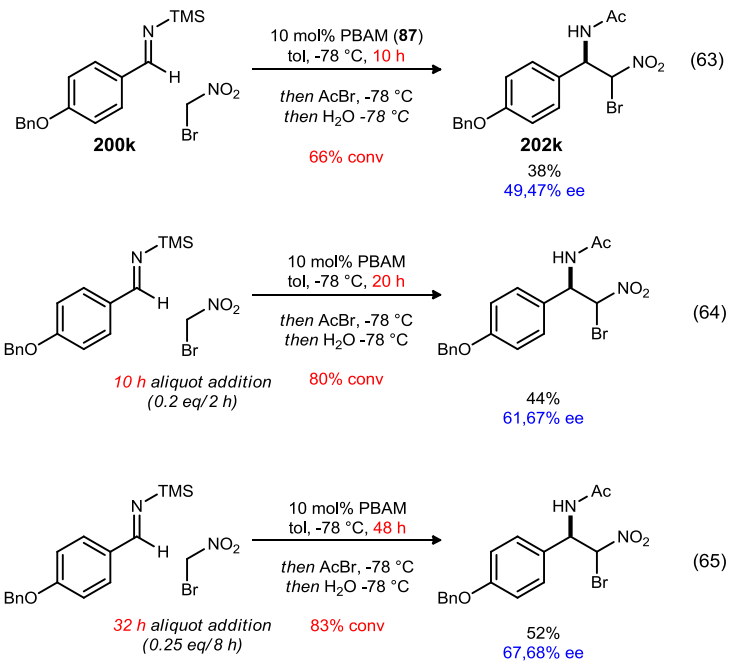


		Fmoc-Cl, 0 °C		AcBr, -78 °C		
entry	Ar	% yield	% ee[b]	% conv[c]	% yield	% ee[b]
1		76 (**j**)	59,62	93	61 (**j**)	70,69
2		66 (**k**)	72,74	80	44 (**k**)	61,67

a) Bromonitromethane added in aliqot additions over 10 h (0.2 eq every 2 h) to the imine and catalyst at -78 °C before stirring overnight. Acetylating agent was then added. *b*) Product isolated as 1:1 mixture of diastereomers; enantiomeric excess reported for the major, minor diastereomer. *c*) Reaction quenced at -78 °C with excess H_2O. Conversion based on aldehyde resulting from imine hydrolysis.

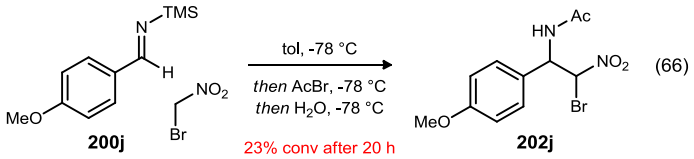
While it appeared that the lower enantioselection was not a result of warming the reaction too soon, it was clear that these reactions were slightly slower. This is especially true in the case of the ^{p}BnO imine (**200k**)- after 10 h, the timeframe over which bromonitromethane is added, the addition to this imine had only reached 66% conversion (Scheme 53, eq 63). It was therefore thought that perhaps the aliquot addition of bromonitromethane was being done over too short of a time period. If the added 0.2 equivalents of this reagent was not given sufficient time to react before the next addition, the concentration of bromonitromethane would gradually build, leading to decreased enantioselectivity. Therefore, a reaction was done in which bromonitromethane was added in aliquots over 32 hours to imine **200k** (Scheme 53, eq 65). While the yield of adduct **202k** was slightly improved, the enantiomeric excess remained relatively unchanged from the 8 hour addition reaction (Scheme 53, eq 64).

Scheme 53. Further work with ^{p}BnO-imine.



It was therefore clear that something other than the low reactivity of these substrates was contributing to the decrease in enantioselection. At this point, it was realized that the rate of the uncatalyzed background reaction in the addition to electron rich imines had not yet been examined. It was known that the addition of bromonitromethane to both electron rich and electron poor TMS-imines occurs quite readily at room temperature, without the need for an added base. However, with electron poor imines this background reaction was almost negligible at -78 °C (Table 9, entry 1). Because electron rich imines seemed to be less reactive, it was assumed that the background reaction would be comparable to, if not slower than, what was seen in electron deficient imines. However, a surprising result was observed in the reaction of ^{p}MeO TMS-imine **200j** with bromonitromethane at -78 °C, in the absence of PBAM. A significant amount of the ^{p}MeO Ac-adduct **202j** was seen (23% conversion at 20 hours, Scheme 54, eq 66).

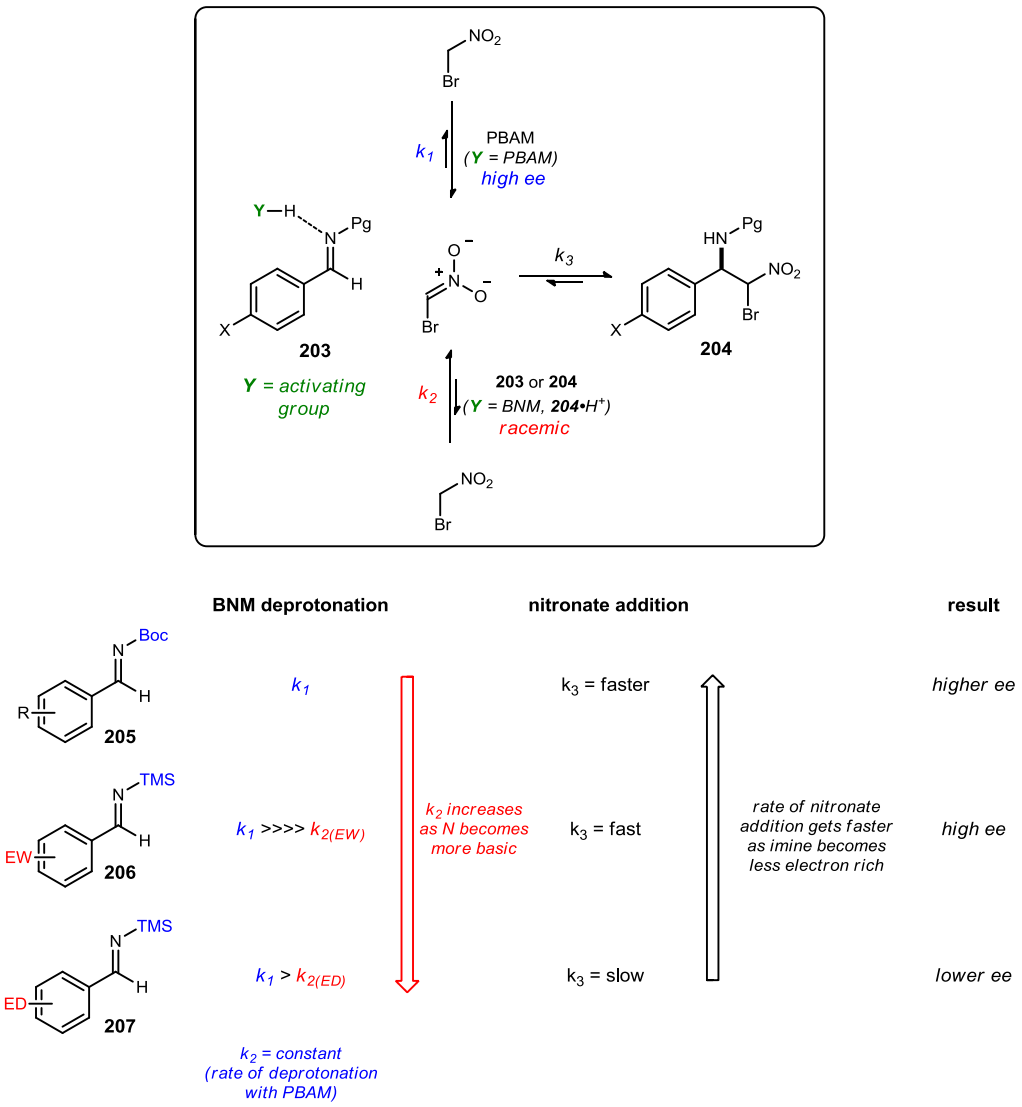
Scheme 54. Measurement of the non-catalyzed reaction rate by conversion using an electron rich imine.



(66)

The aza-Henry reaction involves the addition of nitronate to an activated imine **203**. In order to form these two reactive intermediates, PBAM deprotonates bromonitromethane at a rate assigned here as k_1 (Figure 11). This complex can activate the imine through hydrogen bonding (Lewis acid- Lewis base complexation). The three dimensional nature of this catalyst-substrate complex is the source of stereocontrol in the addition step. In the case of Boc-imines (**205**), this addition is presumably fast. However, the silyl imines (**203**) are more basic at the nitrogen of the imine, and the addition product **204** is more basic as well. These two (**203**, **204**) may be able to compete with PBAM in the deprotonation of bromonitromethane, at a rate assigned as k_2. This competing deprotonation reaction, the rate of which would be higher in electron rich imines (**207**), would result in activation of the imine by either bromonitromethane or the protonated amine intermediate (**204**·H^+), leading to nonselective addition.

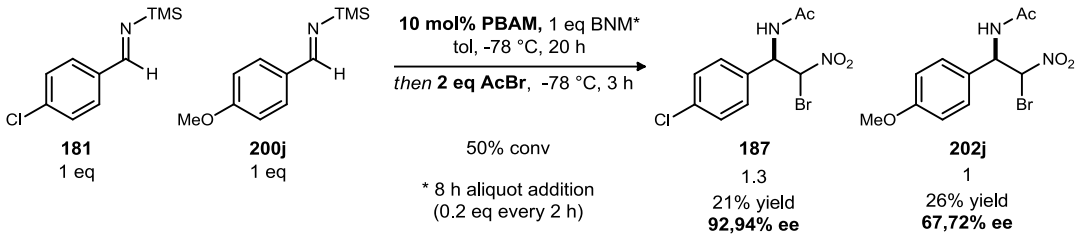
Figure 11. Mechanistic hypothesis of observed reactivity and enantioselection.



In order to determine if the protonated product (**204**·H^+) was catalyzing the addition reaction, a competition reaction was performed between the ^{p}Cl and ^{p}MeO aryl imines. By adding a single equivalent of bromonitromethane to 1 equivalent of the ^{p}Cl imine **181** and 1 equivalent of the ^{p}MeO imine **200j**, we sought several relative rates. By observing the relative amounts of the products formed (**187**, **202j**), it would be possible to directly compare the differences in reactivity between the two imines. Additionally, by observing the enantiomeric excess of each product, insight could be gained into the

mechanism leading to low levels of enantioselection with electron rich imines. If the product of the aza-Henry addition with these imines (**204**•H^+, or **202j** in this example) was indeed catalyzing the reaction, a similar decrease in the enantiomeric excess of the ^{p}Cl addition product (**187**) should be observed.

Scheme 55. Competition reaction between ^{p}Cl imine **181** and ^{p}MeO imine **200j**.



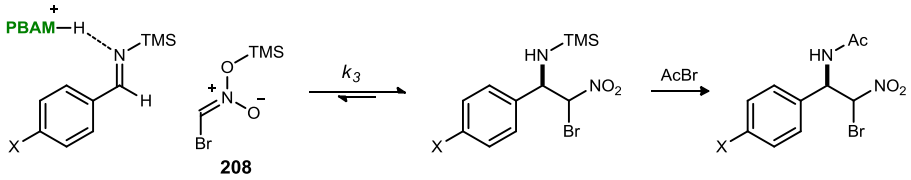
After subjecting **181** and **200j** to standard addition conditions for 3 hours, they were quenched with acetyl bromide.^{1}H NMR analysis of the crude reaction mixture indicated that the addition had gone to 50% completion, with a 1.3:1 ratio of the products **187** and **202j**. This indicated that the reactivities of these two imines were very similar, with the ^{p}Cl imine reacting slightly faster. When these products were isolated, and the enantiomeric excess determined for each compound, it was surprising to see that the levels of enantioselection observed were essentially the same as what we had seen in previous reactions. The two diastereomers of the ^{p}Cl α-bromo nitroalkane **187** were formed in 92 and 94% ee, respectively, and the two diastereomers of the ^{p}OMe α-bromo nitroalkane **202j** were formed in 67 and 72% ee, respectively (Scheme 55). Therefore, the product **202j** is not catalyzing non-selective aza-Henry addition. It is also not the case that the low levels of enantioselectivity observed with electron rich imines are due to a large difference in reactivity. Instead, it seems that it is the increased basicity of the imine

nitrogen that is problematic. Based on these results, we hypothesize that the competing pathway in which bromonitromethane is deprotonated by the imine, activating it towards non-selective addition, is leading to lower levels of enantioselectivity.

This reaction mechanism is also able to explain some of the trends seen with addition to TMS-imines. PBAM, the most Brønsted basic of the BAM catalysts, was the only catalyst which was able to give high levels of enantioselectivity, most likely because it was able to deprotonate bromonitromethane at a much faster rate (increased k_1). Protonation of this catalyst resulted in low levels of enantioselection, as it decreased the basicity of the catalyst (decreased k_1). High concentrations of bromonitromethane also resulted in decreased enantioselectivity. This could be due to the fact that when the concentration of this substrate was higher than that of PBAM, more was deprotonated through the undesired pathway (k_2), as catalyst turnover (k_3, nitronate addition and regeneration of the PBAM free base) would likely be slow.

In order to overcome this background reaction, several options were considered. The first was to decrease the temperature of the reaction, thereby increasing the rate difference between k_1 and k_2, in favor of the enantioselective k_1 pathway. However, this reaction was already done at -78 °C, and performing a reaction at even lower temperatures over the timespan needed for addition was unpractical. The second option was to try to eliminate k_1 and k_2 altogether. We wished to do this by using the silyl-nitronate **208** in place of bromonitromethane (Scheme 56). Eliminating k_1 and k_2 would hopefully give us a true picture of the addition step (k_3) for electron rich TMS-imines. With this reaction setup, the protonated catalyst PBAM·HOTf would have to be used to activate the imine, hopefully in an exclusive manner.

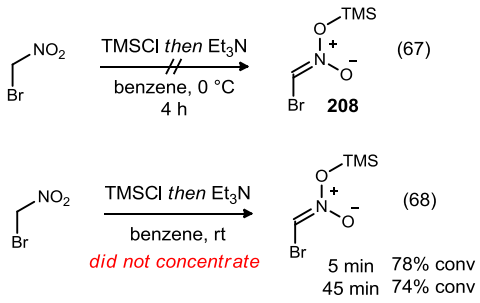
Scheme 56. Using silyl nitronates to eliminate k_1 and k_2.



eliminate k_1 and k_2 by using the silyl nitronate and a protonated catalyst

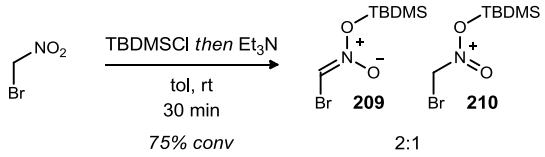
In order to do this, nitronate **208** must first be synthesized. Our first attempt involved treating bromonitromethane first with TMSCl and then triethylamine, in benzene. After concentrating the crude reaction mixture, ^{1}H NMR analysis showed only starting material (Scheme 57, eq 67). It was thought that perhaps the product was forming, but was reverting to starting material upon concentration. Therefore, the same reaction was performed in which an aliquot was taken from the reaction and observed by ^{1}H NMR prior to concentration. We were pleased to see that the desired product **208** was present and that the reaction had reached 78% conversion after 5 minutes. Unfortunately, after letting the reaction stir for an additional 40 minutes, we observed a slight decrease in conversion (Scheme 57, eq 68).

Scheme 57. Attempts to make silyl nitronate **208**.



Several other reaction conditions were tried, none of which resulted in full conversion. Since concentration and purification of **208** was not possible, we attempted to synthesize a more stable silyl nitronate. After treating bromonitromethane with TBDMSCl and then triethylamine, nitronate **209** was observed as the major product, even after concentration (Scheme 58). Also present, however, was the TBDMS-protected nitroalkane **210**, as well as remaining starting material. Since this nitronate appeared to be more stable, an attempt was made to purify it by distillation. Unfortunately, the desired product distilled concomitantly with bromonitromethane, as well as TBDMSCl.

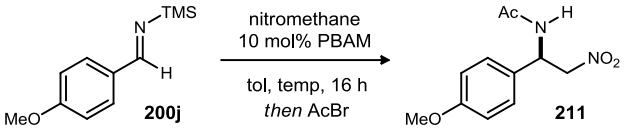
Scheme 58. Attempts to make silyl nitronate **209**.



Because nitronates **208** and **209** were not able to be synthesized in pure form, we weren't able to use them in the subsequent aza-Henry addition. In both cases, the main contaminant was bromonitromethane, which would react with imine and not allow accurate results to be obtained for the addition of the nitronate. Therefore, we next turned to other methods to attempt to slow the background reaction. The first was to use nitromethane in place of bromonitromethane. Because nitromethane is less acidic than bromonitromethane, it was thought that perhaps the nitrogen of the imine would not be sufficiently basic to deprotonate this reagent, thus eliminating the background reaction. Imine **200j** was treated with nitromethane under standard reaction conditions at -78 °C, but no conversion was observed after 16 hours (Table 14, entry 1). Therefore, the reaction was run at warmer temperatures. At -20 °C, only trace amounts of product were observed (Table 14, entry 2). At 0 °C and room temperature, the desired product **211**

could be isolated, but in low yield (16% and 20%, respectively) as well as low enantiomeric excess (20% and 19%, respectively).

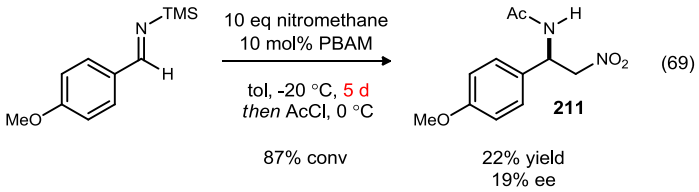
Table 14. Addition of nitromethane to ^{p}MeO imine **200j**.



entry	temp (°C)	% conv	% yield	% ee
1	-78	0	–	–
2	-20	trace	–	–
3	0	59	16	20
4	rt	95	20	19

Though the addition of nitromethane was slow at -20 °C, we wished to determine the enantioselection at that temperature. Therefore, a reaction was run in which the reactants were stirred at -20 °C for 5 days. Curiously, the results were very similar to those at higher temperatures, with a 22% yield and 19% enantiomeric excess (Scheme 59, eq 69).

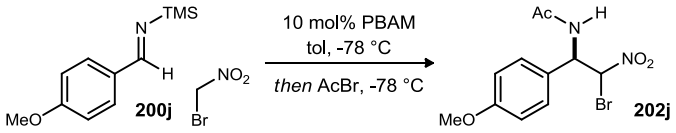
Scheme 59. Addition of nitromethane to ^{p}MeO imine **200j**.



The final attempt to overcome the background reaction was to try and add bromonitromethane to the reaction in even smaller aliquots. Because it seemed that the background reaction occurred to a greater extent when the concentration of bromonitromethane was higher, it was thought that if the concentration of this reagent was kept even lower in these reactions it may result in an increase in enantioselectivity.

When we added 0.1 equivalents of bromonitromethane every hour, as opposed to 0.2 equivalents, we saw a decrease in yield and no change in enantiomeric excess (Table 15, entry 2). Adding bromonitromethane in even smaller portions, 0.05 equivalents every 30 minutes, raised the enantiomeric excess of the product by only 1% (Table 15, entry 3). It was therefore clear that the limiting the concentration of bromonitromethane past a certain extent was not beneficial.

Table 15. Addition of bromonitromethane in smaller aliquots.

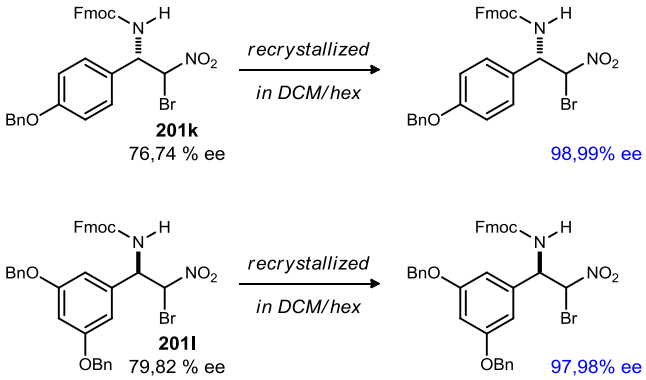


entry	rate of bromonitromethane addition	% yield	% ee[b]
1	0.2 eq/1 hr	61	70,69
2	0.1 eq/1 hr	40	70,69
3	0.05 eq/30 min	40	71,71

a) Bromonitromethane added to imine and catalyst at -78 °C in aliquots over the designated addition time. Reaction then stirred at -78 °C overnight before the addition of acetyl bromide. Reactions quenced at -78 °C with excess H_2O. *b*) Determined for each diastereomer.

Despite a background reaction seen with electron rich imines, it is worth noting that the present reaction conditions give levels of enantioselection that are synthetically useful. Using the case of poorest selectivity (^{p}OMe, 62, 62% ee, Table 12, entry 11), a 4:1 mixture of diastereomers would be anticipated after amide coupling. Additionally, we have found that many of the Fmoc-protected α-bromo nitroalkane adducts are able to be fractionally recrystallized to give the product as a single enantiomer (Scheme 60).

Scheme 60. Fractional recrystallization of Fmoc-protected α-bromo nitroalkane adducts.



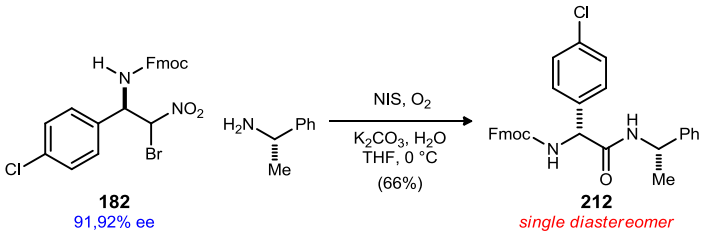
In this way, α-bromo nitroalkanes **201k** and **201l** were able to be obtained in very high levels of enantiopurity. These compounds were of special interest to us, as hydroxyphenylglycine and dihydroxyphenylglycine amino acids are found in a number of biologically active natural product peptides, such as the potent antibacterial compound vancomycin.[128]

3.2.3 UmAS Coupling of Protected α-Bromo Nitroalkane Donors

After synthesizing the protected α-bromo nitroalkanes, the next step was to submit them to umpolung amide synthesis (UmAS) coupling conditions in order to access the corresponding protected amino amides. It was exciting that the first adduct coupled, *N*-Fmoc-protected **182**, resulted in a good yield (66%) of the desired amide **212** (Scheme 61). There was some concern that the Fmoc protecting group would not survive the slightly basic conditions of this coupling, as it is typically deprotected with base (e.g. piperidine, morpholine, etc.); however, Fmoc cleavage was not detected in this case. It was also exciting to see that the dipeptide was isolated as a single diastereomer, again indicating that no epimerization occured at the otherwise acid aryl glycine residue.

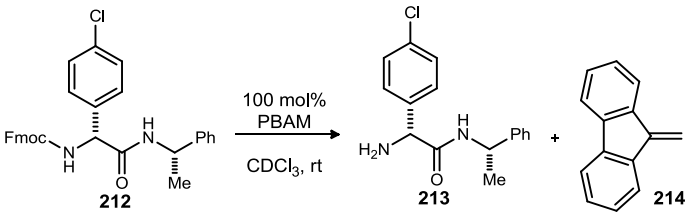
[128] McCormick, M. H.; Stark, W. M; Pittenger, G. E.; McGuire, G. M.; *Antibiot. Annu.* **1955**, 606.

Scheme 61. Umpolung amide coupling of *N*-Fmoc-protected α-bromo nitroalkane **182**.



While no signs of Fmoc-deprotection were seen in the coupling of **182**, several NMR studies were done to determine the stability of product **212** to both aza-Henry reaction conditions and UmAS reactions conditions. To do this, **212** was first stirred with a full equivalent of PBAM in $CDCl_3$ at rt. After one day, no Fmoc protection was observable (Table 16, entry 1). However, after 3 days approximately 7% and 13% deprotection were measured at 3 and 5 days, respectively (Table 16, entries 2 and 3). While this shows that the catalyst PBAM is sufficiently basic to deprotect an Fmoc group, it does so slowly. Therefore, under the standard aza-Henry reaction conditions and times (10 mol% PBAM, 0 °C, 24 h) it is most likely that little to no Fmoc-deprotection occurs.

Table 16. Determining Fmoc-deprotection by PBAM.

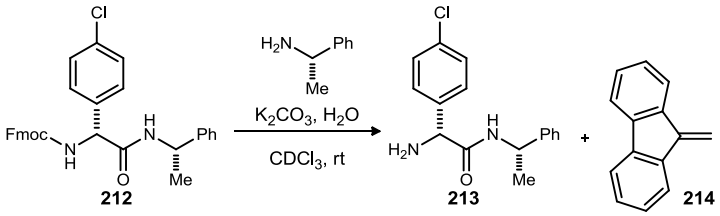


entry	time (d)	deprotection (%)[a]
1	1	0
2	3	7
3	5	13

[a] Based on 1H NMR analysis of crude reaction mixture, measuring relative amount of fulvene **214** to remaining amide **212**.

The standard UmAS reaction conditions were tested in the same way. Amide **212** was stirred at room temperature in $CDCl_3$ with the amine, K_2CO_3 and water. After stirring for a day under these conditions, a small amount of Fmoc-deprotection was observed (5%, Table 17, entry 1). After 3 and 5 days, 8% and 11% Fmoc-deprotection was observed, respectively (Table 17, entries 1 and 2). These results show that the Fmoc-protected dipeptide is somewhat susceptible to deprotection under our reaction conditions. However, this should only be a significant problem when longer reaction times are used.

Table 17. Determining Fmoc-deprotection by UmAS reaction conditions.

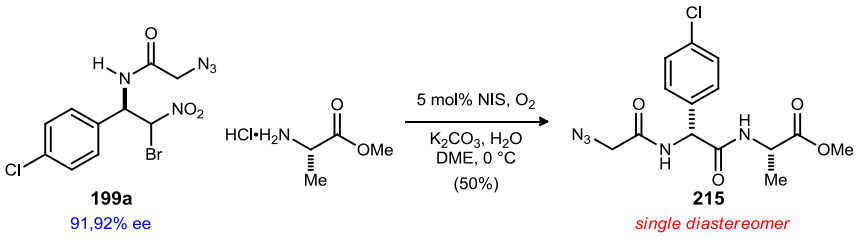


entry	time (d)	deprotection (%)[a]
1	1	5
2	3	8
3	5	11

[a] Based on ^{1}H NMR analysis of crude reaction mixture, measuring relative amount of fulvene **214** to remaining amide **212**.

It was also exciting that α-bromo nitroalkane **199a** was able to be coupled to the methyl ester of alanine to give dipeptide **215** in 50% yield (Scheme 62). As mentioned previously, this azido acetate protecting group is very synthetically useful. It could be reduced to give a glycine residue or used in click chemistry[127] or a Staudinger ligation.[9]

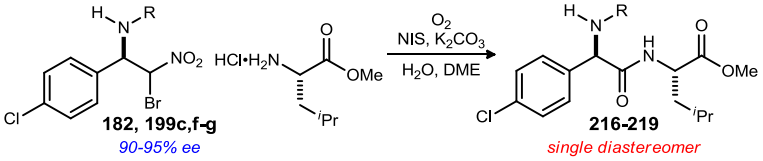
Scheme 62. Catalytic umpolung amide coupling of *N*-azidoacetate-protected α-bromo nitroalkane **199a**.

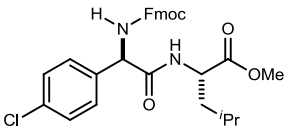
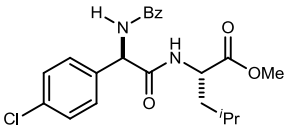
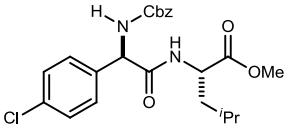
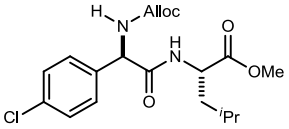


After successfully coupling α-bromo nitroalkanes **182** to a simple amine and **199a** to the methyl ester of alanine, attention was next turned to coupling several adducts bearing protecting groups commonly found in peptide synthesis. Specifically, we wished to couple the *N*-Fmoc, Bz, Cbz and Alloc (**182**, **199c,f-g**) protected adducts to an amino acid, thus incorporating these protected residues into a dipeptide fragment. However,

when these compounds were submitted to UmAS conditions, the yields of the desired dipeptides (**216**-**219**) were lower than expected (Table 18, entries 1-4). Only the *N*-Bz adduct **199c** gave the corresponding dipeptide **217** in an acceptable yield (65%, Table 18, entry 2). The other protected adducts gave slightly lower yields (52-57%, Table 18, entries 1,3,4), prompting optimization of these coupling conditions.

Table 18. UmAS coupling of differentially protected α-bromo nitroalkanes with alanine methyl ester.



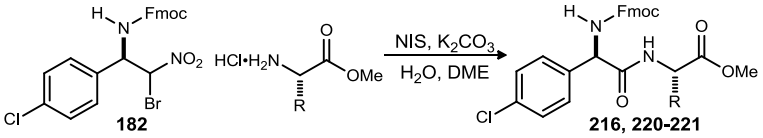
entry	product		yield (%)[a]
1		**216**	52
2		**217**	65
3		**218**	53
4		**219**	57

[a] All reactions run with 2 eq of amine at 0 °C for 2 d.

In order to optimize the UmAS coupling conditions for these substrates, the *N*-Fmoc adduct **182** was coupled under a variety of conditions. It was found that removing the oxygen atmosphere was detrimental to the reaction, resulting in a 43% yield of dipeptide **216** (Table 19, entry 2). In order to make sure the low yield was not due to the amino acid coupling partner, **182** was also coupled to alanine and valine residues. These

couplings resulted in no improvement, with similar yields (46 and 44%, respectively, Table 19, entries 3 and 4) of the corresponding dipeptides **220** and **221**.

Table 19. Optimization of UmAS coupling of **182** with amino acids.



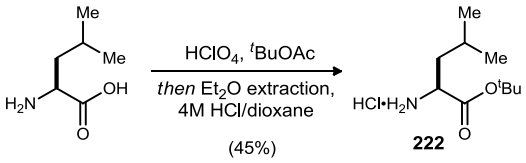
entry	amino acid	time (d)[a]	product	yield (%)
1[a]	HCl·H_2N·Leu·OMe	2	**216**	52
2	HCl·H_2N·Leu·OMe	2	**216**	43
3	HCl·H_2N·Ala·OMe	2	**220**	46
4	HCl·H_2N·Val·OMe	2	**221**	44
5	HCl·H_2N·Leu·OMe	4	**216**	37

[a] Reaction performed under an atmosphere of O_2.

Because the ^{1}H NMR resonances of the starting materials are very broad, it can be very hard to determine the conversion of these reactions. Therefore, a reaction was performed in which the coupling was allowed to run for 4 days, as opposed to 2 days (Table 19, entry 5). The results of this reaction were surprising. Instead of staying the same or increasing, the yield of dipeptide **216** actually decreased. This indicated that the product was decomposing in some way under the coupling conditions. As mentioned previously, Fmoc-deprotection might be possible. However, it had been shown that under these reaction conditions Fmoc-deprotection occurred very slowly. Additionally, no signs of Fmoc-deprotection (e.g. fulvene) were seen in the crude reaction mixtures for any of the couplings. A second decomposition pathway was therefore considered. Hydrolysis of the methyl ester could theoretically occur under the reaction conditions, which include K_2CO_3 and water. If this were to happen, the resulting acid would most likely be lost to the aqueous layer during workup and would not be observed in the crude reaction mixture.

In order to test this possibility, an amino acid residue was needed that was less susceptible to hydrolysis. Therefore, the *tert*-butyl ester of leucine was synthesized.[129] Because the ^{t}Bu ester **222** was volatile as the free amine, the HCl salt of this compound was formed. In order to do this without deprotecting the newly-formed *tert*-butyl group, a work-up was devised in which the free amine was extracted into ether and then treated with 4M HCl in dioxane. It was found that in any other solvent, *tert*-butyl deprotection occurred upon concentration to return starting material. In this way, the *tert*-butyl ester of leucine (**222**) was synthesized in 45% yield (Scheme 63).

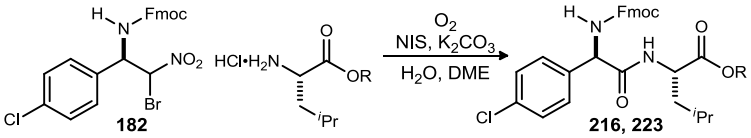
Scheme 63. Synthesis of the *tert*-butyl ester of leucine.



Following preparation of the required *tert*-butyl amino acid, several reactions were planned to compare the stability of the *tert*-butyl ester dipeptide **223** to that of the methyl ester dipeptide **216**. Coupling **182** to the *tert*-butyl ester of leucine afforded dipeptide **223** in 62% after 2 days, 10% higher than the yield of **216** produced from the coupling of the methyl ester (Table 20, entries 1 and 2). When these reactions were run for a longer time, 4 days, a remarkable difference in yield was seen. While the coupling with the *tert*-butyl ester yielded **223** in 65% yield, a 2% increase from the 2 day reaction, the coupling with the methyl ester yielded **216** in 37% yield, a 15% *decrease* from the 2 day reaction (Table 20, entries 3 and 4).

[129]Chen, H.; Feng, Y.; Xu, Z.; Ye, T. *Tetrahedron* **2005**, *61*, 11132.

Table 20. Comparison of the *tert*-butyl and methyl esters of leucine in UmAS coupling of **182**.

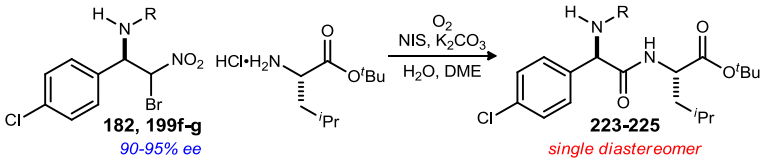


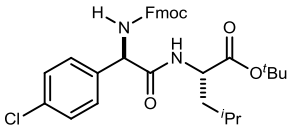
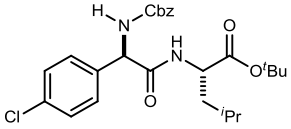
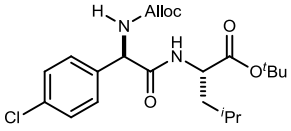
entry	amino acid	time (d)[a]	product	yield (%)
1	HCl·H_2N·Leu·OMe	2	**216**	52
2	HCl·H_2N·Leu·O^{t}Bu	2	**223**	62
3	HCl·H_2N·Leu·OMe	4	**216**	37
4	HCl·H_2N·Leu·O^{t}Bu	4	**223**	65

[a] Reactions run with 2 eq of amine at 0 °C.

These results suggested that hydrolysis of the methyl ester was responsible, in part, for the low yield of the dipeptides after UmAS coupling, and that the corresponding *tert*-butyl esters were much more resistant to hydrolysis. Therefore, the protected adducts **182**, **199f** and **199g** were all coupled to the *tert*-butyl ester of leucine, resulting in good yields (62-68%) of the dipeptides **223**, **224** and **225**, respectively (Table 21, entries 1-3).

Table 21. UmAS coupling of differentially protected α-bromo nitroalkanes with the *tert*-butyl ester of alanine.



entry	product		yield (%)[a]
1		**223**	62
2		**224**	63
3		**225**	68

[a] All reactions run with 2 eq of amine at 0 °C for 2 d.

It was pleasing to see that these protecting groups commonly used in peptide synthesis were compatible with the UmAS coupling conditions. This, combined with the fact that no epimerization was observed during any of these couplings, makes the aza-Henry addition to TMS-imines a powerful methodology to introduce variously protected aryl glycine residues into peptides. In three steps from inexpensive aldehydes, amino acid residues can be synthesized and incorporated into peptides in a highly stereocontrolled manner. Additionally, due to the novel use of *N*-TMS imines, this is the first example of an enantioselective amino acid synthesis in which the protecting group is not determined by the method used. This methodology allows for the incorporation of a number of protecting groups, including the widely used Fmoc group which is not readily accessible by most methods of enantioselective amino acid synthesis.

3.2.4 Heteroaromatic and Aliphatic N-TMS Imines

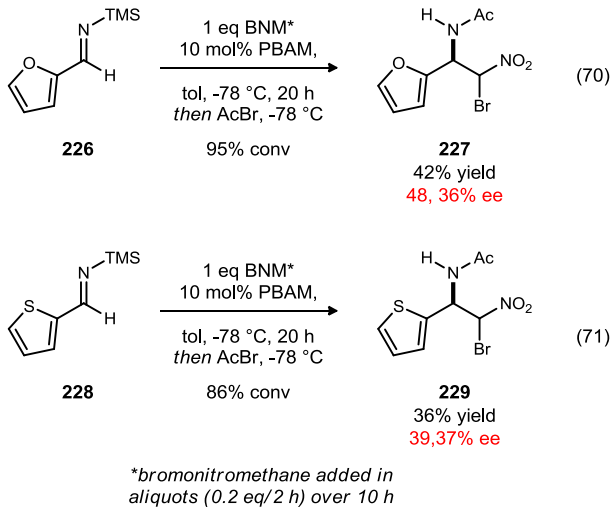
While work thus far had focused on the synthesis and incorporation of aryl glycine residues, extending this methodology to include other non-natural amino acids was a logical next step. The number of readily available aldehydes is vast, allowing for the synthesis of a wide variety of amino acid side chains. We therefore wished to extend this chemistry to include both heteroaromatic and aliphatic substrates in order to broaden the utility of this methodology.

Attention was first turned to heteroaromatic aldehydes, as it was thought they should behave most similarly to aromatic substrates. Several examples of heteroaromatic *N*-TMS imines could be found in the literature,[130,131,132] and it is known that these

[130] Betschart, C.; Schmidt, B.; Seebach, D. *Helevetica Chimica Acta* **1998**, *71*, 1999.

compounds are relatively stable. The first substrates subjected to enantioselective aza-Henry conditions were the known furanyl[130] and thiophenyl[131] *N*-TMS imines (**226** and **228**). Upon slow addition of bromonitromethane, followed by acetyl bromide quench, the desired α-bromo nitroalkanes (**227** and **229**) were isolated. However, the reactions were low yielding, and the observed enantioselection was moderate (48, 36% ee for **227**, eq 70, and 39, 37% ee for **228**, eq 71, Scheme 64). While unfortunate, based on the reactivity of electron rich aryl imines, these results were not surprising.

Scheme 64. Preliminary aza-Henry addition to heteroaromatic *N*-TMS imines **226** and **228**.

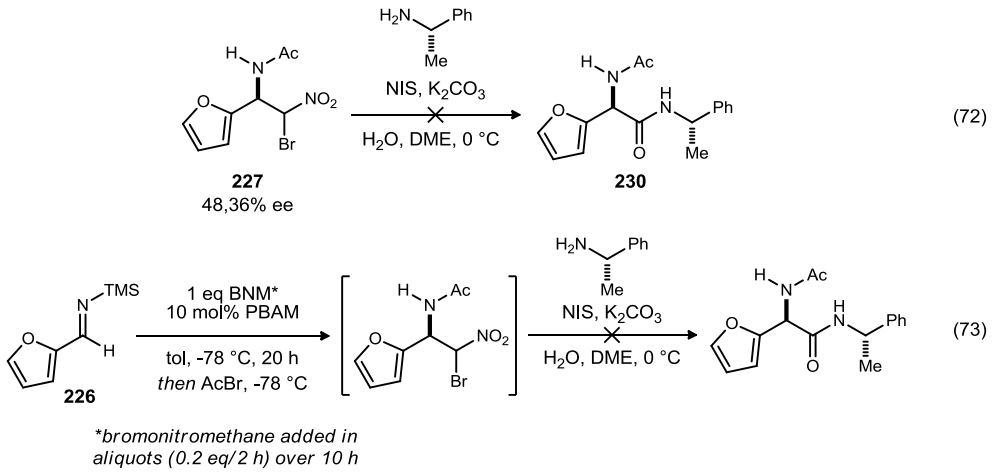


Additionally, it was observed that these adducts slowly racemized upon standing and were not stable for extended periods of time. Therefore, these compounds were immediately subjected to umpolung amide synthesis (UmAS) conditions, in the hope that the resulting amides would be more stable. Unfortunately, when the furanyl derivative **227** was stirred with α-methyl benzylamine, in the presence of base and NIS, none of the desired product **230** was observed (eq 72, Scheme 65). At the same time, a coupling was

[131] Ramanchandran, P.; Burghardt, T. *Chem. Eur. J.* **2005**, *11*, 4387.
[132] Hart, D.; Kanai, K.; Thomas, D.; Yang, T. *J. Org. Chem.* **1983**, *48*, 289.

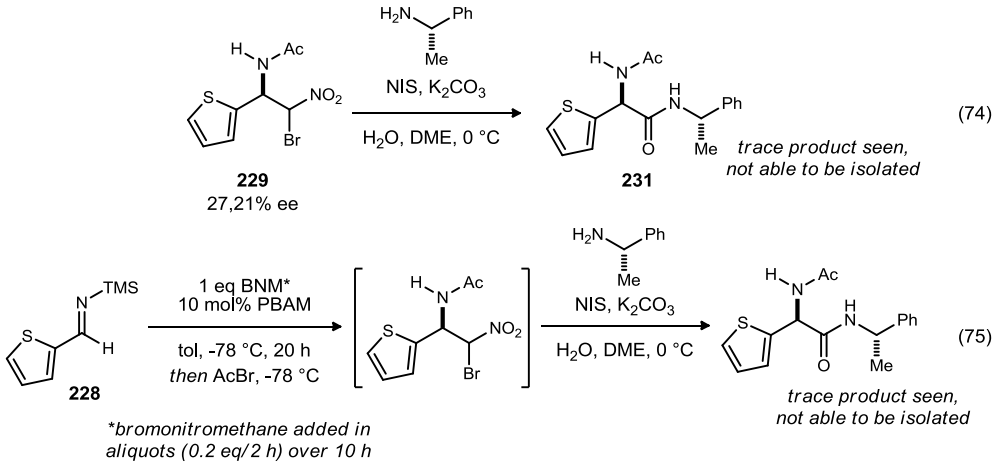
attempted in which the crude aza-Henry reaction mixture was subjected to the UmAS conditions. It was hoped that the α-bromo nitroalkane **227** would react before it had a chance to racemize. This coupling also resulted in none of the desired amide **230** (eq 73, Scheme 65).

Scheme 65. Attempted UmAS coupling of **227**.



The same couplings were attempted with the thiophene derivative **229**. In both attempted UmAS couplings, with the pure α-bromo nitroalkane **229** (eq 74, Scheme 66) as well as the crude (eq 75, Scheme 66), trace amounts of the desired amide **231** were detected by ^{1}H NMR analysis. Aromatic thiophene resonances were observed at 7.91, 6.56 and 6.45 ppm, as well as a broad doublet at 5.83 and a broad multiplet at 5.12 ppm which could correspond to the methynes adjacent to the amide nitrogens. However, after purification by column chromatography the amide was not isolated, presumably due to decomposition.

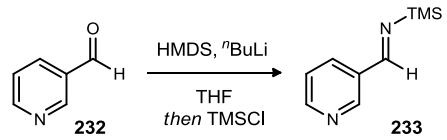
Scheme 66. Attempted UmAS coupling of **229.**



While we were able to achieve moderate levels of enantioselection with the furanyl and thiophenyl *N*-TMS imines (**226** and **228**), the fact that the resulting adducts (**227** and **229**) were unstable and not able to be coupled under UmAS conditions prompted us to move to a less electron-rich imine. Therefore, the known[132] pyridyl *N*-TMS imine **233** was synthesized. All previous *N*-TMS imines were successfully synthesized using the protocol by Vidal and Collet,[124] in which the aldehyde and LHMDS are stirred at ambient temperature in THF before being diluted with hexanes and filtered under an inert atmosphere. However, when we used these conditions with pyridine carboxaldehyde **232**, none of the desired imine **233** was seen after filtration (Table 22, entry 1). Several known procedures for the synthesis of this imine called for reaction temperatures as low as -78 °C. Therefore, the reaction temperature was lowered to -78 °C, and the same filtering procedure used. Again, no product was observed (Table 22, entry 2). A third attempt, in which the reaction was kept at low temperatures during filtration step as well, finally yielded some of the desired imine **233** (Table 22, entry 3). However, the crude reaction mixture was messy and, due to its instability, the imine was

unable to be purified *via* distillation. Therefore, the filtration step was eliminated, and the imine **233** isolated as a crude mixture with LiCl (Table 22, entry 4).

Table 22. Synthesis of pyridine *N*-TMS imine **233**.

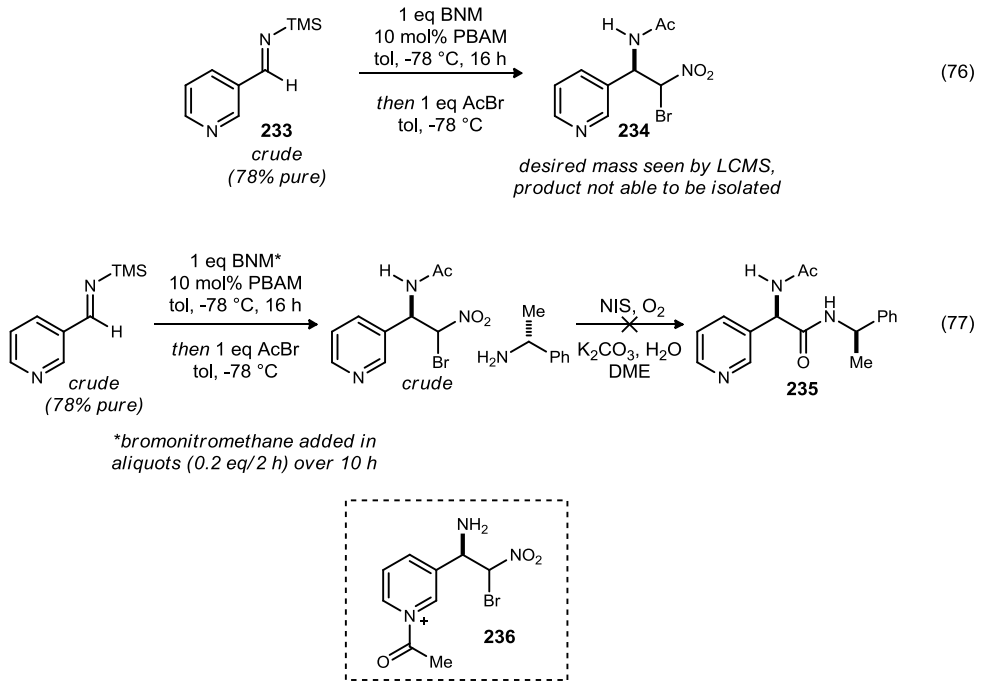


entry	conditions	result[a]
1	**rt**, diluted with hexanes and filtered	no product
2	**-78 °C**, diluted with hexanes and filtered	no product
3	-78 °C, diluted with **cold** hexanes and filtered	messy, product present
4	-78 °C, **did not filter**	product present (crude with LiCl)

With the crude pyridyl imine **233** in hand, we next subjected it to standard aza-Henry conditions. Initially, we chose to quench the addition with acetyl bromide in the hopes that we would be able to judge the conversion of the reaction after 16 hours. However, the desired amide could not be identified in the NMR of the crude reaction mixture. While some remaining aldehyde could be seen, indicating that the reaction had not reached complete conversion, the ^{1}H NMR resonances of the other products of this reaction were very broad and could not be readily identified. The crude reaction mixture was subjected to column chromatography, and a polar fraction was collected which contained a product with a mass that matched that of the desired product **234**, as indicated by LCMS. However, this product co-eluted with the pyridine carboxaldehyde and the PBAM catalyst. After subjecting this mixture to column chromatography a second time, none of the desired product could be isolated, indicating that it is unstable under these

purification conditions (eq 76, Scheme 67). An attempt was made to couple the crude α-bromo nitroalkane **234**, since purification of this compound proved challenging. However, upon treatment of the crude aza-Henry reaction mixture with standard UmAS coupling conditions, none of the desired amine **235** was observed (eq 77, Scheme 67).

Scheme 67. Aza-Henry addition to *N*-TMS imine **233**: AcBr protection.

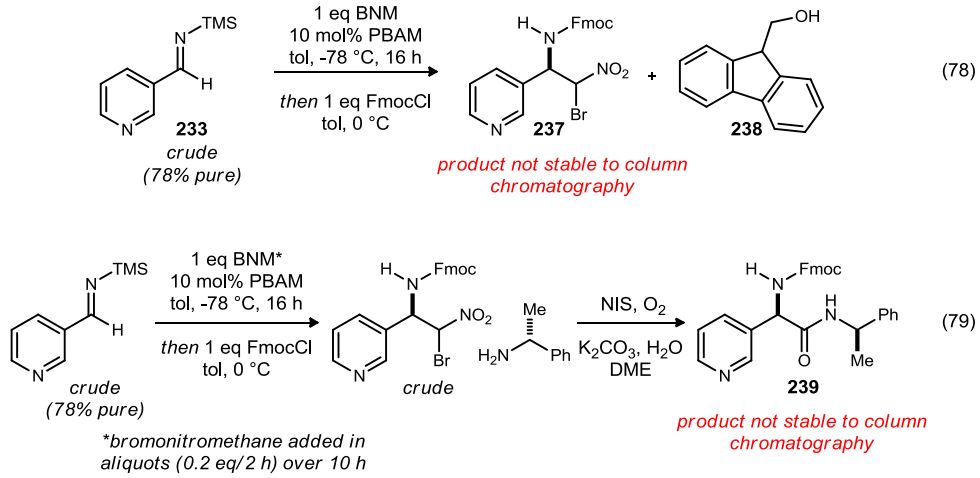


While it is unclear whether or not the desired product was formed, it is possible that, due to the high reactivity of the acetyl bromide, the pyridyl nitrogen was acylating before the *N*-TMS protected amine, to give the pyridyl salt **236** which has the same mass as the desired product **234**. This would explain the observed polarity, as well as the instability, of the observed product. It would also explain why the amide **235** was not observed in the crude reaction mixture for the coupling.

Because the acylation with acetyl bromide seemed to be causing problems, attention was next turned to quenching the addition reaction with FmocCl. It was hoped

that due to the bulkiness of this reagent, the pyridyl nitrogen would not react, and only the TMS-amine would be protected. Additionally, the Fmoc protecting group should make the product less polar and easier to isolate. When this reaction was carried out, the desired product could be seen by both crude NMR as well as LCMS (eq 78, Scheme 68). Upon column chromatography, some of the product could be isolated, but as a mixture with the FmocOH **238**. The presence of this side product, which would result from hydrolysis of the corresponding fulvene, indicates Fmoc-deprotection. It was therefore not surprising that repurification failed to return the desired product. We hypothesized that the α-bromo nitroalkane **237** was deprotecting on the column, resulting in decomposition.

Scheme 68. Aza-Henry addition to *N*-TMS imine **233**: FmocCl protection.



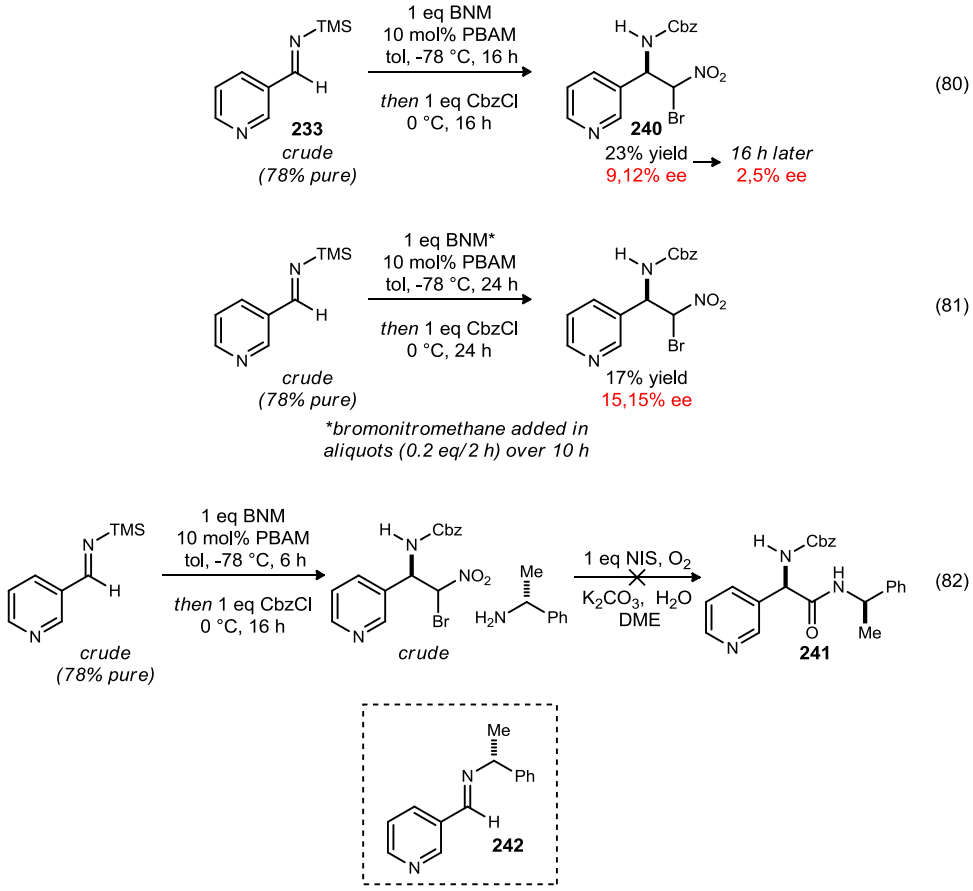
In order to prevent this from occurring, several different column conditions were used, including using DCM/MeOH as the eluent and running the column with neutral alumina, neither of which were successful. Because it is likely that the basic pyridyl nitrogen is responsible for the Fmoc-deprotection, a column was also run in which AcOH was added as an additive to the EtOAc/hex eluent. This was done to try and form the

acetic acid salt of the product, thereby masking the basicity of the pyridyl nitrogen. Unfortunately, these conditions were equally unsuccessful.

Since the α-bromo nitroalkane **237** proved to be unstable under purification conditions, we decided to take it directly on to the amide **239**. Therefore, the crude aza-Henry reaction mixture was submitted to UmAS coupling conditions. We were pleased to see that the mass of the desired amide **239** could be seen by LCMS (eq 79, Scheme 68); however, upon attempted purification of this product, the same problems were encountered. The product could be isolated after column chromatography as a mixture with the FmocOH **238**, but upon repurification could not be isolated. As before, several different column conditions were examined, but none resulted in isolation of amide **239**.

It was clear at this point that the Fmoc protecting group also would not work with this substrate. Therefore, we next turned to Cbz-protection. By quenching the aza-Henry addition reaction with CbzCl, we were excited to see that the desired Cbz-protected pyridyl α-bromo nitroalkane **240** could be isolated in 23% yield. Unfortunately the enantioselection observed in this reaction was quite low (9, 12% ee, eq 80, Scheme 69). This was surprising, as the pyridyl imine should be less electron rich, and thus have less of a background reaction, than the furanyl and thiophenyl derivatives that gave higher levels of enantioselection (48, 36% ee and 37, 36% ee, respectively, Scheme 64). We hypothesize that this low enantioselectivity most likely is a result of the basic pyridyl nitrogen, which could compete with PBAM to catalyze a non-selective addition pathway.

Scheme 69. Aza-Henry addition to *N*-TMS imine **233**: CbzCl protection.

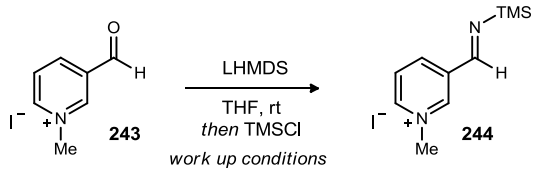


Additionally, it was observed that upon standing in solution, the adduct **240** readily racemized (eq 80, Scheme 69). Thus, after a slow addition reaction with this substrate, the product was quickly purified and subjected to HPLC analysis. The ee of adduct **240**, isolated in 17% yield, was only slightly higher (15, 15% ee, eq 81, Scheme 69). An attempt was also made to quickly couple the α-bromo nitroalkane **240**, in order to prevent racemization of this intermediate. Therefore, the crude aza-Henry reaction mixture was subjected to UmAS coupling conditions. Unfortunately, the desired product **241** was not observed in the crude reaction mixture. Instead, a product was isolated that contained pyridyl and α-methyl benzylamine peaks by ^{1}H NMR, but no amide or Cbz peaks. The mass of this isolated product corresponded to the imine **242**, which most

likely resulted from a retro-aza-Henry addition of **240** and subsequent transimination with the α-methyl benzylamine.

Due to our evolving hypothesis that the basic nitrogen of the pyridine was responsible for low enantioselection and a difficult isolation, attempts were made to synthesize a pyridyl *N*-TMS imine (**244**) in which the pyridyl nitrogen was protected as the methyl salt. Therefore, the methyl salt of the pyridine carboxaldehyde (**243**) was stirred with LHMDS in THF at ambient temperature. After the reaction was complete, it was quenched with TMSCl, diluted with hexanes and filtered under an inert atmosphere (Table 23, entry 1). Usually, the filtration step removes only the LiCl produced as a byproduct of the reaction. However, in this case a large amount of red solid was filtered off, and the filtrate contained none of the desired imine. It is thought that the imine was not soluble in hexanes, and was simply filtered off. Therefore, a second attempt was made in which the filtration step was removed. This resulted in a crude reaction mixture that was completely insoluble in $CDCl_3$. By dissolving this mixture in d_6-DMSO a crude ^{1}H NMR could be obtained which indicated that there was still a significant amount of the starting aldehyde **243** present. However, a second compound could be observed which appeared to be the desired imine **244** (Table 23, entry 2).

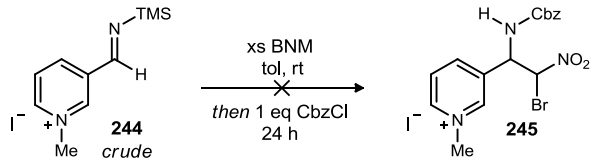
Table 23. Synthesis of the Me-protected pyridyl *N*-TMS imine **244**.



entry	conditions	result[a]
1	diluted with hexanes and filtered	no product
2	concentrated, with no filtration	^{1}H NMR in DMSO-aldehyde still present, some imine

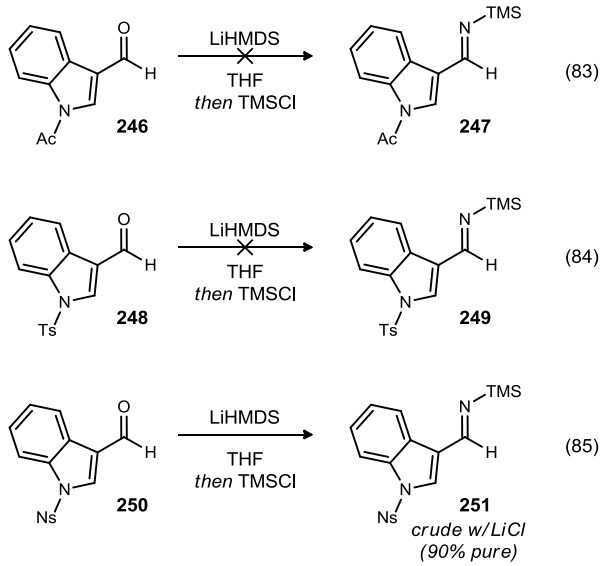
Since it appeared some imine had been produced, a portion of the crude reaction mixture containing **244** was stirred with excess bromonitromethane in toluene at room temperature to see if any aza-Henry addition would occur (Scheme 70). The crude material was completely insoluble in toluene, but seemed to be slightly soluble in bromonitromethane. After stirring for several hours, the reaction was quenched with CbzCl and allowed to stir overnight. After concentrating the reaction mixture, ^{1}H NMR analysis in $CDCl_3$ revealed only remaining bromonitromethane and CbzCl. Analysis by ^{1}H NMR in d_6-DMSO, allowed us to determine that no aldehyde or imine remained. However, while there were pyridine-containing products, none of the resonances exhibited the appearance typical of a mixture of diastereomers, as the desired product **245** would. Furthermore, the mass of the desired product **245** could not be seen when the crude reaction material was analyzed by LCMS.

Scheme 70. Attempted aza-Henry addition to Me-protected pyridyl *N*-TMS imine **244**.



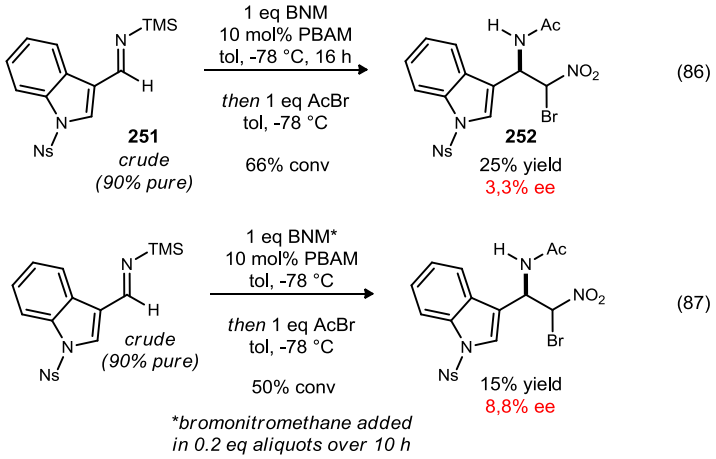
Due to the lack of success with pyridyl *N*-TMS imines provided, we returned to inherently electron rich aryl aldimines in the form of a protected indole *N*-TMS imine. Initially, synthesis of the acetyl-protected indole *N*-TMS imine **247** was attempted. Unfortunately, upon addition of LHMDS to the aldehyde **246**, an insoluble substance precipitated from the reaction mixture, and none of the desired imine could be recovered (eq 83, Scheme 71). It is thought that the LHMDS either deprotected the acetyl group, or deprotonated at the methyl position, leading to an undesired reaction pathway such as polymerization of the substrate. Therefore, attention was next turned to the synthesis of the tosyl-protected indole *N*-TMS imine **249**. The synthesis of this imine was performed on small scale (>250 mg of aldehyde **248**), and while it appeared some of the desired imine **249** was present, the crude reaction mixture was complex, and there was at least one other major product (eq 84, Scheme 71). Instead of attempting to synthesize this imine on larger scale, we instead decided to move to a nosyl-protected indole *N*-TMS imine (**251**). It was hypothesized that the electron-withdrawing nature of this protecting group should help with the reactivity of this substrate in the subsequent aza-Henry addition step. We were pleased to see that after reacting aldehyde **250** with LHMDS, and subsequently quenching with TMSCl, the desired imine **251** could be isolated as a crude mixture with LiCl (eq 85, Scheme 71).

Scheme 71. Synthesis of a protected indole *N*-TMS imine.



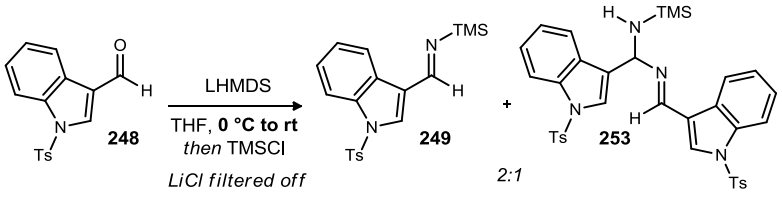
When unpurified imine **251** was subjected to standard aza-Henry reaction conditions, we were pleased to see that the desired α-bromo nitroalkane **252** could be isolated in 25% yield. However, the isolated product was nearly racemic (3, 3% ee, eq 86, Scheme 72). Upon slow addition of bromonitromethane, the enantioselection was increased slightly, to give the product **252** in 15% yield and 8, 8% ee (eq 87, Scheme 72). These results made little sense to us, as this imine, like the pyridyl derivative, should be less electron rich than the furanyl and thiophenyl *N*-TMS imines. If only the electronics of the imine are considered, the Ns-protected indole *N*-TMS imine **251** should have given higher levels of enantioselectivity than observed. Therefore, it is hypothesized that perhaps the nitro-group of the Ns-protecting group is interfering in the enantioselective step in some way, perhaps through a hydrogen bonding mechanism.

Scheme 72. Aza-Henry addition to *N*-TMS imine **251**.



Because the Ns-protected indole *N*-TMS imine **251** gave surprising results, we decided to return to the Ts-protected indole carboxaldehyde **248** with the hope that the synthesis of the corresponding *N*-TMS imine **249** would be more facile on a larger scale. When this was attempted, the desired *N*-TMS imine **249** was again present in addition to a second major compound. It was determined that this product was dimer **253**, formed by nucleophilic addition of the *N*-TMS imine nitrogen to a second equivalent of imine. By ^{1}H NMR analysis, it was determined that these two products were present in a 2:1 (**249**:**253**) ratio (Scheme 73).

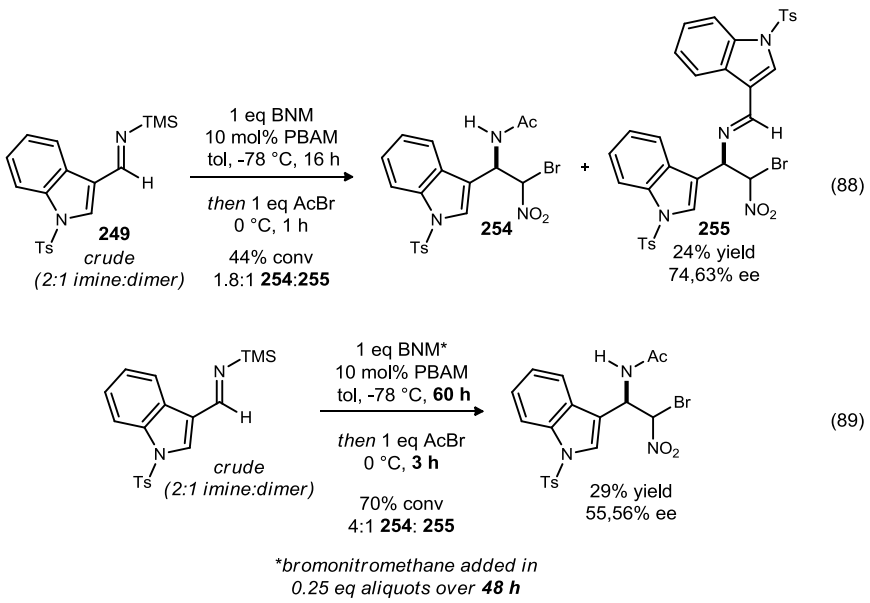
Scheme 73. Returning to the Ts-protected indole *N*-TMS imine **249**.



This mixture was subsequently subjected to aza-Henry reaction conditions. While the conversion was low (44%), it was possible to see the desired product **254** by ^{1}H NMR analysis of the crude reaction mixture. However, a second major product was also

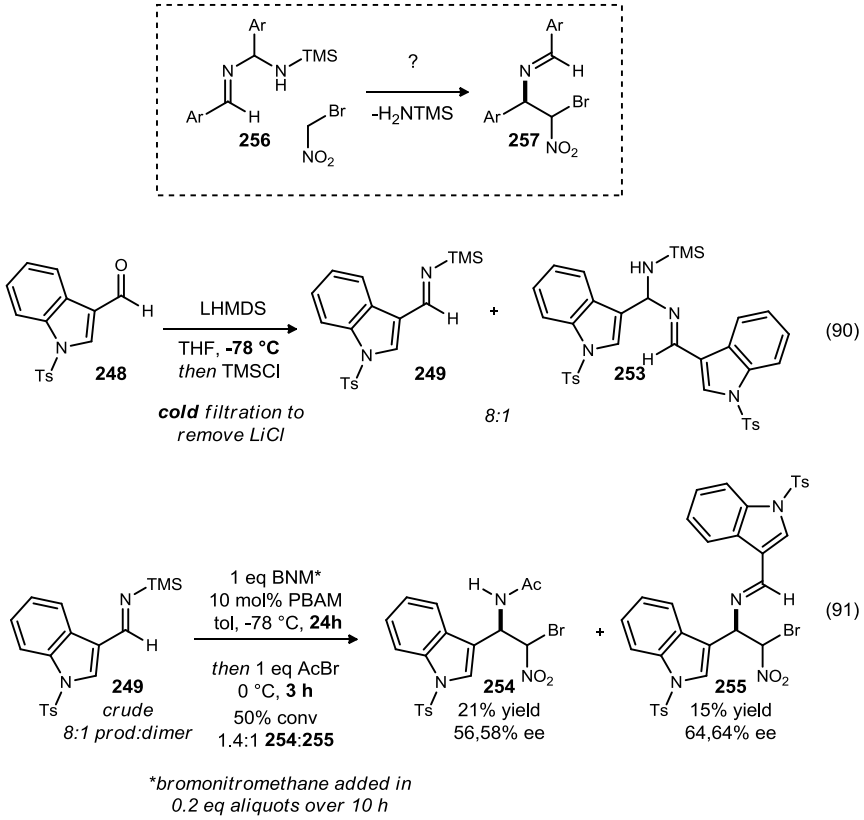
observed, the transimination product **255**. This product had been observed previously in our work with aryl imines- it usually occurs when the reaction has not gone to complete conversion. By NMR analysis it was determined that these two products were present in a 1.8:1 ratio (**254**:**255**). Upon column chromatography, only the transimination product **255** was initially isolated, in 24% yield. It was exciting to see that this side product had a fairly high level of enantiopurity, with an ee of 74, 63% (eq 88, Scheme 74). While this was not the desired acylated product **254**, the two should theoretically have very similar levels of enantioselectivity. Because of these promising results, a second reaction was done in which bromonitromethane was added to the crude mixture of imine **249** and dimer **253** over 48 h. This extended reaction time was used in order to try to increase the conversion of the reaction and prevent the formation of transimination product **255**. This did seem to help somewhat, as the reaction proceeded to 70% conversion, and the ratio of **254**:**255** was determined to be 4:1. The desired α-bromo nitroalkane **254** was isolated in 29% yield and 55, 56% ee (eq 89, Scheme 74), which are the best results obtained so far for a heteroaromatic *N*-TMS imine substrate.

Scheme 74. Aza-Henry addition to the Ts-protected indole *N*-TMS imine **249**.



While these results were promising, the yield of **254** was still lower than what would be synthetically useful, mostly due to the low conversion of the reaction as well as the formation of the undesired transimination product **255**. While a longer reaction time helped somewhat, we thought that perhaps the presence of the imine dimer **253** was contributing to these problems. It is possible that bromonitromethane addition to **256**, followed by elimination of $TMSNH_2$, could form the transimination product **257** (Scheme 75). Even if this were not the case, and the dimer **256** was simply unreactive, this would then contribute to the low conversion of the reaction.

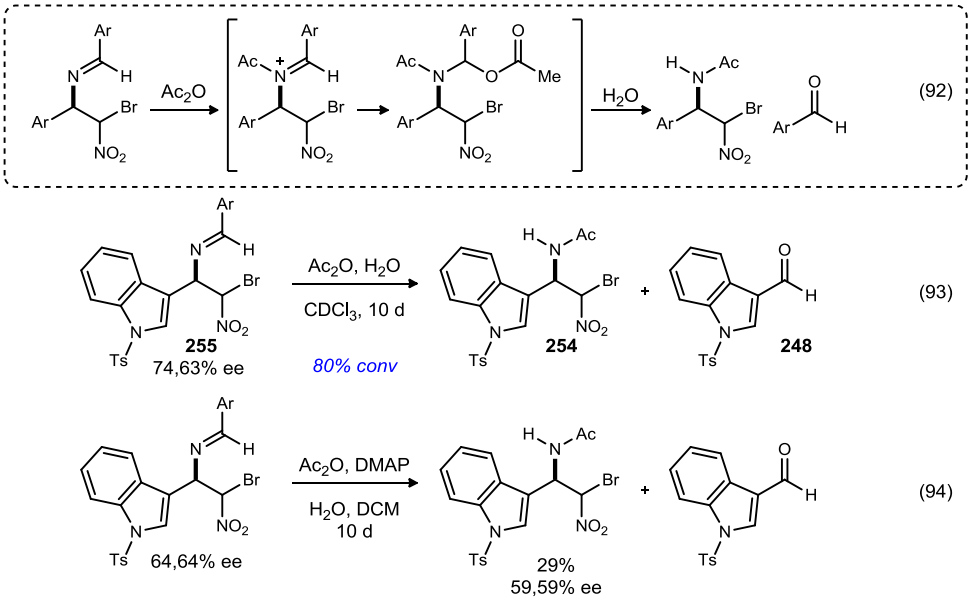
Scheme 75. Attempted optimization of synthesis and aza-Henry addition to *N*-TMS imine **249**.



Therefore, indole *N*-TMS imine **249** was synthesized a second time. By reducing the reaction temperature to -78 °C, the ratio of desired product **249** to imine dimer **253** could be increased to 8:1 (eq 90, Scheme 75). A slow addition of bromonitromethane to this mixture was carried out over 10 hours. Acetyl bromide was then added to quench the reaction. The results obtained from this reaction were unfortunately not what was expected. The conversion was only 50%, and the ratio of the desired product **259** to transimination product **255** was 1.4:1 The α-bromo nitroalkane **254** could be isolated in 21% yield and 56, 58% ee, and the transimination product **255** was isolated in 31% yield, as a mixture with the starting aldehyde **248**, and 64, 64% ee (eq 91, Scheme 75).

Since so much of the transimination product **255** was forming in these reactions, it was decided to attempt to convert this product into the acylated product **254**. It was hypothesized that this could be done by treating **255** with acetic anhydride and a catalytic amount of water. Nucleophilic addition of acetic acid to the imine and subsequent acyl transfer and collapse of the tetrahedral intermediate could give the desired product **254** (eq 92, Scheme 76).

Scheme 76. Conversion of transimination product **255** to acetylated product **254**.



In order to test this, a small amount of the transimination product **255** was dissolved in $CDCl_3$. One equivalent of Ac_2O and a catalytic amount of water were added, and the mixture was monitored by ^1H NMR. A trace amount of the desired product **254** could be seen after 2 days, along with some of the aldehyde **248**, and after 10 days, the conversion to **254** was determined to be 80%. While this transformation was slow, we were excited to be able to convert the undesired product **255** to the desired α-bromo nitroalkane **254**, thereby increasing the overall yield of the aza-Henry addition.

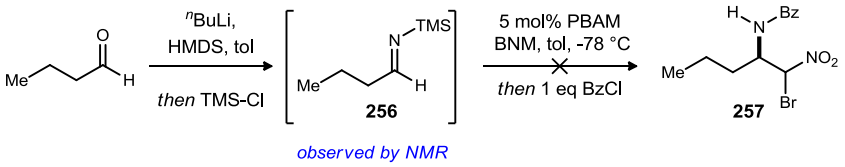
Therefore, the transimination product produced from the aza-Henry addition in Scheme 75 (eq 91) was subjected to these conditions. After 10 days, the acylated product **254** was isolated in 29% yield and 59, 59% ee, increasing the total yield of the aza-Henry addition to 25%.

While the results obtained with the tosyl-protected indole imine (**249**) were the best to date for a heteroaromatic substrate, it was clear that these substrates were too electron rich to be used successfully in our chemistry at this time. We therefore decided to turn our attention to aliphatic *N*-TMS imines, with the hope that these would be more successful. However, it was known that aliphatic *N*-TMS imines are less stable than their aromatic counterparts. Specifically, they are volatile and not stable at high temperatures, and are therefore often difficult to isolate. In fact, most aliphatic *N*-TMS imines are prepared and reacted *in situ* in order to avoid isolation.[104]

With this in mind, we attempted to synthesize the aliphatic α-bromo nitroalkane **257** directly from butyraldehyde. Known butyl *N*-TMS imine **256**[104] was first prepared by adding LHMDS to the aldehyde in toluene. After stirring for 30 minutes at room temperature, complete conversion to the *N*-TMS imine (**256**) could be observed by ^{1}H NMR. The reaction mixture was cooled to -78 °C and bromonitromethane was added along with the chiral PBAM catalyst. After stirring overnight at -78 °C, the reaction was quenched with benzoyl chloride and concentrated. Analysis of the crude reaction mixture by ^{1}H NMR revealed full conversion of imine **256**; however, the major product of this reaction was not the desired α-bromo nitroalkane (**257**). It appeared that addition to the imine had occurred but that the benzoyl protecting group had not been incorporated into the major product of this reaction. While we were able to isolate this product after

column chromatography, it was unfortunately not sufficiently stable for full characterization and structure elucidation. However, it was clear that this one-pot reaction sequence was not following the desired reaction pathway to produce α-bromo nitroalkane **257** (Scheme 77).

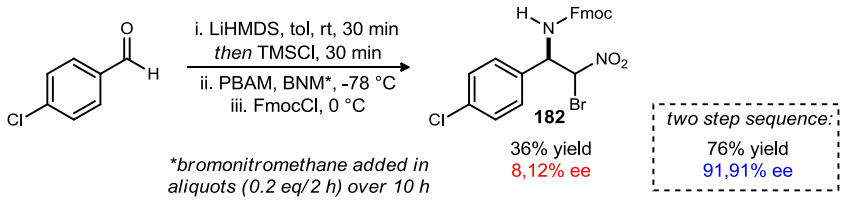
Scheme 77. Synthesis of aliphatic *N*-TMS imine **256** and *in situ* aza-Henry addition.



At this point we decided to reevaluate the synthesis of *N*-TMS imines *in situ* with this methodology. While we were unable to synthesize aliphatic α-bromo nitroalkane **257**, it was unclear if this was due to the reactivity of aliphatic *N*-TMS imines or the fact that the imine had been synthesized *in situ*. Therefore, a test reaction was carried out in which ^{p}Cl-benzaldehyde was treated with LHMDS in toluene at room temperature. After stirring for 30 minutes, TMSCl was added and the reaction was stirred for an additional 30 minutes before it was cooled to -78 °C. This reaction mixture was then subjected to our standard aza-Henry conditions for *N*-TMS imines. The results of this reaction were surprising. While the α-bromo nitroalkane (**182**) was isolated, the yield of the reaction was low and the enantioselection significantly decreased (36% yield, 8, 12% ee, Scheme 78). When compared to the results acquired when a two-step reaction sequence was carried out (76% yield, 91, 91% ee), it was clear that forming the imine *in situ* is detrimental to the subsequent addition reaction. Because the conditions for imine synthesis are quite basic, it is hypothesized that trace amounts of these reagents remained

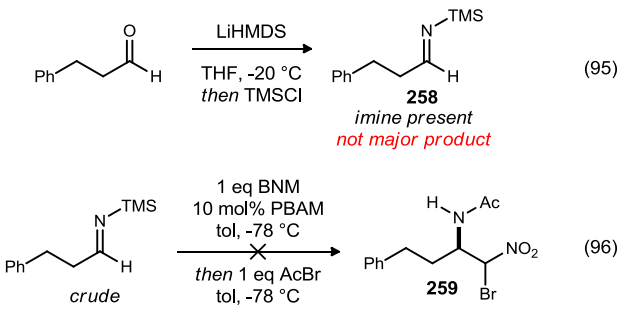
unquenched in the reaction mixture and interfered in the subsequent base-catalyzed aza-Henry addition step.

Scheme 78. Making the *N*-TMS imine *in situ*: A test reaction.



Based on this result, we surmised that for the aza-Henry addition to *N*-TMS imines to be successful, one must be able to concentrate the desired *N*-TMS imine after its synthesis to remove the volatile reagents and sideproducts. Therefore, alkyl *N*-TMS imine synthesis was next attempted with an aldehyde that was less volatile than butyraldehyde, with the hope that the corresponding imine could be isolated by filtering and concentrating the crude reaction mixture. Towards this end, hydrocinnamaldehyde was treated with LHMDS in THF. The reaction was quenched with TMSCl, filtered under argon and concentrated to give a crude reaction mixture in which *N*-TMS imine **258** was determined to be present by ^{1}H NMR analysis. Unfortunately, imine **258** did not appear to be the major product, as it was accompanied by several other unidentified products (eq 95, Scheme 79). Regardless, this crude material was submitted to standard aza-Henry reaction conditions and subsequently quenched with acetyl bromide. When the resulting crude reaction was analyzed by ^{1}H NMR, a complex mixture was observed which did not appear to contain desired α-bromo nitroalkane **259** (eq 95, Scheme 79).

Scheme 79. Synthesis of hydrocinnamyl *N*-TMS imine **258** and attempted aza-Henry addition.

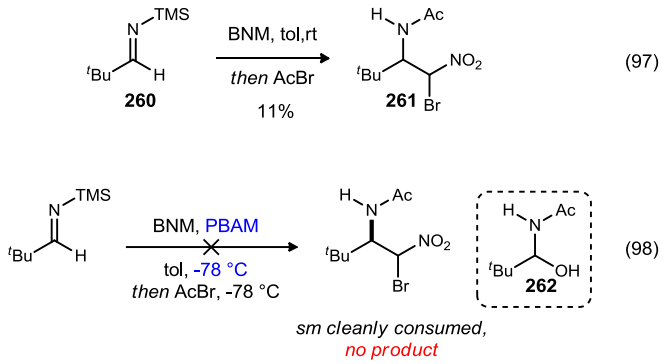


It is known that aliphatic *N*-TMS imines are susceptible to enamine formation, perhaps due to the basic conditions used for their synthesis and the similar bond dissociation energies of alkene and imine π-bonds.[104] In the case of *N*-TMS imine **258**, it is possible that enamine formation occured, so non-enolizable aliphatic aldehydes were prepared for evaluation in this chemistry.

The simplest non-enolizable aldehyde, *tert*-butyraldehyde, was used to synthesize known ^{t}Bu *N*-TMS imine **260**.[114] This imine could be purified by distillation, allowing use of pure **260** in the aza-Henry reaction. In order to synthesize racemic α-bromo nitroalkane **261**, imine **261** was treated with bromonitromethane in toluene at room temperature and then quenched with acetyl bromide. From this reaction, we were excited to isolate desired product **261** in 11% yield (eq 97, Scheme 80). However, when the reaction temperature was lowered, and the PBAM catalyst added, none of α-bromo nitroalkane **261** could be isolated. The major product of this reaction was determined to be hemiaminal **262**, a product type which has been observed in other work by our group in aza-Henry additions to imines.[133] It is thought that the formation of this product over desired product **261** can be attributed to the steric bulk of imine **260**, which may make it difficult for bromonitromethane to add.

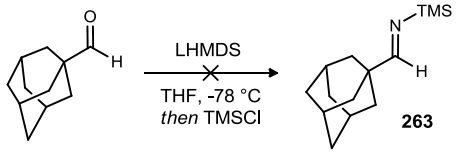
[133] Wilt, J. C.; Johnston, J. N. *unpublished results.*

Scheme 80. Aza-Henry addition to ^{t}Bu *N*-TMS imine **260**.



The next imine attempted to be synthesized was the adamantyl *N*-TMS imine **263**. While the adamanyl group is quite bulky, it was hoped that the cage-like structure of this substituent would decrease the steric hindrance around the electrophilic imine carbon by constraining the neighboring methylene carbons. Unfortunately, upon treatment of adamantyl aldehyde with LHMDS, no evidence of desired imine **263** could be observed by ^{1}H NMR analysis. Clean conversion of the aldehyde was observed, however it was difficult to determine what product was produced in this reaction as no resonances downfield of 2.5 ppm were present (Scheme 81).

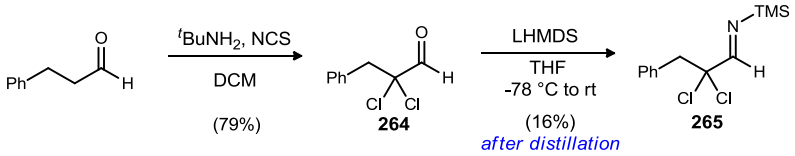
Scheme 81. Attempted synthesis of adamantyl *N*-TMS imine **263**.



It was thought that perhaps an α-halogen substituted aliphatic *N*-TMS imine might be less sterically hindered than the fully-carbon substituted derivatives just tried. Therefore, α,α-dichloro hydrocinnamaldehyde **264** was synthesized by treating hydrocinnamaldehyde with ^{t}BuNH$_2$ and NCS. Aldehyde **264** was then treated with

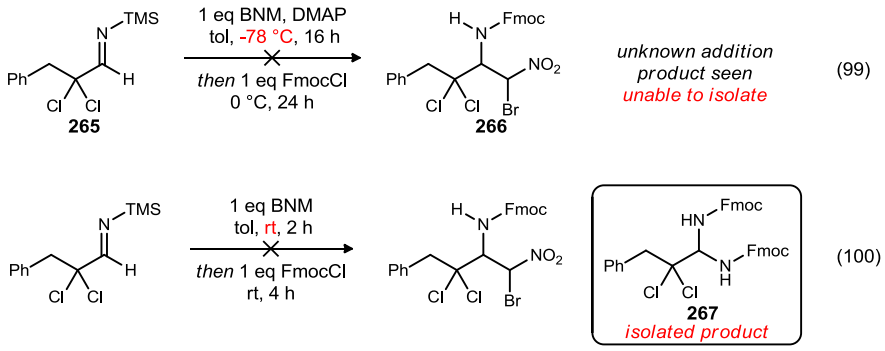
LHMDS in THF. We were excited to find that desired *N*-TMS imine **265** was sufficiently stable to isolate *via* distillation (Scheme 82).

Scheme 82. Synthesis of α,α-dichloro hydrocinnamyl *N*-TMS imine **265**.



We first attempted the synthesis of racemic α-bromo nitroalkane **266** by treating aldehyde **265** with bromonitromethane at -78 °C in the presence of a catalytic amount of DMAP. After stirring overnight and quenching with FmocCl, ^{1}H NMR analysis of this reaction showed that the imine had fully reacted, and that an addition product had formed as evidenced by the presence of a broad doublet around 6 ppm. This resonance could correspond to the methine *alpha* to the amine. However, this addition product did not appear to be the desired α-bromo nitroalkane **266**, as the resonance at 6 ppm appeared to be split only by the *N*-H of the amine, and no peak could be seen which would correspond to the methine at the α-bromo nitro center. Additionally, an unassigned resonance at 8.1 ppm was observed. This product was not isolated following purification attempts by column chromatography (eq 99, Scheme 83).

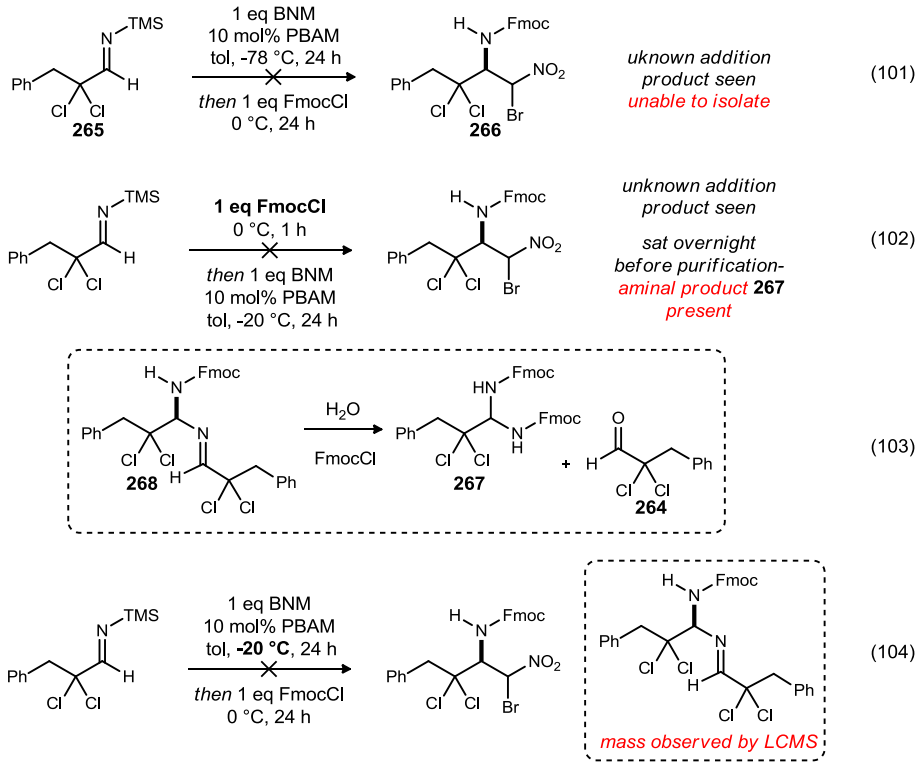
Scheme 83. Racemic aza-Henry addition to α,α-dichloro hydrocinnamyl *N*-TMS imine **265**.



We next attempted to synthesize racemic α-bromo nitroalkane **266** at room temperature in the absence of any catalyst. After quenching with FmocCl, a major product was seen by crude ^{1}H NMR analysis that was determined to be different from both the observed product in eq 99, as well as desired **266**. Upon purification and characterization, this compound was assigned to be aminal **267** (eq 100, Scheme 83).

While it was unclear how the aminal side product **267** formed, we decided to attempt to synthesize α-bromo nitroalkane **266** by enantioselective methods since we had not observed **267** in the reaction at low temperature (eq 99). Therefore, imine **265** was subjected to our standard aza-Henry conditions at -78 °C. Analysis of the resulting crude reaction mixture showed that the same unknown product in eq 99 had formed (eq 101, Scheme 84). Again, attempts to purify this product were unsuccessful.

Scheme 84. Attempted aza-Henry addition to α,α-dichloro hydrocinnamyl *N*-TMS imine **265**.

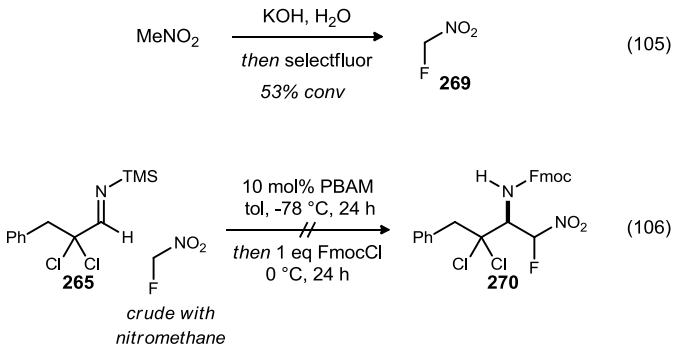


A second attempt to synthesize **266** was carried out, in which *N*-TMS imine **265** was reacted with FmocCl before the addition of bromonitromethane with the hope that the *N*-Fmoc imine would form in solution, and that this would give results different from the *N*-TMS imine. It was seen that this was not the case, as the crude reaction mixture appeared much the same by ^{1}H NMR analysis - again, the unknown addition product could be seen. However, before this mixture could be purified it sat open to the atmosphere for several hours. After this time period, analysis by TLC showed the presence of aminal **267**, which was not present earlier in the crude reaction mixture. Subsequent ^{1}H NMR analysis confirmed the presence of **267** and the absence of the unassigned addition product (eq 102, Scheme 84). In addition to this, it could be seen that the mixture now contained more of aldehyde **264** and less unreacted FmocCl. Therefore, it was hypothesized that the unassigned addition product observed in these reactions might be the Fmoc-protected imine dimer **268**, which could convert to aminal **267** in the presence of atmospheric water and unreacted FmocCl (eq 103, Scheme 84). In order to confirm this, a third aza-Henry reaction was performed with imine **265**. After the reaction was complete, the crude material was kept dry and subjected to LCMS analysis. Indeed, the mass of dimer **265** could be observed as a major component of the crude reaction mixture (eq 104, Scheme 84).

It is thought that this undesired imine dimerization is once again a result of the steric bulk of the imine. It was clear that imine addition was occurring at a faster rate than the desired addition of bromonitromethane. Addition to the imine can occur, but perhaps bromonitromethane is sterically too large. Therefore, attempts were made to synthesize fluoronitromethane (**269**), which should be less sterically bulky. In order to do this,

nitromethane was treated with KOH in water. After stirring for 1 hour, Selectfluor® was added. The presence of fluoronitromethane (**269**) was supported by ^{1}H NMR analysis; however, the reaction had proceeded to only 53% conversion (eq 105, Scheme 85). From our previous studies of this reaction, we knew that nitromethane would not add to *N*-TMS imines at -78 °C. Therefore, fluoronitromethane (**269**) was added to *N*-TMS imine **265** as a mixture with nitromethane. Unfortunately, ^{1}H NMR analysis showed that while none of imine dimer **268** was present, only starting material could be observed and α-fluoro nitroalkane **270** had not formed (eq 106, Scheme 85).

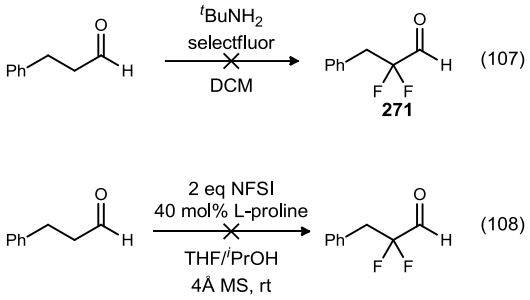
Scheme 85. Synthesis of flouronitromethane and addition to *N*-TMS imine **265**.



Since fluoronitromethane seemed to be unreactive toward imine **265**, a different approach was attempted to reduce the unfavorable steric interactions in this reaction. The synthesis of α,α-difluoro hydrocinnamaldehyde **271** was attempted. By replacing the chlorine substitutents with fluorines, it was hoped that the resulting *N*-TMS imine would be less hindered, and therefore more reactive toward bromonitromethane addition. Unfortunately, the synthesis of aldehyde **271** proved challenging. By simply treating cinnamaldehyde with ^{t}BuNH$_2$ and Selectfluor®, we were unable to see any of the doubly-fluorinated product **271**, as only single fluorination was observed (eq 107, Scheme 86).

We next turned to a known procedure for the synthesis of aldehyde **271**.[134] In this procedure, the authors did not isolate the aldehyde directly, but instead used it in crude form in a reductive amination. This may be due in part to the instability of the product, as in our hands aldehyde **271** could not be isolated (eq 108, Scheme 86).

Scheme 86. Attempts to synthesize α,α-difluoro hydrocinnamaldehyde **271**.

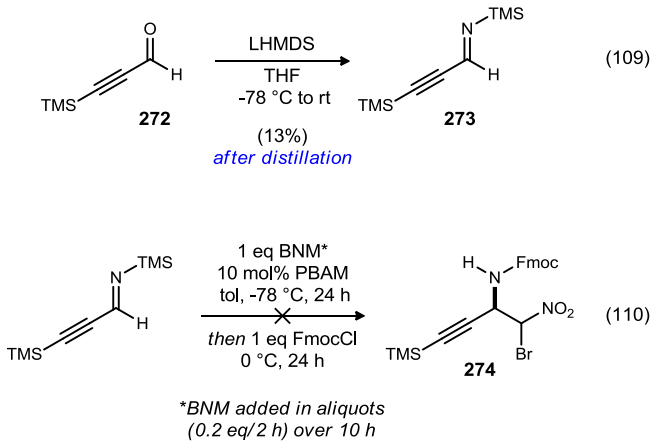


Thus far, we had seen that unsubstituted aliphatic imines were unstable and prone to enamine formation, giving complex reaction mixtures after aza-Henry addition, and that fully substituted aliphatic imines were too sterically hindered for bromonitromethane addition. Therefore, we decided to turn to unsaturated aliphatic imine derivatives. These imines should be stable, as enamine formation is prevented, and significantly less hindered than the saturated aliphatic imines. We first synthesized alkynyl imine **273** by treating TMS-alkynyl aldehyde **272** with LHMDS in THF. The desired imine (**273**) could be isolated by distillation, however, the isolated yield was quite low (13%, eq 109, Scheme 87). Regardless, a sufficient amount of pure imine **273** was obtained to submit this compound to our standard aza-Henry conditions. After quenching with FmocCl, we were disappointed to see no sign of desired α-bromo nitroalkane **274** by ^{1}H NMR analysis of the crude reaction mixture. While imine **273** had been completely consumed, large amounts of remaining bromonitromethane and FmocCl were observed, suggesting

[134] Fadeyi, O.; Lindsley, C. W. *Org. Lett.* **2009**, *11*, 943.

that aza-Henry addition had not occurred. A number of unidentified TMS resonances were also observed around 1-2 ppm, but no other clues as to the fate of alkynyl imine **273** could be detected (eq 110, Scheme 87). It was noted at this point that the pure sample of alkynyl *N*-TMS imine **273** had turned from a light yellow oil to a viscous dark brown oil. Subsequent ^{1}H NMR analysis of this material showed that imine **273** had completely decomposed to give a similar composition as was seen after the aza-Henry reaction- only TMS resonances between 1 and 2 ppm were observed. This led us to conclude that alkynyl *N*-TMS imine **273** quickly decomposed under the aza-Henry reaction conditions before addition could occur.

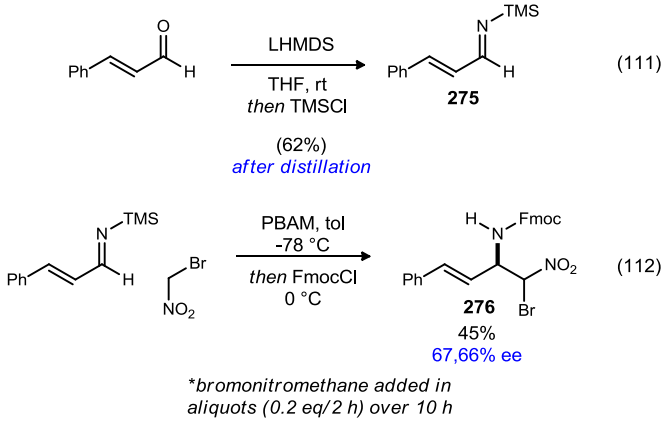
Scheme 87. Synthesis of alkynyl *N*-TMS imine **273** and attempted aza-Henry addition.



Attention was therefore next turned to the synthesis of known cinnamyl *N*-TMS imine **275**.[114] After treating cinnamaldehyde with LHMDS in THF and filtering under an inert atmosphere, desired imine **275** was isolated in 62% yield after distillation (eq 111, Scheme 88). When imine **275** was submitted to our standard aza-Henry reaction conditions and quenched with FmocCl, we were pleased that the desired α-bromo nitroalkane **276** could be isolated in 45% yield. Additionally, the two diastereomers produced in this reaction were determined to be 67 and 66% ee (eq 112, Scheme 88).

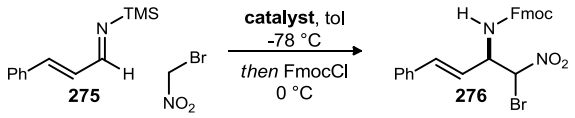
While this level of enantioselection is moderate, it is comparable to the results obtained with the simple phenyl aryl *N*-TMS imine **200g** (Table 12, entry 8, 63% yield, 65, 66% ee for **201g**). It is also the highest level of enantioselection observed to date for a non-aryl imine substrate.

Scheme 88. Synthesis of cinnamyl *N*-TMS imine **275** and aza-Henry addition.



A brief catalyst screen was performed with the catalysts that had provided the highest levels of enantioselection with ^{p}Cl aryl *N*-TMS imine **181**, as an increase in ee was sought. Unfortunately this was not the case, as both ^{6,7}MeO-PBAM (**188**) and Stilb-PBAM (**191**) catalysts gave α-bromo nitroalkane **276** in lower yields and enantioselection (Table 24, entry 2 and entry 3, respectively).

Table 24. Catalyst screen for aza-Henry addition to cinnamyl *N*-TMS imine **275**.

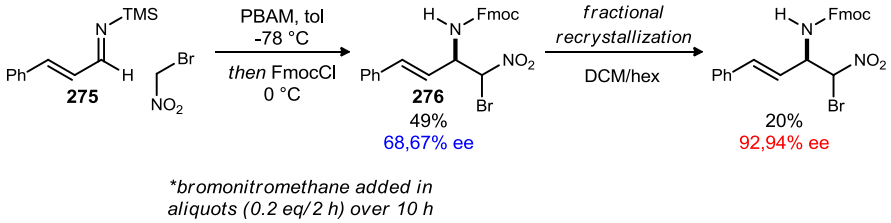


entry	catalyst[b]	yield (%)[a]	ee (%)[c]
1	PBAM (**87**)	45	67,66
2	^{6,7}MeO-PBAM (**188**)	19	9,10
3	Stilb-PBAM (**191**)	34	13,12

[a] An aliquot addition (0.2 eq/2 h) of bromonitromethane over 10 h was used in all cases.[b] Catalyst structures are shown in Table 7.[c] Enantiomeric excess reported for each diastereomer.

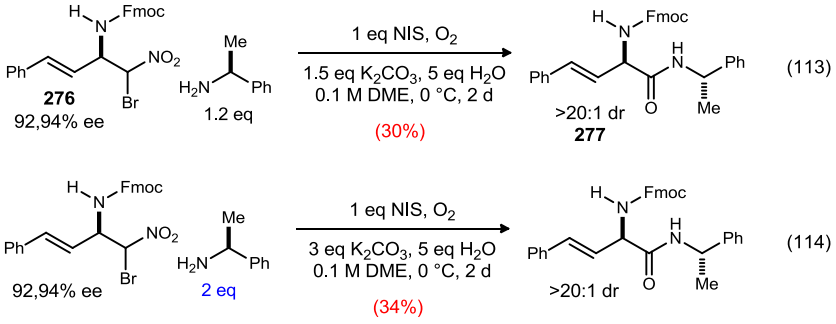
Since these initial results suggested that PBAM was once again the ideal catalyst for this system, we delayed a more complete catalyst screen. Instead, fractional recrystallization of α-bromo nitroalkane **276** was attempted in order to obtain highly enantioenriched material to use in the subsequent UmAS reaction. It was pleasing to see that after a single fractional recrystallization in DCM and hexanes, α-bromo nitroalkane **276** could be recovered in 20% overall yield and 92, 94% ee (Scheme 89).

Scheme 89. Recrystallization of cinnamyl α-bromo nitroalkane **276**.



With this high ee material in hand, an UmAS coupling was attempted between α-bromo nitroalkane **276** and α-methyl benzylamine. After stirring for 2 days in the presence of NIS, K_2CO_3 and H_2O, desired amide **277** could be isolated as a single diastereomer in 30% yield (eq 113, Scheme 90). While it was exciting that **277** was obtained, and that no epimerization was observed, the yield of this reaction (30%) was lower than desired. Therefore, a second coupling in which 2 equivalents of α-methyl benzylamine were used was performed. Unfortunately, this only resulted in a 4% increase in yield (to 34%, eq 114, Scheme 90).

Scheme 90. Initial UmAS coupling of cinnamyl α-bromo nitroalkane **276**.



In order to increase the yield further, a solvent screen for the UmAS step performed. It was found that THF gave a slight improvement in yield for **277** (33%, Table 25, entry 2) over DME (27% yield, Table 23, entry 1), after stirring for 1 day under the reaction conditions. 2-Me-THF gave an unusually low yield (15%, Table 25, entry 3), and TBME resulted in no reaction, as the starting α-bromo nitroalkane **276** was not soluble in this solvent (Table 25, entry 4).

Table 25. Investigation of solvent effects in the UmAS coupling of cinnamyl α-bromo nitroalkane **276**.

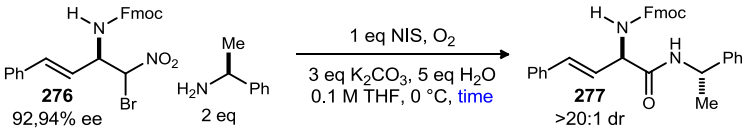
entry	solvent	yield (%)
1	DME	27
2	THF	33
3	2-Me-THF	15
4	TBME	--[a]

[a] **276** was not soluble in TBME, no reaction occurred.

Since THF provided the best results, a series of reactions to explore the optimal reaction time for the UmAS coupling in this solvent were performed. After only 3 hours, amide **277** was isolated in 33% yield (Table 26, entry 1). However, the starting α-bromo nitroalkane (**276**) was also isolated, indicating that the reaction had not yet reached full

conversion. After 6 hours, amide **277** was isolated in 45% yield (Table 26, entry 2). In this case, no starting material was isolated, indicating a complete reaction. Extended reaction times (24 and 72 hours) led to an unexpected drop in yield (Table 24, 33% yield after 24 hours, entry 3, and 27% yield after 72 hours, entry 4). This was troubling, as a decrease in yield over a longer reaction time usually indicates that the product is decomposing in some way.

Table 26. Time study of the UmAS coupling of cinnamyl α-bromo nitroalkane **276**.

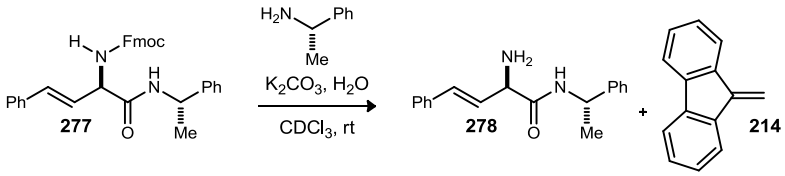


entry	time (h)	yield (%)
1	3	33(41% brsm)
2	6	45
3	24	33
4	72	27

The most obvious pathway for decomposition of amide **277** is Fmoc-deprotection. As discussed in Section 3.2.3, the basic conditions of the UmAS coupling can result Fmoc-deprotection. However, our previous studies (Table 17) had shown that Fmoc-deprotection happens slowly, so that over the standard reaction time (2 days) only trace amounts of deprotection occur. We wondered if amide **277** was more prone to Fmoc-deprotection than other Fmoc-protected peptides previously evaluated. Therefore, pure amide **277** was resubjected to the UmAS reaction conditions. After 1 day, a small amount of Fmoc-deprotection could be seen (7%, Table 27, entry 1). After 3 days, the amount of Fmoc-deprotection could not be determined, as the ^{1}H NMR resonances were too broad for accurate integrations (Table 27, entry 2). However, it was clear that a large fulvene (**214)** peak was present at this time. After 5 days, it was confirmed that a significant

amount of Fmoc-deprotection had occurred (65% deprotection, Table 27, entry 3). This confirmed our fears that amide **277** had limited stability under the alkaline coupling conditions.

Table 27. Resubmitting Fmoc-protected amide **277** to reaction conditions.

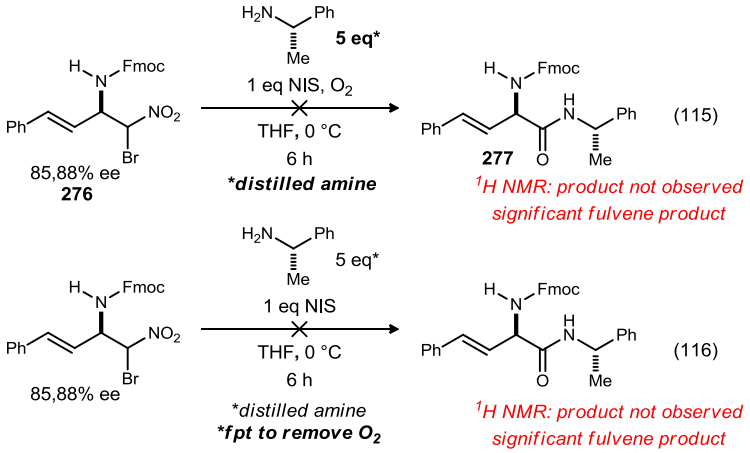


entry	time (d)	deprotection (%)[a]
1	1	7
2	3	--[b]
3	5	65

[a] Based on ^{1}H NMR analysis of crude reaction mixture, measuring relative amount of fulvene **214** to remaining amide **277**.[b] ^{1}H NMR too broad to accurately integrate peaks.

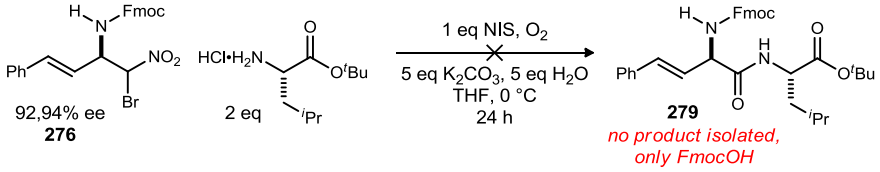
It was hypothesized that the Fmoc-deprotection was occurring as a result of the K_2CO_3 and H_2O present in the reaction mixture. Therefore, two reactions were performed in which these reagents were eliminated and the equivalents of amine, which can also act as a base to deprotonate α-bromo nitroalkane **276**, were increased. One reaction was done under an atmosphere of O_2, and one under an atmosphere of Ar, as we know that under these conditions the UmAS coupling can proceed through two distinct mechanisms.[27] Unfortunately, in both of these reactions, no product was observed in the crude reaction mixture. By ^{1}H NMR analysis, a large fulvene resonance was observed at 6.1 ppm, indicating Fmoc-deprotection (eq 115 and 116, Scheme 91). These results seem to support the conclusion that the basic amine is primarily responsible for Fmoc-deprotection in these coupling reactions.

Scheme 91. UmAS coupling of α-bromo nitroalkane **276** without K_2CO_3 and H_2O.



In order to avert Fmoc-deprotection by the basic α-methyl benzylamine, a coupling was attempted between α-bromo nitroalkane **276** and the HCl salt of leucine. It was hoped that using the protonated salt form of this amino acid would attenuate the basicity of the amine and lower the amount of Fmoc-deprotection observed. This proved to not be the case, however, as amide **279** could not be isolated from this reaction (Scheme 92). What was isolated from this reaction was a large amount of FmocOH, indicating Fmoc-deprotection had occurred under these conditions as well.

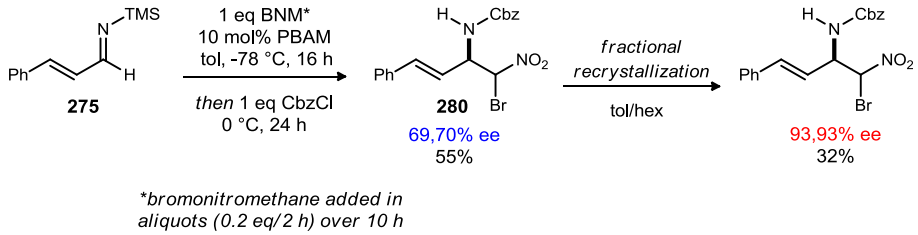
Scheme 92. Attempted UmAS coupling of α-bromo nitroalkane **276** with HCl·H_2N·Leu·O^{t}Bu.



At this point, it was clear that the Fmoc-protecting group was hindering our attempts to successfully couple **276** using UmAS conditions. Therefore, it was decided to investigate a different protecting group that might be more stable under our coupling conditions. By quenching the aza-Henry addition to cinnamyl *N*-TMS imine **275** with CbzCl, Cbz-protected α-bromo nitroalkane **280** could be isolated in 55% yield and

69/70% ee (Scheme 93). It was pleasing to see that the enantiopurity of this product could be enriched through fractional recrystallization in toluene and hexanes, to give Cbz-protected α-bromo nitroalkane **280** in 32% overall yield and 93, 93% ee (Scheme 94).

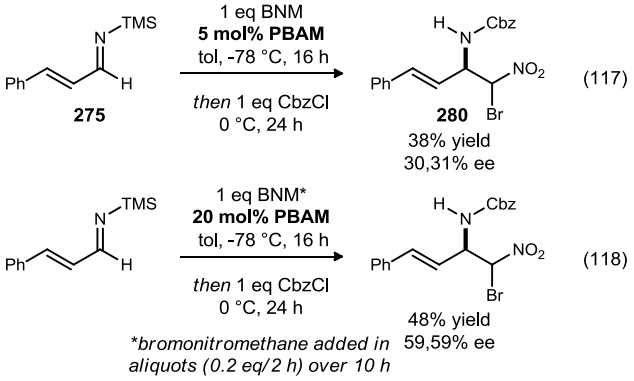
Scheme 93. Synthesis and recrystallization of cinnamyl α-bromo nitroalkane **280**.



Although the ee of α-bromo nitroalkane **280** could be enriched through recrystallization, several reactions were performed with the hope of optimizing the enantioselectivity of the aza-Henry addition of bromonitromethane to imine **275**. In order to determine the effect a slow addition of bromonitromethane had on the enantioselection of the reaction, a reaction was performed in which bromonitromethane was added as a single portion at the beginning of the reaction. The ee of the α-bromo nitroalkane product (**280**) was only 30, 31%, indicating that the enantioselectivity of the addition to *N*-TMS imine **275** is highly dependent on the concentration of bromonitromethane (eq 117, Scheme 94). This outcome is similar to what was observed with aryl *N*-TMS imines. Based on these results, a second reaction was attempted in which the bromonitromethane was added slowly over 10 h, and the catalyst loading was increased to 20 mol% (from 10 mol%, Scheme 94). It was hypothesized that by increasing the catalyst loading, the relative ratio of bromonitromethane to catalyst would be lowered, increasing the enantioselection of the addition. This was not the case, however, as a lower yield and ee was observed in this reaction (48% yield, 59, 59% ee, eq 118, Scheme 94). While it is

unclear why a higher catalyst loading is detrimental in this case, it is clear that the optimal catalyst loading for this reaction is 10 mol%.

Scheme 94. Attempted optimization of the aza-Henry addition to cinnamyl *N*-TMS imine **275**.

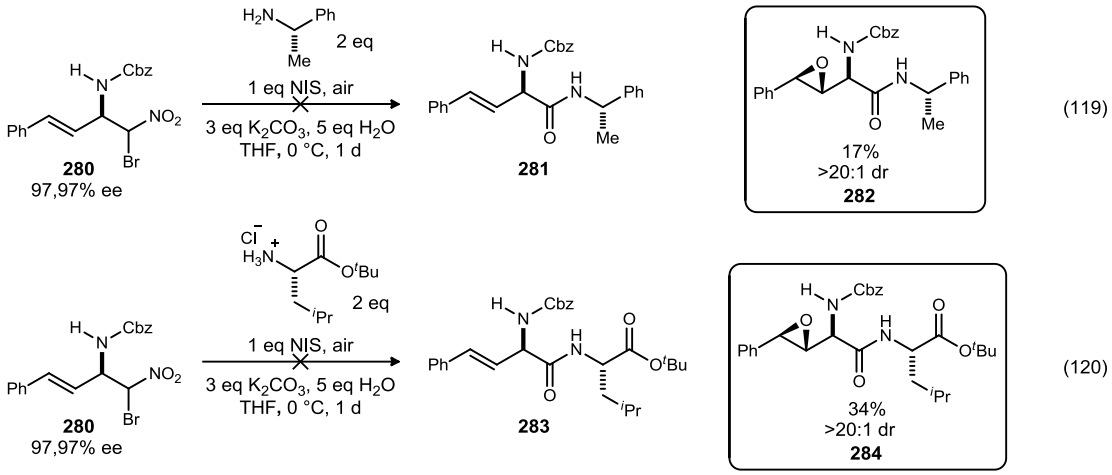


Attention was next turned to the UmAS coupling of α-bromo nitroalkane **280**. When this compound was subjected to standard coupling conditions, in the presence of 2 equivalents of α-methyl benzylamine, a single major product was observed by ^{1}H NMR analysis of the crude reaction mixture. Upon isolation we were surprised to see this compound was not the desired amide **281**, but was instead the epoxy amide **282**, isolated as a single diastereomer in 17% yield (eq 119, Scheme 95).[135]

Since the results of this reaction were surprising, a second coupling was performed using leucine ^{t}butyl ester as the amine component. While the aminal side product was not observed in this reaction, the main product was again not the desired amide **283**, but the epoxy amide **284** (34% yield, eq 120, Scheme 95). This suggests that this unusual epoxide formation is common to α-bromo nitroalkane **280**, regardless of the amine coupling partner.

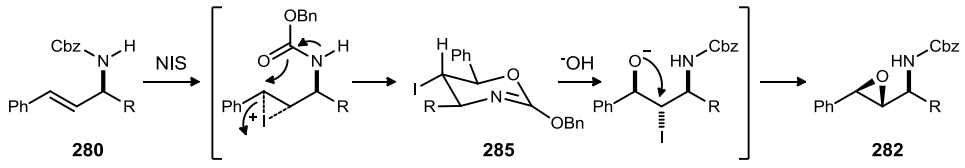
[135] The relative stereochemistry of the epoxide has not yet been determined. Attempts obtain a crystal structure are underway. Based on our mechanistic hypothesis, the epoxide has been temporarily assigned as *syn* to the amine.

Scheme 95. UmAS coupling of cinnamyl α-bromo nitroalkane **280**.



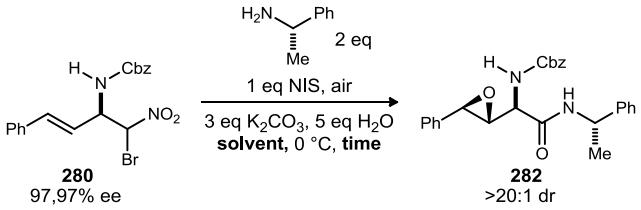
While it was surprising that epoxidation of the double bond was occurring under these reaction conditions, a mechanism for this transformation can be drawn which would account for the high degree of observed diastereoselection. In the presence of an electrophilic source of iodine, the double bond could be activated towards nucleophilic addition through the formation of a cyclic iodonium species. This intermediate could then react with water, to form the iodo alcohol first and then the epoxide. However, because this epoxidation occurs with a high level of stereocontrol, it is possible that the carbamate functionality of the Cbz-protecting group assists with the hydrolysis. This could happen through the formation of a cyclic oxazine intermediate **285**, which would form the iodo alcohol after hydrolysis. A subsequent S_N2 would result in the observed epoxide **282** (Scheme 96).

Scheme 96. Proposed mechanism for formation of epoxy amide **282**.



While epoxy amide **282** was not the expected product of the UmAS coupling of α-bromo nitroalkane **280**, this unexpected transformation could be a useful way to affect amide coupling and double bond functionalization in a single synthetic step. Therefore, we decided to optimize the UmAS reaction while increasing the yield of this product. After stirring for one day in THF, epoxy amide **282** was isolated in 17% yield (Table 28, entry 1). By increasing the reaction time to 2 d, the yield of **282** was increased to 36% (Table 28, entry 2). Performing this reaction in DME did not significantly increase the yield of epoxy amide **282** (30% yield, Table 28, entry 3), and longer reaction times in this solvent unfortunately proved unhelpful (24% yield of **282**, Table 28, entry 4), as did using an excess of α-methyl benzylamine (Table 28, entry 5). Based on this observation, a reaction was run with only a slight excess of α-methyl benzyl amine (1.2 equiv) instead of the 2 equiv used previously. However, this also resulted in a lower yield of epoxy amide **282** (30%, Table 28, entry 6). A slight improvement was seen when 2-Me-THF was used as the solvent, which gave a less complex crude reaction mixture and increased yield of epoxy amide **282** (40%, Table 28, entry 7). In order to try and promote the epoxidation, a reaction was run with an excess of NIS and H_2O. Unfortunately, this resulted in only trace amounts of epoxy amide **282**. By ^{1}H NMR analysis, it was revealed that the major component of the crude reaction mixture was the α-iodinated α-bromo nitroalkane **287** (Table 28, entry 8).

Table 28. Optimization studies of the UmAS coupling of cinnamyl α-bromo nitroalkane **280**.

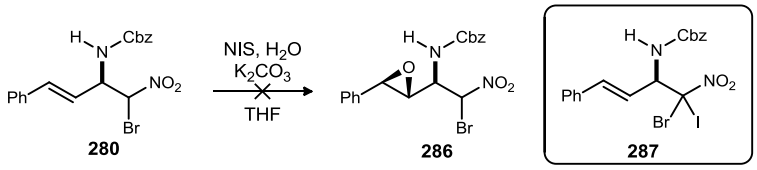


entry	solvent	time (d)	**282** yield (%)
1	THF	1	17
2	THF	2	36
3	DME	1	30
4	DME	2	24
5[b]	DME	2	trace[a]
6[c]	THF	2	30
7	2-Me-THF	2	40
8[d]	THF	2	trace[a]

[a] Based on ^{1}H NMR analysis of crude reaction mixture. [b] Excess of amine (5 eq) used as base in this reaction in place of K_2CO_3. [c] 1.2 eq amine, 1.5 eq of K_2CO_3 used in reaction. [d] 1.2 eq amine, 1.5 eq K_2CO_3, 3 eq NIS, 15 eq H_2O used in reaction. [e] In all cases, amide **281** was not isolated.

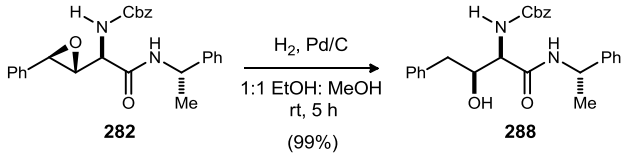
At this point, it was still unclear whether the epoxidation of the double bond was occurring before or after amide coupling. Therefore, a test reaction was performed in which α-bromo nitroalkane **280** was stirred with NIS and H_2O in THF. ^{1}H NMR analysis of the crude reaction mixture revealed clean formation of α-iodo α-bromo nitroalkane **287**, and none of the epoxy α-bromo nitroalkane **286** was observed (Scheme 97). This suggests that epoxide formation occurs after amide formation, or even perhaps at some point during amide formation.

Scheme 97. Attempted formation of **286**.



While the epoxy amide (**282**) formed under these conditions is an interesting and potentially useful non-natural amino acid residue in its own right, it was subjected to hydrogenolysis conditions to form the 4-phenyl threonine derivative **288**. After subjecting **282** to H_2 and 10% Pd/C, β-hydroxyl-α-amino amide **288** was isolated in quantitative yield (Scheme 98).

Scheme 98. Hydrogenation of product **282**.



While unexpected, this unusual epoxidation allows us to use this methodology to access non-natural functionalized aliphatic amino acid residues. Further work will be done to determine whether this transformation occurs exclusively with cinnamyl substrates, or if other alkene side chains undergo a similar epoxidation under the UmAS reaction conditions.

CHAPTER IV

PROGRESS TOWARDS THE TOTAL SYNTHESIS OF FEGLYMYCIN

4.1 Introduction and Background

When used in conjunction with Umpolung Amide Synthesis (UmAS), the enantioselective aza-Henry addition of bromonitromethane to *N*-TMS imines provides a powerful new pathway for the synthesis of aryl glycine containing peptides. In three steps from the aldehyde, aryl glycine residues can be synthesized and incorporated into peptides with a very high degree of stereocontrol. Additionally, multiple protecting groups can now be accessed through this methodology, allowing for its use in orthogonal peptide synthesis.

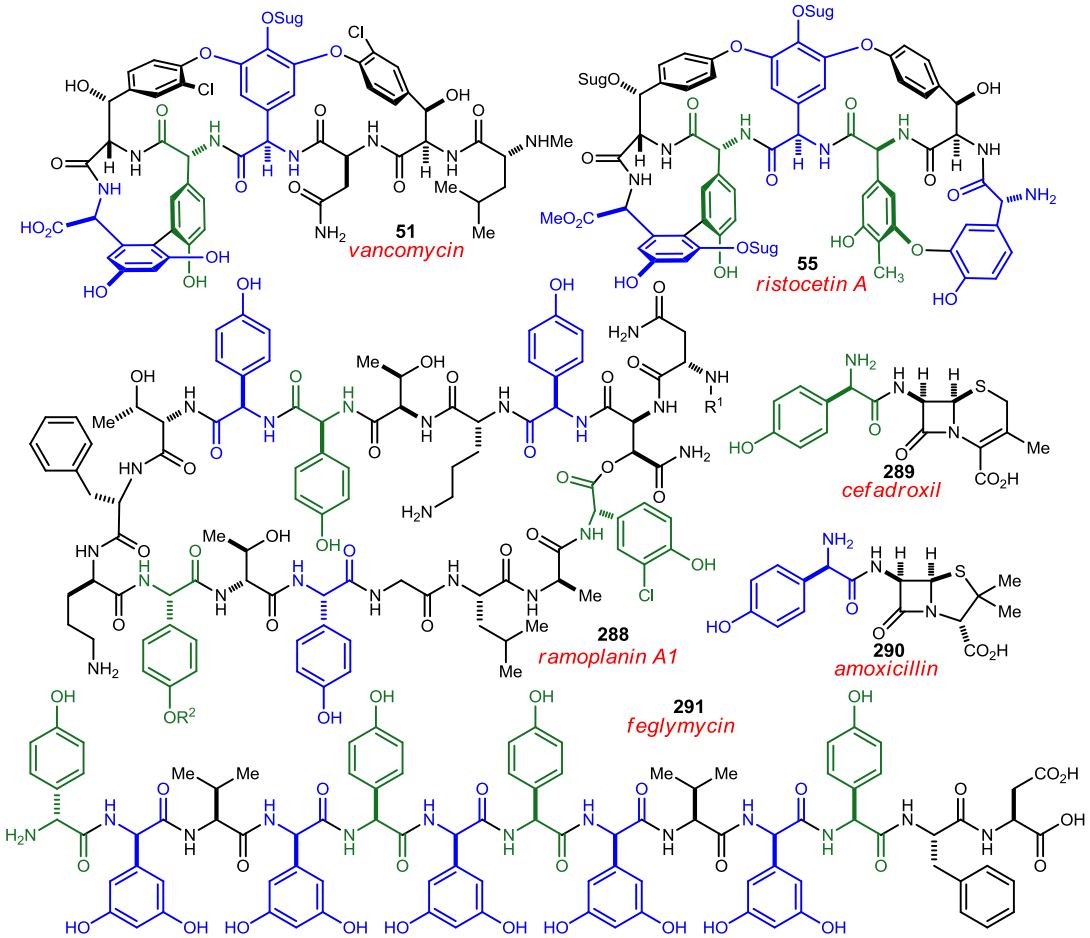
In order to demonstrate the utility of this methodology, we decided to apply it to the synthesis of an aryl glycine-containing natural product. There are several notable aryl glycine-containing natural products, seen in Figure 12, most of which possess potent antibacterial activity. As discussed in Section 2.1.1, the most prominent of these is perhaps vancomycin (**51**),[46] which generated much synthetic interest following its discovery.[49,50] This interest was driven by the fact that, due to its potent antibacterial activity, vancomycin is used as a "line of last defense" against bacteria that have become resistant to other antibiotics.[45] The vancomycin-related ristocetin A (**55**)[136] and the more recently discovered cyclic peptide ramoplanin A1 (**288**)[137] are also clinically used to fight

[136] Phillip, J. E.; Schenck, J.R.; Hargie, M.P. *Antibiot. Annu.* **1956**, 699.
[137] Farver D. K.; Hedge D.D.; Lee S.C. *Ann. Pharmacother.* **2005**, *39*, 863.

certain resistant strains of bacteria. Additionally, some commonly used antibiotics, such as cefadroxil (**289**) and amoxicillin (**290**), also contain aryl glycine residues.

While our methodology would be useful in the synthesis of any of these medicinally important compounds, we decided to first pursue the total synthesis of the newly discovered straight-chain peptide natural product feglymycin (**291**, Figure 12).[138] Like other aryl glycine containing peptides, this compound exhibits interesting biological activity, including antibacterial activity. This, along with the high proportion of aryl glycines present in the molecule made it an attractive target for our chemistry.

Figure 12. Aryl glycine-containing natural products: potent antibiotics.



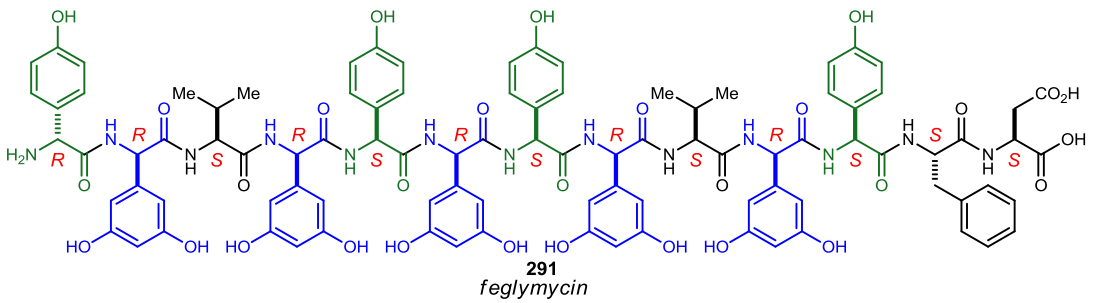
[138] Vértesy, L.; Artez, W.; Knauf, M.; Markus, A.; Vogel, M.; Wink, J. *J. Antibiot.* **1999**, *52*, 374.

4.1.1 Feglymycin

Isolation and Structure Determination

Feglymycin (**291**) was isolated in 1999 from a fermentation culture of *Streptomyces* sp. DSM 11171.[138] It was isolated by using solid phase extraction, size exclusion chromatography and reverse-phase chromatography. Upon its isolation, it was determined by mass spectroscopy that the molecular weight of the compound was 1900.90 g/mol and that the molecular formula was $C_{95}H_{97}N_{13}O_{30}$. ^{1}H and ^{13}C NMR analysis revealed that feglymycin contained 13 amino acid residues, four of which are 4-hydroxy phenylglycine (Hpg) residues and five of which are 3,5-dihydroxy phenylglycine (Dpg) residues. The other four amino acid residues were identified as L-valine (2), L-phenylalanine and L-aspartic acid after peptide hydrolysis in aqueous HCl. The linear arrangement of these residues was determined by 2D NMR analysis (HSQC, HMBC, COSY, TOCSY and NOESY) and confirmed by MS-MS analysis.[138] The relative stereochemistry of each amino acid residue was assigned in 2005, when the crystal structure of feglymycin was obtained.[139] The absolute stereochemistry of the phenylglycine residues were then able to be assigned by correlation to the known stereocenters of the L-valine, L-phenylalanine and L-aspartic acid residues (Figure 13).

Figure 13. Structure of feglymycin (**291**).

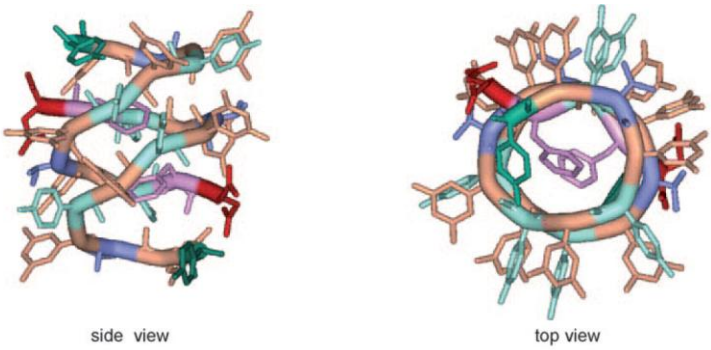


291
feglymycin

[139] Bunkoczi, G.; Vertesy, L.; Sheldrick, G. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1340.

Through the crystal structure of feglymycin (**291**), several interesting aspects of its structure were brought to light. The first is that the absolute stereochemistry of the phenylglycine residues is not conserved throughout the molecule. Three of the 4-hydroxy phenylglycine residues were assigned as L-Hpg, while the terminal 4-hydroxy phenylglycine residue had the opposite configuration (D-Hpg). All of the 3,5-dihydroxy phenylglycine residues were assigned as D-Dpg (Figure 13).[139]

Figure 14. Double-helical dimer of feglymycin (**291**).[140]



As observed with other alternating D,L-peptides,[141] the crystal structure of feglymycin showed that it had formed a double-helical dimer upon crystallization (Figure 14). When lined up end to end, the feglymycin dimers form an infinite helical structure which can be described as a right-handed, wide, antiparallel, double-stranded β-helix.[139]

Biological Activity

At the time of its isolation, feglymycin (**291**) was reported to have weak antibacterial activity against Gram positive bacteria (IC_{50} of 32-64 μg/mL against several strains of *Staphylococcus aureus*). However, later biological studies performed by Süssmuth and coworkers revealed that this peptide was active against methicillin-

[140] Copied with permission from: Dettner, F.; Hanchen, A.; Schols, D.; Toti, L.; NuBer, A.; Süssmuth, R. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 1856.
[141] This is also seen with the membrane channel peptide gramicidin: Langs, D. A. *Science* **1988**, *241*, 188.

resistant *Staphylococcus aureus* (MRSA) with an IC_{80} value of 2 μg/mL.[142] This finding prompted further studies into the mechanism of action of feglymycin (**291**). Based on the structure and molecular weight of feglymycin, it was thought that it might have a similar mechanism of action to other aryl glycine containing peptides, such as vancomycin (**51**) or ramoplanin (**55**). These compounds interfere in cell wall biosynthesis by inhibiting the late stages of peptidoglycan production, as do most clinically important antibiotics. However, initial studies by Süssmuth and coworkers indicated feglymycin had no effect on the last two stages of peptidoglycan biosynthesis, but instead was inhibiting earlier biosynthetic steps. Based on this observation, the authors examined feglymycin's effect on enzymes Mur A-F, which catalyze the first six steps of peptidoglycan synthesis. They found that feglymycin noncompetitively inhibited the enzymes Mur A (IC_{50} of 3 μM) and Mur C (IC_{50} of 1 μM), making it the first known natural inhibitor of these enzymes. This unique mechanism of action could make feglymycin a useful antibiotic against resistant bacterial strains.[142]

In addition to possessing antibacterial activity, feglymycin was also reported to strongly inhibit the formation of HIV syncytia *in vitro* (IC_{50} of ~5 μM).[138] Syncytia are multinucleate cells which are formed by the joining of two or more single nucleate cells.[143] A hallmark of HIV infection, syncytia formed through the joining of multiple CD^{4+} T-cells can often be seen in the patient's blood stream. The mechanism of syncytia formation in HIV infected cells involves the viral membrane fusion protein gp41. This glycoprotein, which is a subunit of the envelope protein complex of the HIV retrovirus, is responsible for the second step by which HIV infects white blood cells. After the virus is

[142] Rausch, S.; Hanchen, A.; Denisiuk, A.; Lohken, M.; Schneider, T.; Sussmuth, R. D. *Chem. Bio. Chem.* **2011**, *12*, 1171.
[143] Daubenmire, R. F. *Science* **1936**, *84*, 533.

bound by the CD^{4+} T-cell, gp41 acts to fuse the HIV to the cell membrane of the T-cell, allowing it to enter into the cell.[144]

After HIV invades a healthy CD^{4+} T-cell, it induces the cell to produce viral proteins, including the membrane fusion protein gp41, which are then displayed on the cell membrane. These proteins then allow the infected cell to fuse to other nearby CD^{4+} helper T-cells, through the same mechanism with which HIV enters a cell. Once fused, the cell membrane of these cells will join, forming a large, non-functional syncytium.[145] In this way, a single HIV virion can infect and kill many CD^{4+} T-cells. Syncytia formation is often monitored as a way to assay a compound's efficacy at inhibiting the binding of the viral membrane fusion protein gp41 to a cell membrane. Because this protein plays a vital role in both HIV infection and syncytia formation, a compound that successfully inhibits syncytia formation will likely also inhibit HIV infection.

Though the molecular mechanism of the antiviral activity of feglymycin has not yet been investigated, its structure offers clues as to how this peptide might function. While similar helical peptides[141] have been shown to function as membrane transport proteins, it is unlikely that feglymycin performs a similar function. The feglymycin helix is not long enough to span a cell membrane, and its channel is blocked by the phenylalanine side chains. Vértesy and co-workers suggest that perhaps feglymycin could act as an ion carrier instead, providing a mechanism for membrane penetration which may disrupt the binding of the fusion protein gp41.[139]

[144] Kim P. S.; Malashkevich V. N.; Chan D. C.; Chutkowski C. T. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 9134.
[145] Huerta, L.; López-Balderas, N.; Rivera-Toledo, E.; Sandoval, G.; Gŕmez-Icazbalceta, G.; Villarreal, C.; Lamoyi, E.; Larralde, C. *The Scientific World Journal* **2009**, *9*, 746.

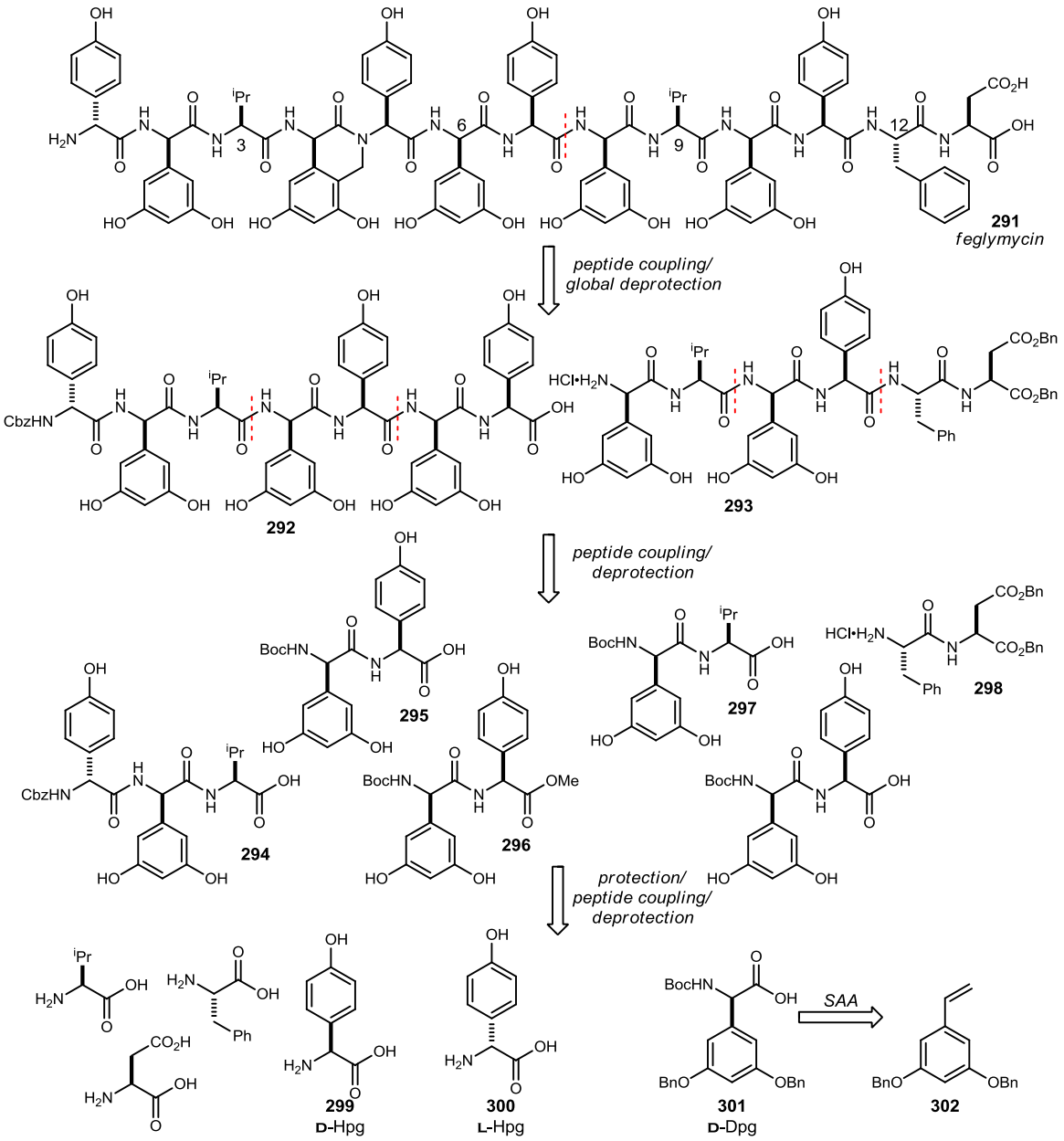
4.1.2 Previous Synthesis of Feglymycin

The total synthesis of feglymycin has been achieved only once, by Süssmuth and co-workers in 2009.[146] They utilize a highly convergent approach in which di- and tripeptide fragments are synthesized and then condensed to give the 13 amino acid residue peptide. The retrosynthetic approach used by the authors can be seen in Scheme 99. They envisioned that a disconnection could be made between Hpg residue 7 and Dpg residue 8, breaking feglymycin (**291**) into two smaller peptide fragments (**292** and **293**) which would subsequently come from six di- and tripeptide fragments (**294**-**298**). These fragments could then be synthesized from the commercially available amino acids valine, phenylalanine, aspartic acid, D-Hpg **299** ($1/g from Sigma Aldrich) and L-Hpg **300** ($10/g from Sigma Aldrich). The only residue which is not commercially available, D-Dpg **301**, could come from the Sharpless asymmetric aminohydroxylation (SAA) of styrene **302**.

As mentioned previously, phenylglycine residues readily epimerize under standard peptide coupling conditions. This holds especially true for the highly racemization prone amino acid 3,5-dihydroxy phenylglycine (Dpg). With this in mind, the authors specifically designed this approach to avoid activation of Dpg when condensing the di- and tripeptide fragments, as they knew it would be more difficult to separate diastereomers at later stages of the synthesis (Scheme 99).[146]

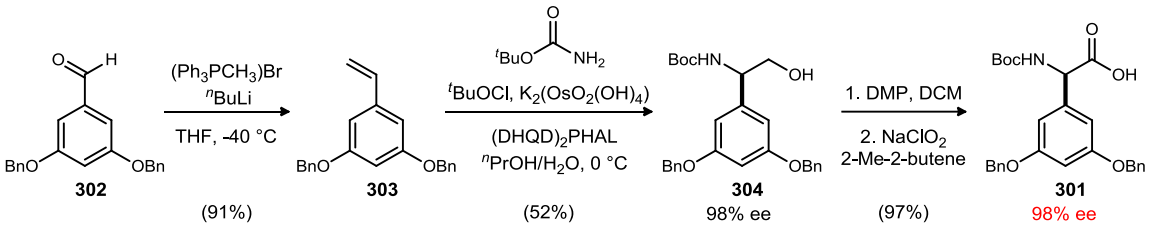
[146] Dettner, F.; Hanchen, A.; Schols, D.; Toti, L.; NuBer, A.; Süssmuth, R. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 1856.

Scheme 99. Sussmuth's retrosynthetic approach to feglymycin (**291**).



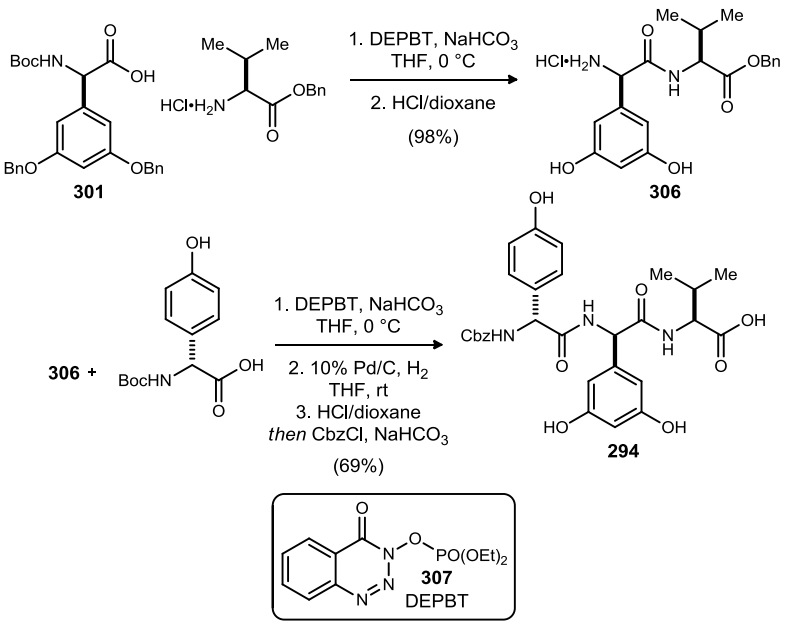
The authors began with the synthesis of protected D-Dpg **301**. Starting from 3,5-dibenzyloxy benzaldehyde **303**, a Wittig reaction provided styrene **302** in 91% yield. A subsequent Sharpless asymmetric aminohydroxylation (SAA) gave the amino alcohol **304** in 52% yield and 98% ee. A two-step oxidation provided the desired carboxylic acid **301** in 97% yield, with no loss in enantiopurity (Scheme 100).[146]

Scheme 100. Süssmuth's synthesis of (*R*)-Dpg **301**.



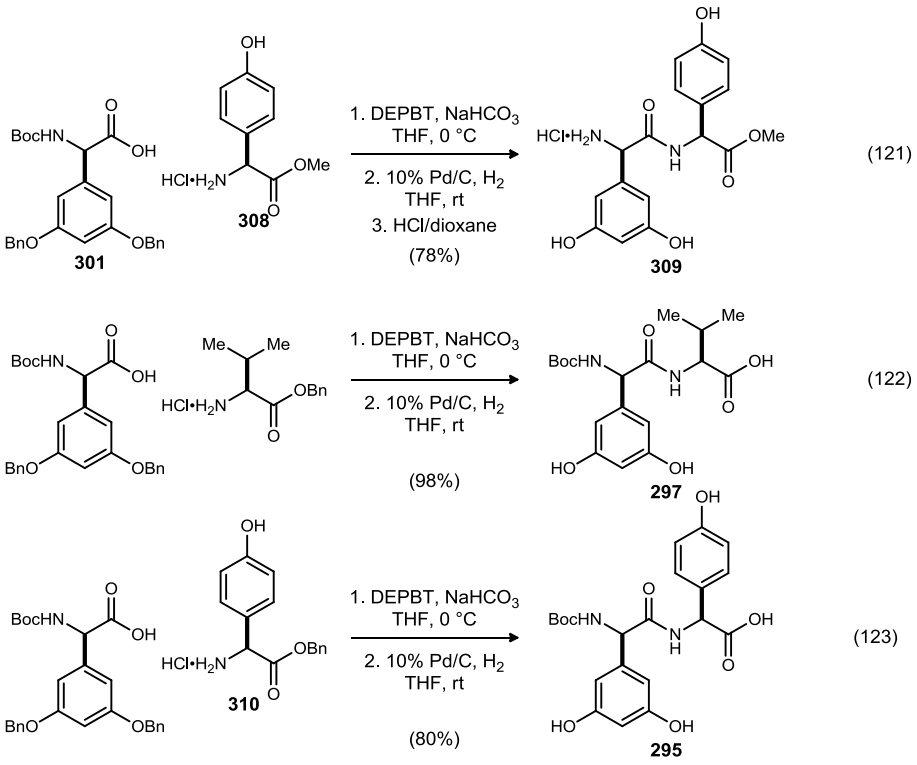
With **301** successfully synthesized, the di- and tripeptide fragments were synthesized through condensative amide coupling. The authors found that the coupling reagent 3-(diethyloxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (DEPBT, **305**, $10/g from Sigma Aldrich) was the only reagent able to successfully couple Dpg **301** without significantly epimerizing the α-stereocenter. All other coupling reagents resulted in lower conversion and substantial epimerization of the hydroxyphenyl glycine amino acids.[146] Using 2 equiv DEPBT, Dpg **301** was coupled to valine benzyl ester to give the dipeptide **306** in 98% yield, after Boc-deprotection. A second DEPBT coupling and protecting group manipulation gave the tripeptide fragment **307** in 69% yield (Scheme 101).[146]

Scheme 101. Süssmuth's synthesis of the tripeptide fragment **308**.



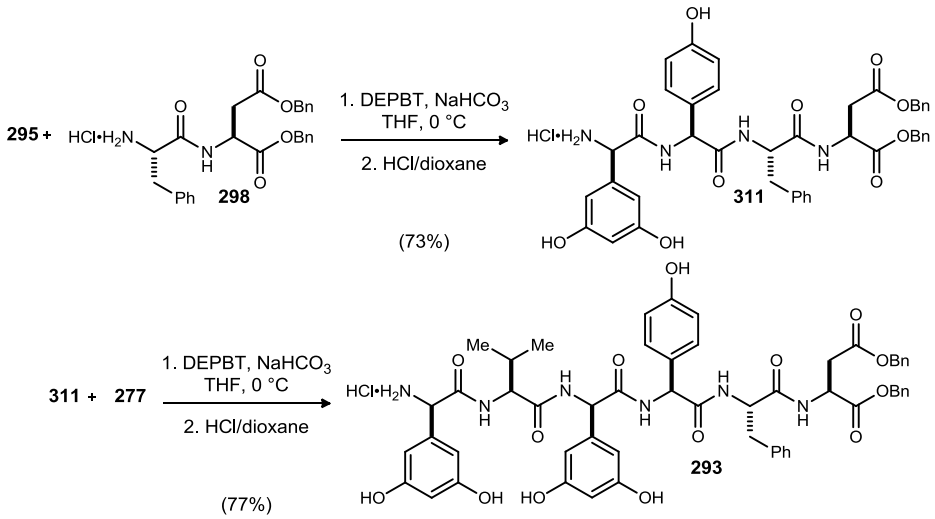
The synthesis of the dipeptide fragments proceeded in similar fashion. Using 2 equiv DEPBT, Dpg **301** was coupled to the Hpg methyl ester (**308**) in 78% yield, giving the free amine dipeptide **309** after hydrogenolysis and Boc-deprotection (eq 121, Scheme 102). Dpg **301** was also successfully coupled to the benzyl ester of valine and the benzyl ester of Hpg (**310**), giving the free acid dipeptides **297** and **295**, respectively, after hydrogenolysis (eq 122 and eq 123, Scheme 102). The authors found it necessary to fully deprotect the Dpg residues at the dipeptide stage, as condensation of the protected dipeptides resulted in peptide fragments with very low solubility in both aqueous and organic solvents.[146]

Scheme 102. Süssmuth's synthesis of the dipeptide fragments of feglymycin **291**.



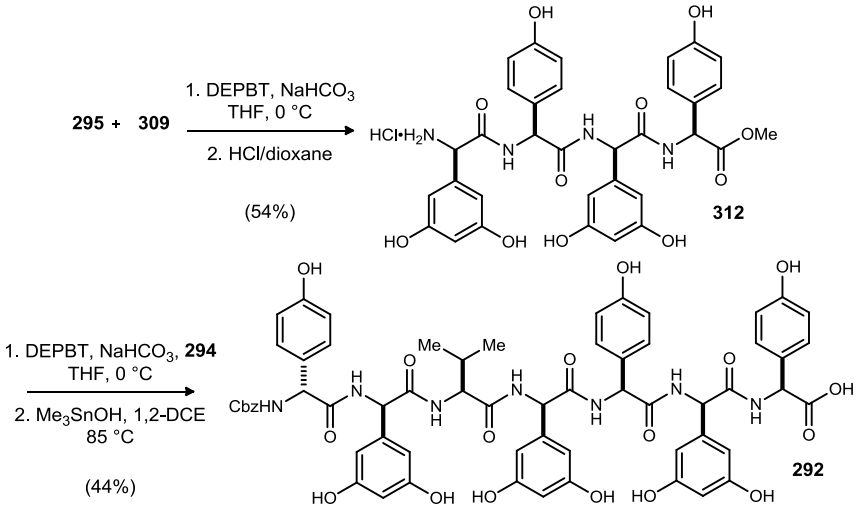
With the di- and tripeptide fragments synthesized, the authors proceeded to assemble the two larger peptide fragments **292** and **293**. DEPBT coupling of **295** with the dipeptide **298**, synthesized from the EDT coupling of phenylalanine and the benzyl ester of aspartic acid, gave the tetramer **311,** after Boc-deprotection. **311** was then coupled to **297** to give the peptide fragment **293** which constitutes the eastern portion of feglymycin **291**, in good yield (Scheme 103).[146]

Scheme 103. Condensation of the dipeptide fragments to form the peptide **293**.



The western portion of feglymycin **291** was synthesized in a similar fashion. Dipeptides **295** and **309** were coupled to give the tetramer **312** in 54% yield after Boc-deprotection. This was then coupled to the tripeptide fragment **294**, providing the free acid **292** after saponification with trimethyltin hydroxide (Scheme 104).[146]

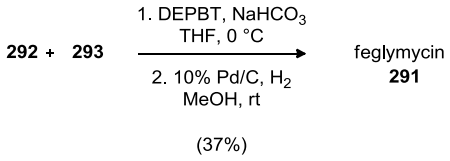
Scheme 104. Condensation of the di- and tripeptide fragments to form peptide **292**.



The peptide fragments **292** and **293** were then condensed, through another DEPBT coupling, to provide feglymycin **291** in 37% yield after global deprotection by

hydrogenolysis (Scheme 105). Thus, the authors were able to complete the synthesis of feglymycin **291** in 34 steps (14 steps in the longest linear sequence) and 4% overall yield. By using the specialized coupling reagent DEPBT, they were able to minimize the epimerization of the sensitive Hpg and Dpg amino acid residues and synthesize feglymycin as a single diastereomer.[146]

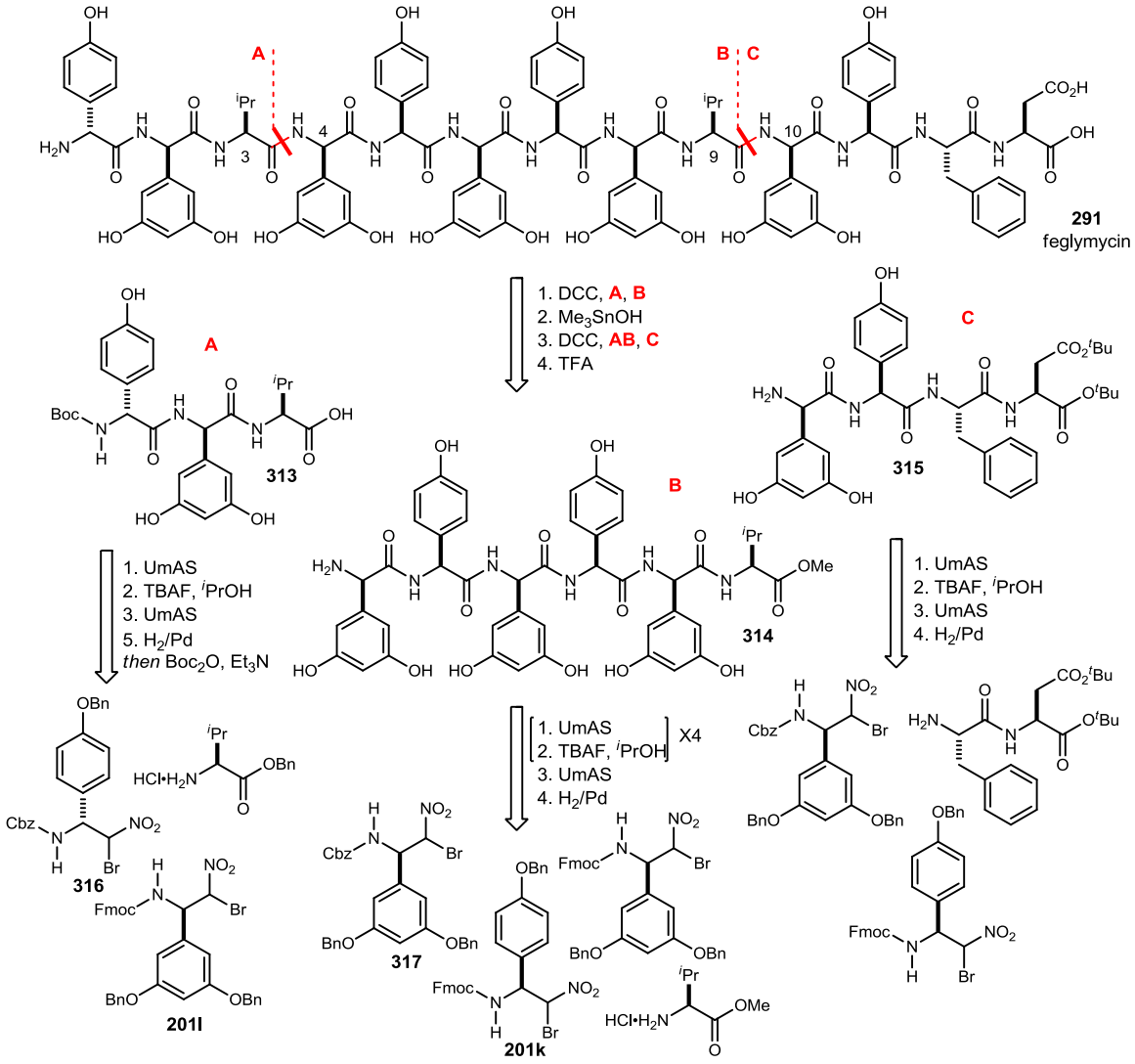
Scheme 105. Süssmuth's completion of feglymycin **291**.



4.2 Proposed Retrosynthesis of Feglymycin

Because Umpolung Amide Synthesis (UmAS) is by its nature an iterative method of amino acid homologation, it is most useful when used in a complementary manner with standard peptide coupling methods. The synthesis of feglymycin **291** provides an excellent opportunity for us to demonstrate this concept, as this peptide contains multiple sensitive arylglycine residues as well as several canonical amino acid residues. In order to make the synthesis of this compound a convergent one, we envisioned the amide bonds between Val residue 3 and Dpg residue 4, and Val residue 9 and Dpg residue 10 could be formed through conventional amide coupling methods. These key disconnections would lead to three smaller peptides, assigned as fragment A (**313**), fragment B (**314**) and fragment C (**315**), which could be synthesized using iterative UmAS chemistry (Scheme 106).

Scheme 106. First generation retrosynthesis of feglymycin **291**.



An orthogonal protecting group strategy was devised for the synthesis of feglymycin (**291**) in which the internal aryl glycine residues of the three peptides will be protected with an Fmoc group, allowing the *N*-terminal amine to be deprotected while leaving the benzyl-protected phenols and *C*-terminal esters untouched. We wish to protect the terminal aryl glycine residues with a Cbz group, allowing for concomitant deprotection of the benzyl-protected phenols and *N*-terminal amine after synthesis of the peptide fragments is complete. The *N*-terminal free amine of fragment A (**313**) will then

be reprotected with a Boc group before coupling to fragment B (**314**). Subsequent saponification of the methyl ester of the resulting peptide will give the *C*-terminal carboxylic acid, allowing for this to be coupled to the *N*-terminal free amine of fragment C (**315**). Acid-mediated deprotection of the *N*-terminal Boc group and the *C*-terminal *tert*-butyl esters will then give the natural product (Scheme 106).

The three peptides could therefore be synthesized from the protected canonical amino acids L-Val, L-Phe and L-Asp, as well as the α-bromo nitroalkane precursors to the Hpg and Dpg amino acid residues. This would include the Fmoc-protected 4-benzyloxy aryl α-bromo nitroalkane **201k** and 3,5-dibenzyloxy aryl α-bromo nitroalkane **201l** synthesized in Section 3.2.2 (Table 12, entries 12 and 13). The two additional α-bromo nitroalkanes needed for the synthesis of feglymycin would be the Cbz-protected 4-benzyloxy aryl and 3,5-dibenzyloxy aryl derivatives **316** and **317**, which could be easily obtained through a CbzCl quench of the aza-Henry addition reaction to the appropriate *N*-TMS aryl imine (Scheme 106).

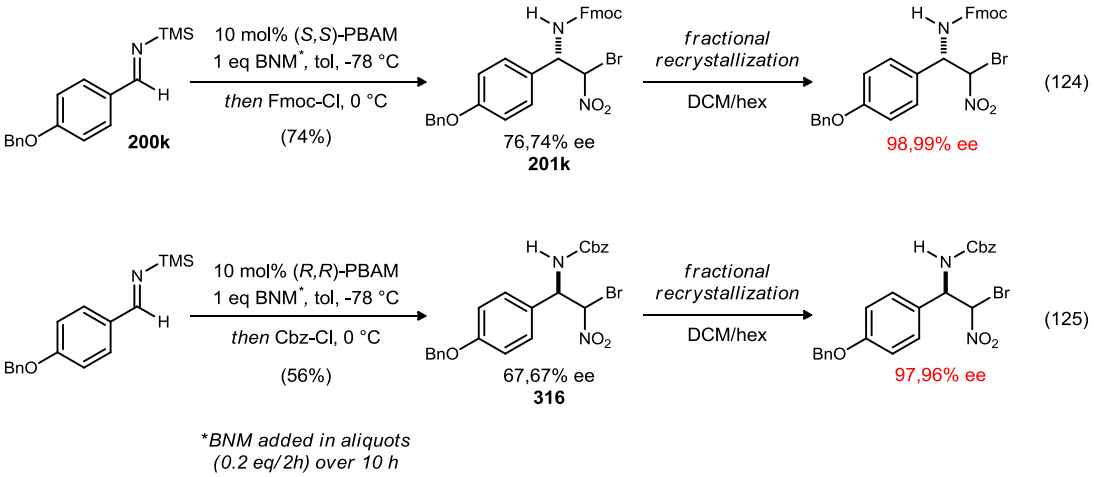
4.3 Total Synthesis of Feglymycin

4.3.1 Synthesis of the α-Bromo Nitroalkane Donors

As mentioned previously, Fmoc-protected 4-benzyloxy aryl α-bromo nitroalkane **201k** had been previously synthesized, through the aza-Henry addition of bromonitromethane to *N*-TMS imine **200k**, in the presence of (*S,S*)-PBAM, and subsequent quench with FmocCl. This procedure provided **201k** in 74% yield and 76, 74% ee. While this enantioselection was relatively good for an electron rich substrate, in order to use this material in the synthesis of feglymycin, a higher level of enantiopurity was needed. Therefore, a fractional recrystallization of **201k** was performed in

dichloromethane and hexanes, providing the α-bromo nitroalkane in 97/97% ee (eq 124, Scheme 107). A similar procedure was used to synthesize Cbz-protected 4-benzyloxy aryl α-bromo nitroalkane **316**. By treating imine **200k** with bromonitromethane in the presence of (*R,R*)-PBAM, and quenching with CbzCl, **316** could be obtained in 56% yield and 67/67% ee. While the enantioselection was slightly lower than what was observed with Fmoc-protected derivative **201k**, the ee of Cbz-protected derivative **316** was also able to be enriched through fractional recrystallization in dichloromethane and hexanes to 97/96% ee (eq 125, Scheme 107). We were pleased with these results, as a 97/96% ee would correspond to a 49:1 ratio of diastereomers after UmAS coupling of the α-bromo nitroalkanes.

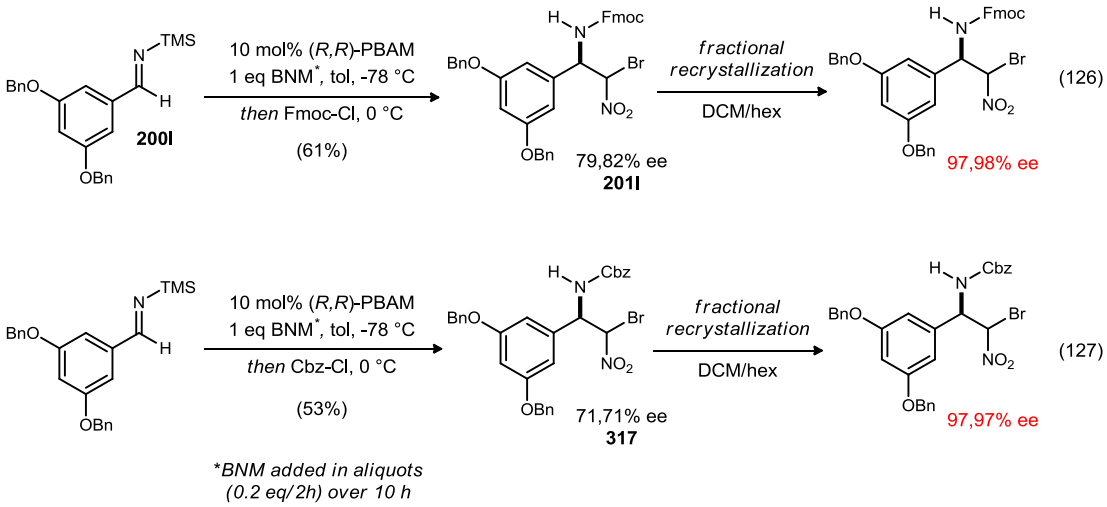
Scheme 107. Synthesis and recrystallization of Hpg α-bromo nitroalkanes **201k** and **316**.



Fmoc-protected 3,5-dibenzyloxy aryl α-bromo nitroalkane **201l**, synthesized previously in 61% yield and 79, 82% ee, was also subjected to fractional recrystallization. In doing so, this product was enriched to 97, 97% ee (eq 126, Scheme 108). A CbzCl quench of the aza-Henry addition to *N*-TMS imine **200l** provided the Cbz-protected 3,5-dibenzyloxy α-bromo nitroalkane **317** in 53% yield and 71, 71% ee. The enantiopurity of

317 was similarly enriched through fractional recrystallization to 97, 97% ee (eq 127, Scheme 108).

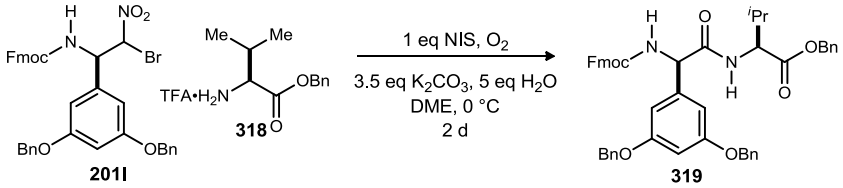
Scheme 108. Synthesis and recrystallization of Dpg α-bromo nitroalkanes **201l** and **317**.



4.3.2 Synthesis of Fragment A

With the required α-bromo nitroalkanes in hand, we first turned to the synthesis of fragment A (**313**). In order to install the first Dpg residue in fragment A, Fmoc-protected 3,5-dibenzyloxy aryl α-bromo nitroalkane **201l** was coupled to the TFA salt of valine benzyl ester **318**. Under standard UmAS conditions, the dipeptide **319** was isolated in 47% yield (Table 29, entry 1).

Table 29. UmAS coupling of **201l** with the TFA salt of valine benzyl ester **318**.



entry	eq of α-bromo nitroalkane (**201l**)	eq of amine (**318**)	yield of **319** (%)
1	1	1.2	47
2	1	2	52
3	2	1	27
4[a]	1	1.2	37
5[b]	1	1.2	23
6[c]	1	1.2	35

[a] Reaction performed at room temperature. [b] Reaction not run under an atmosphere of O_2. [c] O_2 balloon refreshed every 2 hours for first 8 hours.

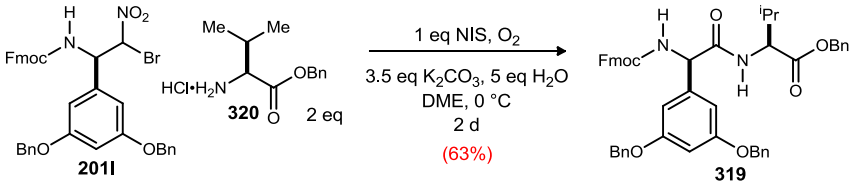
The moderate yield of this reaction prompted optimization of this initial coupling. By increasing the amount of valine benzyl ester **318** to 2 eq, the yield of **319** could be increased slightly, to 52% (Table 29, entry 2). Increasing the equivalents of the α-bromo nitroalkane resulted in a lower yield of **319** (27%, Table 29, entry 3), as did performing the reaction at ambient temperature and removing O_2 from the reaction conditions (37% and 23% yield, respectively, Table 29, entries 4 and 5). The low yield of **319** obtained when the reaction was run without O_2 prompted us to perform a reaction in which the O_2 balloon was refreshed periodically throughout the time period of the reaction. However, this unfortunately also resulted in a lower yield of dipeptide **319** (35% yield, Table 29, entry 6).

Although we previously had success coupling the TFA salts of amines, it was thought that perhaps it was this reagent that was causing the low yield of **319**. The TFA salt of valine benzyl ester **318** had been prepared via a TFA deprotection of the *N*-Boc

protected amino acid, and it was possible that not all of the excess TFA had been removed from the amino acid salt upon concentration of the crude reaction mixture. This excess TFA would have a detrimental effect on the UmAS coupling reaction, as alkaline conditions are needed to deprotonate the α-bromo nitroalkane. Therefore, the HCl salt of valine benzyl ester **320** was prepared, via an HCl/dioxane deprotection of the *N*-Boc amino acid. In this case, the resulting amino acid salt was precipitated from ether and isolated via filtration in order to make sure no excess HCl remained.

It was pleasing to see that when this amino acid was subsequently coupled to α-bromo nitroalkane **201l**, a substantial increase in the yield of the UmAS reaction was observed. The dipeptide **319** was able to be isolated as a single diastereomer in 63% yield (Scheme 109).

Scheme 109. UmAS coupling of **201l** with the HCl salt of valine benzyl ester **320**.



While we were able to optimize the yield of **319** on small scale (50 mg of the starting α-bromo nitroalkane **201l**), several problems were encountered upon scale-up of this coupling reaction. When 250 mg of the starting α-bromo nitroalkane **201l** was used, it was observed that on this scale the starting materials weren't completely soluble at a concentration of 0.2 M in DME. Additionally, this reaction stopped stirring after several hours due to its heterogeneous nature (Table 30, entry 2). In order to solubilize the starting materials, the reaction was diluted to 0.05 M in DME. This did improve the stirring of the reaction, and the dipeptide **319** was able to be isolated. However, the yield

after stirring for 2 days under these conditions was only 52% (Table 30, entry 3). It was hypothesized that the dilute conditions caused the coupling to proceed at a slower rate. This was confirmed when the yield of dipeptide **319** was increased back to 63% after allowing the reaction to stir for 4 days (Table 30, entry 4).

While these conditions worked well on this scale, increasing the amount of starting material further, to 0.5 g of α-bromo nitroalkane **201l**, again resulted in a decrease in yield (38%, Table 30, entry 5). It was hypothesized that this was again due to poor stirring in the reaction. By switching from using a magnetic stir bar to a mechanical stirrer, the scale of the reaction could be increased to 1 g while still maintaining an acceptable yield of dipeptide **319** (59%, Table 30, entry 6). Moreover, it was found that on this scale, a majority of the dipeptide **319** could be isolated through an EtOAc/hexanes recrystallization of the crude reaction mixture, eliminating the need for column chromatography in this step.

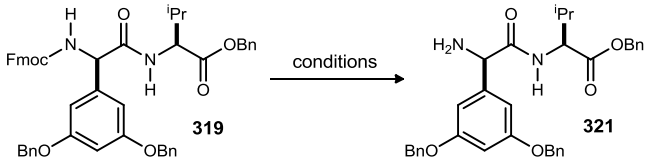
Table 30. Scale up of the UmAS coupling of **201l** with the HCl salt of valine benzyl ester **320**.

entry	scale of reaction (g of **201l**)	concentration (M)	time (d)	yield (%)
1	0.05	0.2	2	63
2	0.25	0.2	2	--[a]
3	0.25	0.05	2	52
4	0.25	0.05	4	63
5	0.50	0.05	4	38
6[b]	1.0	0.1	2	59

[a] Reaction stopped stirring after several hours. Due to low conversion, the yield of this reaction was not determined. [b] Reaction run with mechanical stirring. Product isolated via EtOAc/Hex recrystallization directly from crude reaction mixture.

With the first UmAS coupling towards fragment A (**313**) optimized, we next turned to the Fmoc-deprotection of the dipeptide **319**. The most common method of Fmoc-deprotection, treatment with piperidine in DMF,[147] was first attempted. Unfortunately, these conditions resulted in a complex crude reaction in which only trace amounts of the free amine **321** could be observed (Table 31, entry 1). Deprotection with morpholine in DCM gave better results, with the major product of this reaction determined to be the desired amine **321** by ^{1}H NMR analysis. However, several other baseline products could also be observed (Table 31, entry 2). Treatment of DIEA in DCM resulted in no deprotection, even after stirring for 24 hours (Table 31, entry 3).

Table 31. Screen of conditions for the Fmoc-deprotection of **319**.



entry	conditions	result[a]	yield (%)
1	20% piperidine/DMF	messy, trace product	--
2	50% morpholine/DCM	full conversion, other products observed	--
3	50% DIEA/DCM	no conversion	--
4[b]	TBAF, ^{i}PrOH/THF	clean conversion to **321**	87

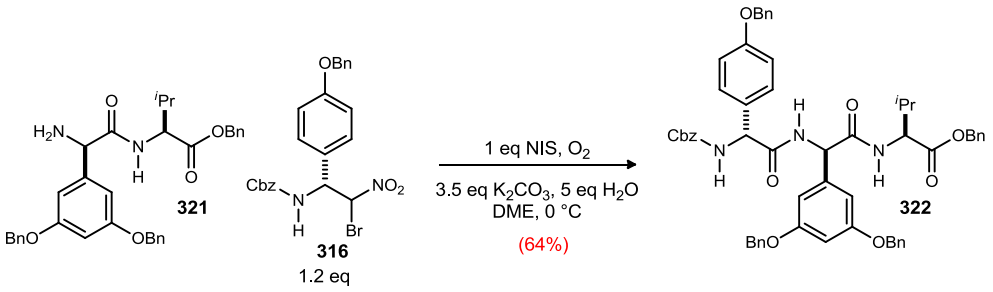
[a] As determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Reaction run with 8 eq TBAF, 10 eq ^{i}PrOH. Product isolated as the free amine by column chromatography, using 10% acetone/hexanes as the eluent.

Upon examining literature concerning the synthesis of Hpg and Dpg containing peptides, it was found that the Fmoc-deprotection of peptides containing these sensitive amino acid residues is most often carried out through treatment with TBAF and ^{i}PrOH.[148]

[147] Albericio, F.; Kneib-Cordonier, N.; Biancalana, S.; Gera, L.; Masada, R. I.; Hudson, D.; Barany, G. *J. Org. Chem.* **1990**, *55*, 3730.
[148] Rew, Y.; Shin, D.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2004**, *126*, 1041.

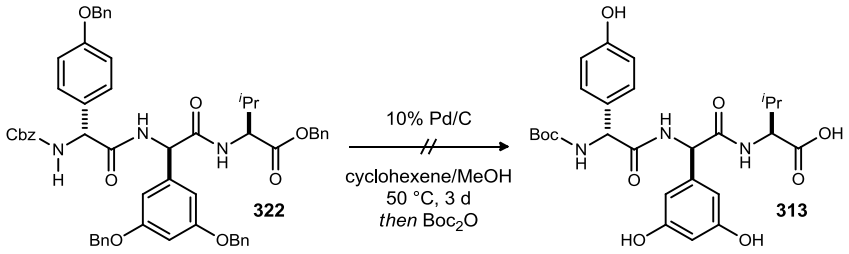
These mildly basic conditions worked well for us, cleanly deprotecting dipeptide **319** to provide the free amine **321** in 87% yield after purification (Table 31, entry 4).

Scheme 110. UmAS coupling of **316** with dipeptide **321**.



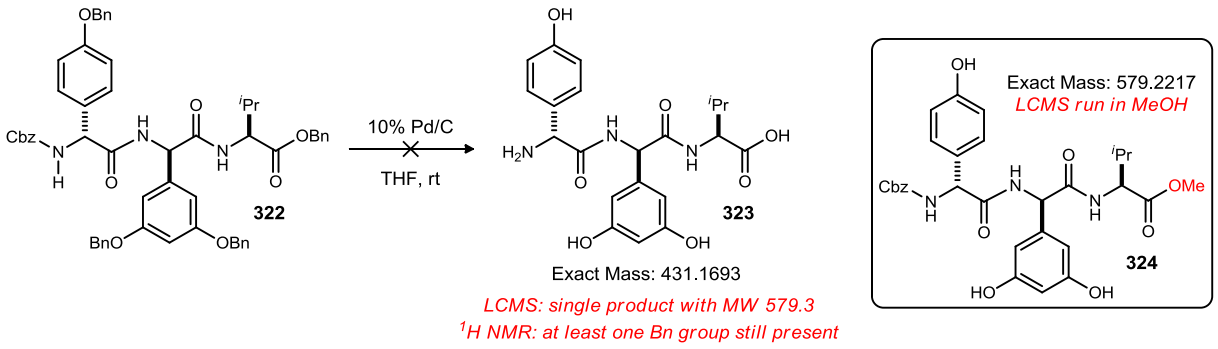
The free amine **321** was then coupled to the Cbz-protected 4-benzyloxy aryl α-bromo nitroalkane **316**, under standard UmAS conditions. We were pleased to see that the protected-fragment **A** (**322**) could be isolated in 64% yield (Scheme 110). In order to complete the synthesis of fragment **A** (**313**), global deprotection and subsequent reprotection of the resulting free amine with a Boc group was necessary. Therefore, a hydrogenolysis of **322** was attempted, using 10% Pd/C and cyclohexene as a source of H_2. After stirring for several days at elevated temperature, the crude reaction mixture was treated with Boc_2O. Unfortunately, based on ^1H NMR analysis of the crude reaction mixture, the desired Boc-protected fragment **A** (**313**) was not present. Instead, a large amount of starting tripeptide **322** was observed, indicating that deprotection had not occurred (Scheme 111).

Scheme 111. Attempted hydrogenolysis of **322**, with concomitant Boc protection.



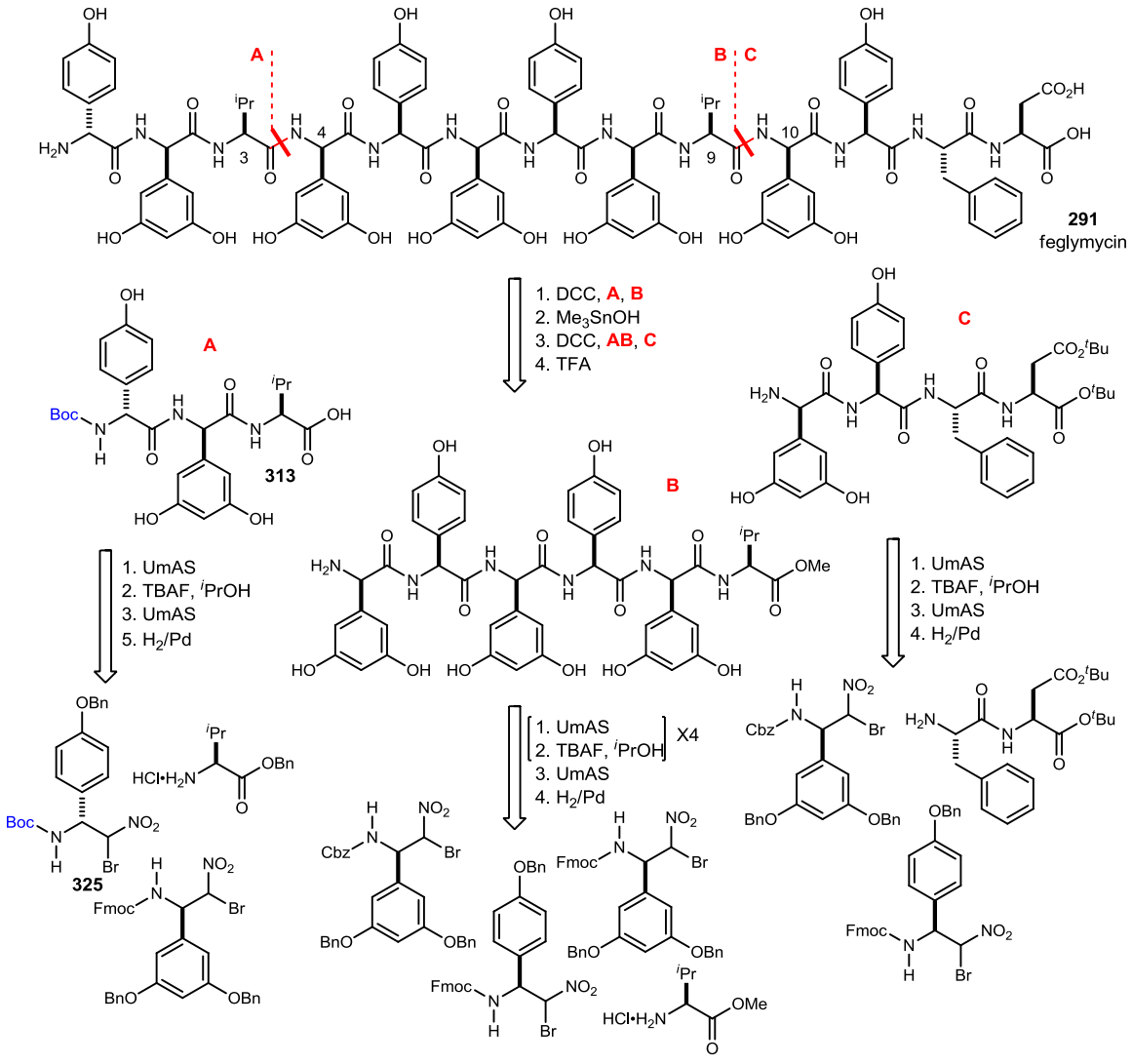
Since it appeared that deprotection of the Cbz and Bn protecting groups in **322** would be more challenging than originally thought, optimization of the deprotection conditions before reprotecting the free amine with a Boc-protecting group was pursued. A second hydrogenolysis, this time using a H_2 balloon, was attempted. After several hours at room temperature, analysis by TLC indicated full conversion of the starting tripeptide **322**. Upon analysis by ^{1}H NMR, however, it was clear that the major product of this reaction still contained at least one benzyl group, suggesting incomplete deprotection. Isolation and full characterization of this product proved difficult, however, upon analysis by LCMS it was determined that it had a MW of 579.3. This mass is consistent with the methyl ester **324**, in which the phenols have been deprotected, but the *N*-terminal amine has not. While conversion from the benzyl ester to the methyl ester is curious, this may be an artifact of the conditions used for LCMS analysis (Scheme 112).

Scheme 112. Attempted hydrogenolysis of **322**.



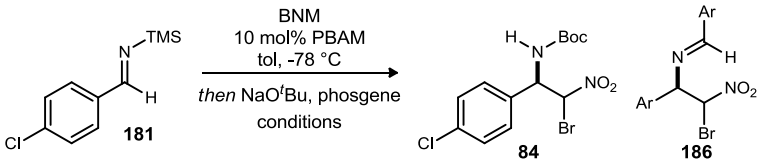
Since deprotection of the Cbz-protecting group was problematic with this substrate, alternative *N*-terminal protecting groups were considered. Boc-protected α-bromo nitroalkane **325** was targeted, as an *N*-terminal Boc-protecting group was ultimately desired. This would eliminate the need for a deprotection/reprotection sequence, simplifying the synthesis of feglymycin **291** (Scheme 113).

Scheme 113. Second generation retrosynthesis of feglymycin **291**.



We anticipated that synthesis of this α-bromo nitroalkane would be challenging. It was previously found that quenching the aza-Henry addition of bromonitromethane to *N*-TMS imines with Boc_2O resulted in a very low yield of desired Boc-protected α-bromo nitroalkane **84** (36%, Section 3.2.2, Table 11, entry 13). Use of acid chlorides and chloroformates worked best in this chemistry, perhaps due to the ability of the chloride (Cl^-) produced as a byproduct of the acylation step to subsequently deprotect the TMS group. We therefore wished to synthesize BocCl, and use that reagent to quench the aza-Henry addition.

Table 32. Attempted *in situ* preparation of BocCl.



entry	conditions	results[a]
1	reagents combined at -78 °C, stirred for 4 h, added to reaction	messy, trace product
2	reagents combined at -78 °C, warmed to rt, stirred for 1 h, added to reaction	2:3 ratio of **84**:**186**
3	same as entry 2, 3 eq of reagents used	mostly **186**
4[b]	same as entry 2, pyridine added	**186** cleanly formed

[a] As determined by ^{1}H NMR analysis of the crude reaction mixture.

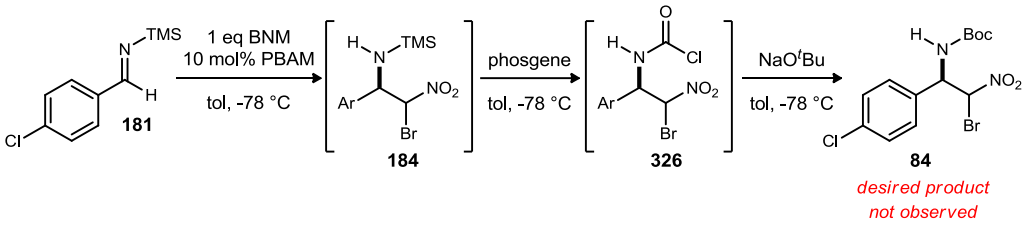
While BocCl is a known compound, [149] it is not an easy reagent to work with. It is a highly volatile compound, with a boiling point of 3 °C at 2 mmHg. It can only be purified using low temperature distillation, as it is unstable at temperatures above 10 °C. It must therefore be stored at low temperatures, as a solution, and lasts no longer than a few days.[149] It is for these reasons we decided it would be best to make BocCl *in situ*, and

[149] Howard, J. C. *J. Org. Chem.* **1981**, *46*, 1720.

immediately add the crude solution containing this product to the aza-Henry reaction in order to quench the *N*-TMS amine.

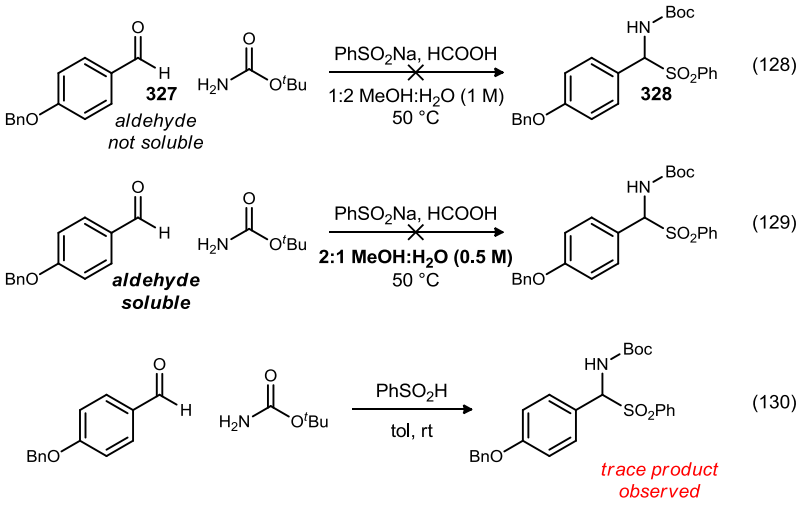
This was first attempted by combining the NaO^{t}Bu and phosgene at -78 °C. The solution was stirred for 4 hours, and then directly cannulated into the aza-Henry reaction of bromonitromethane and ^{p}Cl aryl *N*-TMS imine **181** that had been stirring overnight. Unfortunately, only a trace amount of desired Boc-protected α-bromo nitroalkane **84** was observed by ^{1}H NMR analysis of the crude reaction mixture (Table 32, entry 1). The major product produced in this reaction was the transimination product **186**, which had been observed previously in this chemistry. The formation of this byproduct seems to occur when the acylation of the *N*-TMS amine has not gone to completion. Therefore, we hypothesized that the BocCl may not have formed at such low reaction temperatures (-78 °C), resulting in little acylation of the *N*-TMS amine. In order to test this, a second reaction was done in which the solution of NaO^{t}Bu and phosgene was warmed to room temperature for an hour before recooling to -78 °C and cannulating into the aza-Henry reaction. This did improve the outcome of the reaction, as the product **84** was present in a 2:3 ratio with transimination product **186** (Table 32, entry 2). In order to improve this ratio further, an excess of NaO^{t}Bu and phosgene was used. Unfortunately, this resulted mostly in formation of transimination product **186** (Table 32, entry 3). Finally, in an attempt to promote the formation of BocCl, pyridine was added to the reaction mixture. This also resulted in clean formation of **186** (Table 32, entry 4).

Scheme 114. Attempted stepwise synthesis of **199j**.



Due to the minimal success when preforming BocCl, an attempt was made to introduce the Boc protecting group in a stepwise fashion. After the aza-Henry addition to **181** was complete, phosgene was added to the crude reaction mixture of *N*-TMS amine **184**, and the reaction was stirred for an additional 1 hour at -78 °C. It was hoped that intermediate **326** would form, which would then be reactive towards NaO^{t}Bu. However, after addition of this reagent, desired Boc-protected α-bromo nitroalkane **84** was not observed in the complex crude reaction mixture (Scheme 114).

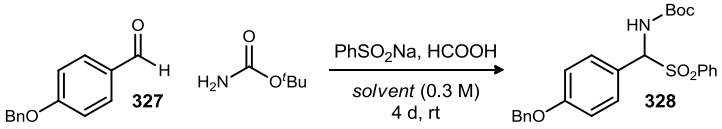
Scheme 115. Previous efforts towards the synthesis of 4-benzyloxy aryl sulfone **328**.



While we had hoped to be able to optimize the aza-Henry addition to *N*-TMS imines to include the introduction of Boc-protecting groups, this was proving to be problematic. Therefore, we decided to approach the synthesis of the Boc-protected 4-

benzyloxy aryl α-bromo nitroalkane **325** in a different way. From previous work, we knew that the enantioselective aza-Henry addition of bromonitromethane to the *N*-Boc imine would be a reliable way to access the Boc-protected α-bromo nitroalkane **325**. However, past attempts to synthesize the sulfone precursor (**328**) to the *N*-Boc imine had not been successful. The 4-benzyloxy benzaldehyde **327** was not soluble under the standard reaction conditions for sulfone synthesis (eq 128, Scheme 115). Increasing the amount of MeOH used and decreasing the concentration of the reaction helped to solubilize aldehyde **327**, however sulfone **328** still could not be synthesized under these conditions, even after stirring for several days at elevated temperatures (eq 129, Scheme 115). Preforming the sulfinic acid and switching to a toluene solvent system resulted in the production of **328**, however only trace amounts of this product were observed by ^{1}H NMR analysis, even after several days (eq 130, Scheme 115).[150]

Table 33. Synthesis of 4-benzyloxy aryl sulfone **328**.



entry	solvent	result
1	1:2 MeOH:H_2O, DCM to dissolve aldehyde	16% conversion[a], **327** and **328** fully soluble in DCM
2	ether, H_2O to dissolve sulfinic acid	0% conversion[a]
3	toluene, H_2O to dissolve sulfinic acid	30% yield, **327** insoluble in tol, **328** soluble

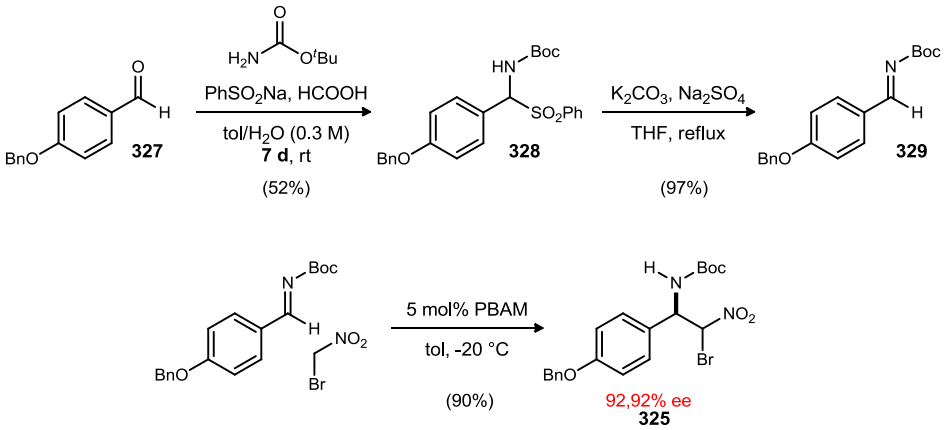
[a] As determined by ^{1}H NMR analysis of the crude reaction mixture.

Based on this final result, we decided to return to re-examine the synthesis of sulfone **328**. Several different solvent systems were examined, and a focus was placed on

[150] Shen, B.; Johnston, J. N. *unpublished results*.

solubilizing all of the starting materials of this reaction. Under standard reaction conditions (1:2 MeOH:H_2O solvent system), we knew that benzaldehyde **327** was not soluble. Therefore, a small amount of DCM was added to the reaction in order to dissolve this compound. We were pleased to see that this resulted in 16% conversion to sulfone **328** (Table 33, entry 1). However, both sulfone **328** and aldehyde **327** were soluble in dichloromethane, which made the isolation of **328** challenging. The ideal solvent system for this reaction would solubilize the starting materials of this reaction, but allow the sulfone product to precipitate out so that it could be isolated via filtration. We therefore chose to use ether as the organic phase in this reaction, as we hypothesized the sulfone **328** would be insoluble in this solvent. Unfortunately, though we were able to solubilize the starting materials through the addition of H_2O, these conditions resulted in no conversion to sulfone **328** (Table 33, entry 2). The final solvent to be screened was toluene, with some added H_2O to solubilize the sulfinic acid. We were excited to see that after stirring for 4 days, a white precipitate had formed. After filtration, this precipitate was confirmed to be sulfone **328**, isolated in 30% yield (Table 33, entry 3).

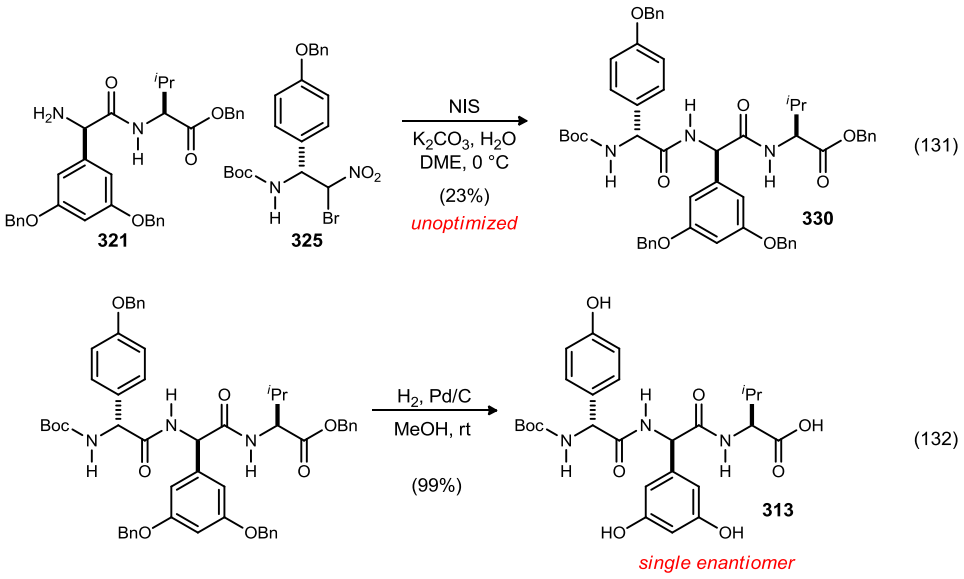
Scheme 116. Optimized synthesis of Boc-protected α-bromo nitroalkane **325**.



By stirring this reaction for a longer period of time, the yield of sulfone **328** was increased to 52% (Scheme 116). Treatment of **328** with K_2CO_3 and Na_2SO_4 resulted in clean conversion to desired *N*-Boc imine **329**. This imine was then subjected to the standard conditions for aza-Henry addition of bromonitromethane to *N*-Boc imines, and we were excited to see that the Boc-protected 4-benzyloxy aryl α-bromo nitroalkane **325** could be synthesized in 90% yield and 92, 92% ee (Scheme 116).

With the Boc-protected α-bromo nitroalkane **325** in hand, the next step was to couple this compound to dipeptide **321**, in order to install the final Hpg residue of fragment **A** (**313**). Under standard UmAS conditions, the Boc-protected tripeptide **330** was isolated, though in low yield (23%, eq 131, Scheme 117).

Scheme 117. Completion of fragment **A** (**313**).



The protected tripeptide **330** was then subjected to hydrogenolysis conditions. We were pleased to see that after stirring at room temperature for 10 minutes, quantitative

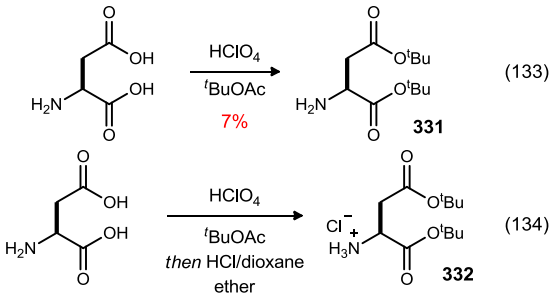
conversion to **313** could be seen by ^{1}H NMR analysis (eq 132, Scheme 117).[151] Future work in this area will include the optimization and scale up of the final UmAS coupling in this sequence.

4.3.3 Synthesis of Fragment C

In order to make fragment **C** (**315**), we first needed to synthesize terminal Phe·Asp di-^{t}butyl ester **334**. We began by following a known procedure[152] for the synthesis of ^{t}butyl esters, in which the free acid is treated with perchloric acid and ^{t}butyl acetate before work up with aqueous base. However, it was found that the resulting free amine aspartic acid di-^{t}butyl ester (**331**) was volatile, leading to a very low isolated yield (7% yield, eq 133, Scheme 118). Therefore, upon repeating this reaction we attempted to form the ammonium salt **332** by treating the organic phase with HCl in dioxane. Unsurprisingly, it was found that the formation of **332** was very sensitive. When dichloromethane was used as the organic phase, only deprotected aspartic acid could be isolated. However, by extracting the free amine into diethyl ether before the addition of HCl in dioxane, **332** could be isolated, though in moderate yield (34% yield, eq 134, Scheme 118).

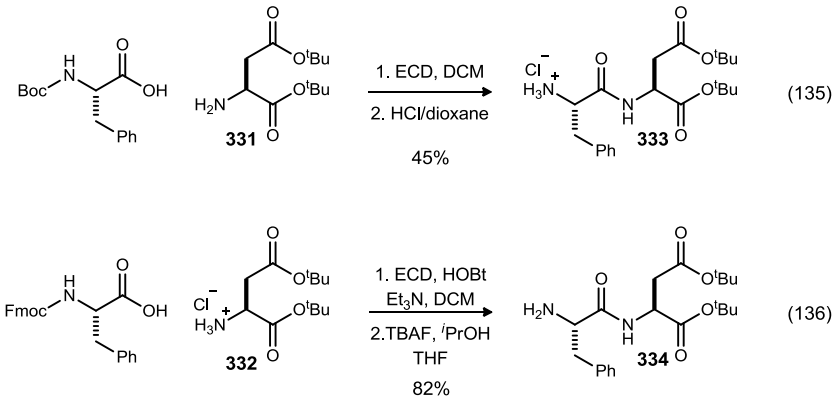
[151] Doody, A. B.; Johnston, J. N. *unpublished results.*
[152] Chen, H.; Feng, Y.; Xu, Z.; Te, Y. *Tetrahedron* **2005**, *61*, 11132.

Scheme 118. Synthesis of aspartic acid di-^{t}butyl ester **332**.



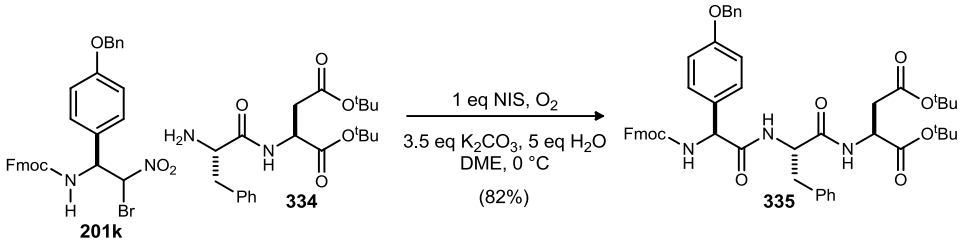
The free amine aspartic acid di-^{t}butyl ester **331** was first coupled to *N*-Boc protected phenyl alanine, as it was readily available. After EDC coupling and subsequent selective deprotection of the *N*-Boc protecting group, the dipeptide ammonium salt **333** was isolated in 45% yield (eq 135, Scheme 119). Upon scale up, the yield of this dipeptide was increased by coupling ammonium salt **332** to *N*-Fmoc protected phenyl alanine. This gave free amine dipeptide **334** in 82% yield after coupling and Fmoc-deprotection (eq 136, Scheme 119).

Scheme 119. Synthesis of free amine dipeptide **334.**



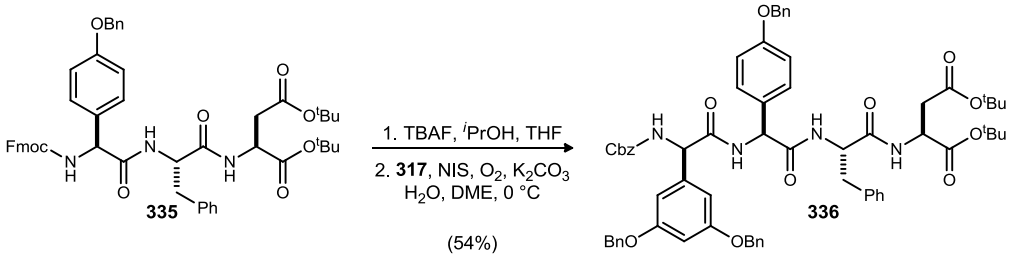
With the dipeptide **334** in hand, we next attempted the UmAS coupling of this substrate with α-bromo nitroalkane **201k**. Pleasingly, we were able to isolate the desired tripeptide **335** in 85% yield, as a single diastereomer (Scheme 120).

Scheme 120. Synthesis of tripeptide **335.**



Similarly, Fmoc-deprotection of **335** and subsequent UmAS coupling with α-bromo nitroalkane **317** gave the protected-fragment **C** (**336**) in 54% overall yield (Scheme 121). Future work will include the scale up of these UmAS coupling reactions, as well as the investigation of deprotection conditions to give fragment **C** (**315**).

Scheme 121. Synthesis of protected fragment **C** (**336**).

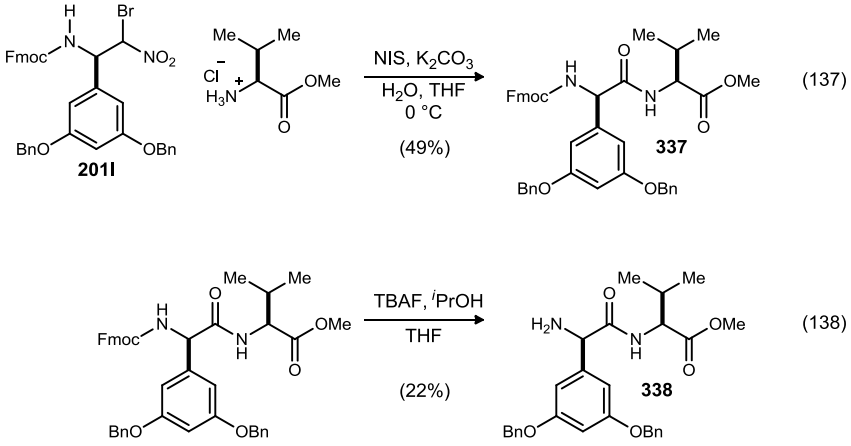


4.3.4 Progress Towards the Synthesis of Fragment B

To synthesize fragment **B** (**314**), we first started with the UmAS coupling of α-bromo nitroalkane **201k** with the methyl ester of valine. While dipeptide **337** was successfully synthesized, the yield was only moderate (49%, eq 137, Scheme 122). Additionally, the yield of the subsequent Fmoc-deprotection to give free amine **338** was also low (22%, eq 138, Scheme 122). While attempts were made to increase the yield of these reactions, none were successful. We thought that the low yields we were obtaining might be a result of the fact that the *C*-terminal carboxylic acid of **337** is protected as a

methyl ester, which can be easily saponified. We had previously observed that ^{t}butyl ester amino acids gave higher yields in UmAS couplings than did their corresponding methyl ester derivatives (Section 3.2.3, Table 20). It is therefore likely that under the UmAS reaction conditions, which include water and K_2CO_3, the methyl ester of **337** is competitively partially saponified. While the free acid product was never observed, this would be lost to the aqueous layer during the work up of the reaction. The low yield of the subsequent deprotection of **337** could likewise be a result of transesterification, as *iso*-propoxide would form under the reaction conditions.

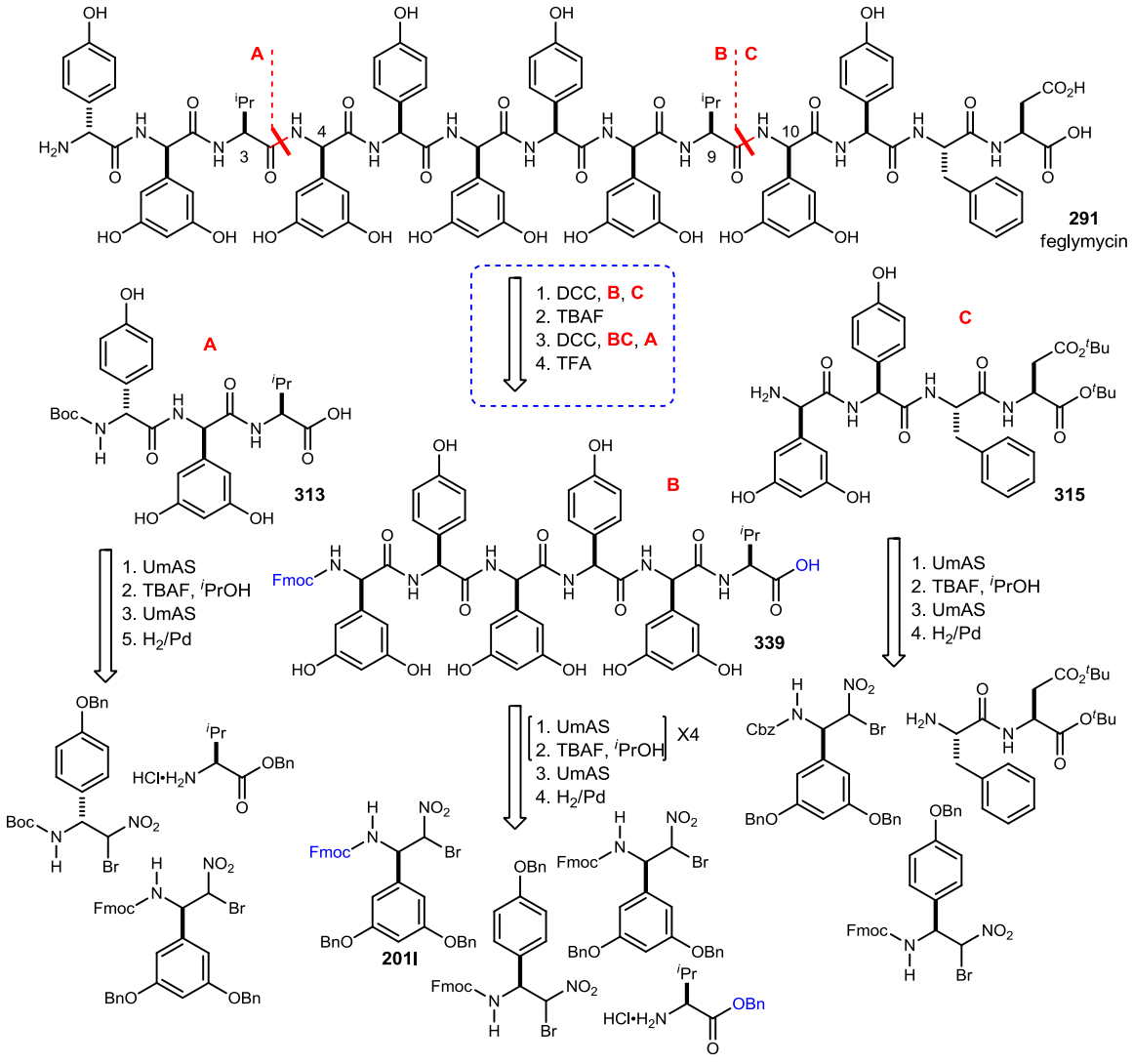
Scheme 122. Synthesis and deprotection of dipeptide **337**.



Though the coupling of α-bromo nitroalkane **201l** to the methyl ester of valine was problematic, we knew that this compound could be successfully coupled to the benzyl ester of valine (63% yield, Scheme 109). Therefore, we reexamined our retrosynthetic approach to feglymycin (**291**) to see if it would be possible to start the synthesis of fragment **B** (**314**) with dipeptide **319**, the same dipeptide successfully used to synthesize fragment **A** (**313**). It was decided that this would be possible if we switched the order of fragment ligation in the end stages of the synthesis. By protecting the *N*-terminal amine of fragment **B** with an Fmoc group (**339**), as opposed to a Cbz group, the

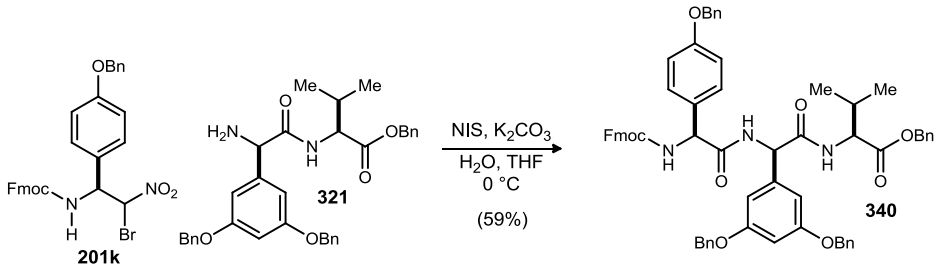
benzyl ethers and benzyl ester could be selectively deprotected while leaving the *N*-terminal amine protected. Fragment **B** (**339**) could then be coupled to fragment **C** (**315**). Following Fmoc-deprotection, this peptide could then be ligated to fragment **A** (**313**), which would then give feglymycin (**291**), after global deprotection (Scheme 123).

Scheme 123. Third generation retrosynthesis of feglymycin **291**.



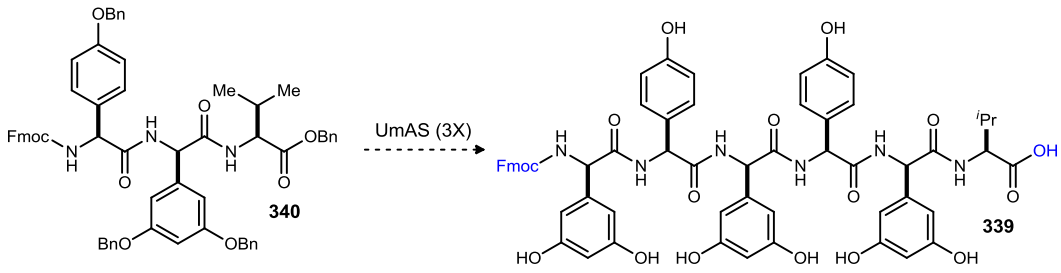
In order to proceed with this new synthetic plan, free amine **321** was coupled to α-bromo nitroalkane **201k**. We were happy to see tripeptide **340** was isolated, in good yield (59%, Scheme 124).

Scheme 124. Synthesis of tripeptide **340.**



Current attempts involve deprotection and homologation of tripeptide **340**. Future work to complete the synthesis of fragment **B** (**339**) from the tripeptide **340** will include three iterative aryl glycine homologations, using UmAS coupling conditions, and subsequent deprotection by hydrogenolysis (Scheme 125).

Scheme 125. Future elaboration of **340** to fragment B (**314**).

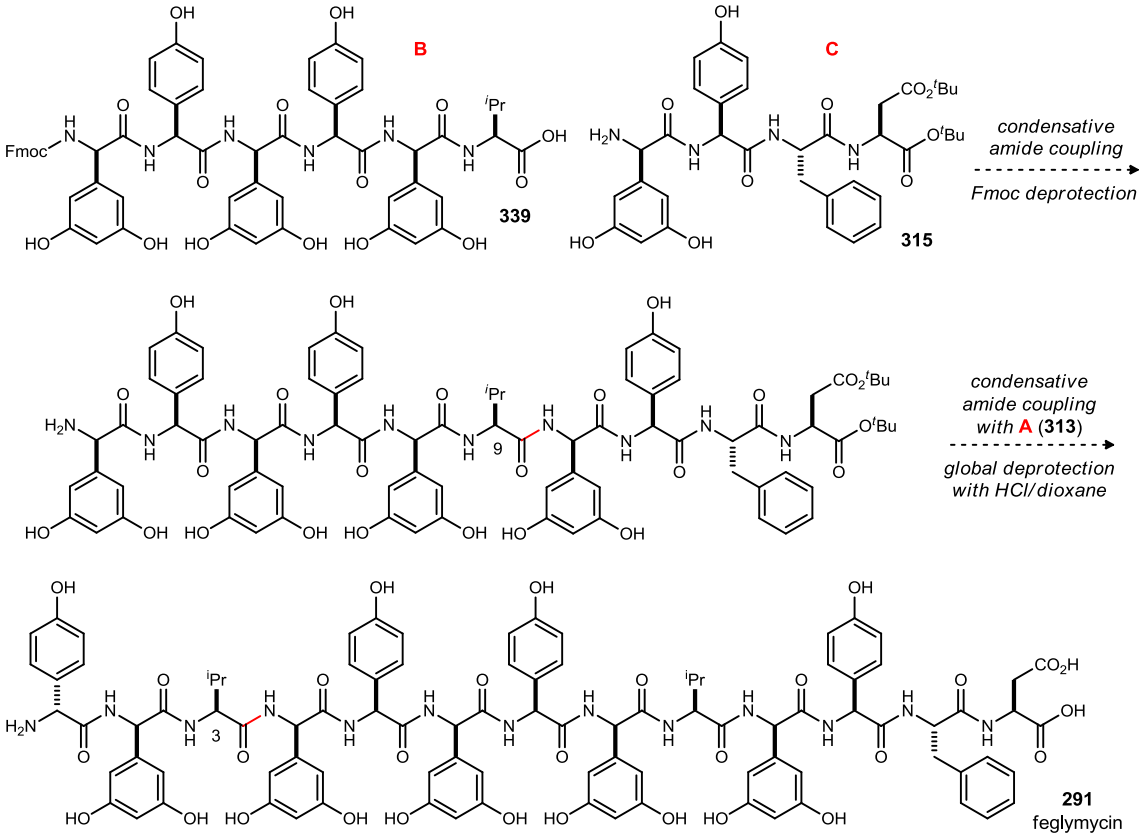


4.3.5 Future Work

In order to complete the synthesis of feglymycin, the deprotection of fragment **C** (**315**) will be carried out, as well as the completion of fragment **B** (**339**). Once complete, these fragments will be ligated, using traditional amide coupling reagents. Because we will be activating the carboxylic acid of hexapeptide **339** as an the active ester, we anticipate the need to screen several carbodiimide coupling reagents in order to find one that enables us to couple these two fragments with no epimerization at valine residue 9. Once this coupling has been optimized, Fmoc deprotection will give the free amine

dipeptide which can then be ligated to fragment **A** (**314**), hopefully avoiding epimerization of valine residue 3. A global deprotection of the *N*-terminal Boc protecting group and *C*-terminal ^{t}butyl esters will then give feglymycin (**291**), as a single diastereomer (Scheme 126).

Scheme 126. Future work: completion of feglymycin (**291**).



CHAPTER V

EXPERIMENTAL

Glassware was oven-dried overnight at 120 °C for all non-aqueous reactions. All reagents and solvents were commercial grade and purified prior to use when necessary. Tetrahydrofuran (THF) was dried by passage through a column of activated alumina as described by Grubbs.[153] This was done to accurately quantitate the amount of water in each reaction. NIS was recrystallized from dioxane/CCl_4.

Thin layer chromatography (TLC) was performed using glass-backed silica gel (250 μm) plates, and flash chromatography utilized 230-400 mesh silica gel from Scientific Adsorbents. Products were visualized by UV light, iodine, and/or the use of ninhydrin, potassium permanganate, *p*-anisaldehyde, ceric ammonium molybdate, and potassium iodoplatinate solutions.

Melting points were measured on a Meltemp melting point apparatus and were not corrected. IR spectra were recorded on a Nicolet Avatar 360 spectrophotometer and are reported in wavenumbers (cm^{-1}). Liquids and oils were analyzed as neat films on a NaCl plate (transmission), whereas solids were applied to a diamond plate (ATR). Nuclear magnetic resonance spectra (NMR) were acquired on a Bruker DRX-400 (400 MHz) or a Bruker AVIII-600 (600 MHz) spectrometer. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to 7.26 and 77.1 for $CDCl_3$. Mass spectra were recorded on a Thermo Electron Corporation MAT 95XP-Trap mass spectrometer by use of chemical ionization (CI), electron impact ionization (EI) or

[153] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

electrospray ionization (ESI) by the Indiana University Mass Spectrometry Facility. A post-acquisition gain correction was applied using sodium formate or sodium iodide as the lock mass. Optical rotations were measured on a Perkin Elmer-341 polarimeter.

Chapter II: Applications in Enantioselective Arylglycine Synthesis

General Procedure A: Sulfone Synthesis

tert-Butyl carbamate (1 equiv) and benzene sulfinic acid (2 equiv) were dissolved in a 1:2 mixture of methanol and water (0.3 M). The aldehyde (1.2 equiv) and formic acid (2 equiv) were added and the reaction was then allowed to stir for a period of 11 to 15 days at rt. The mixture was filtered, and the resulting solid washed several times with ether to remove remaining aldehyde. The solid was then dried under vacuum at 60 °C to give the pure sulfone.

General Procedure B: Synthesis of *N*-Boc-Protected Imines

To a round bottom flask, potassium carbamate (6 equiv) and sodium sulfate (7 equiv) were added. The flask was then flame dried and the contents placed under argon. The sulfone (1 equiv) was then added to the flask, and dissolved in THF (0.1 M). The reaction mixture was then allowed to reflux for 4-5 hours. The solid salts were then filtered off, and the resulting mixture was concentrated *in vacuo* to give the pure imine.

General Procedure C: Bromonitromethane Addition to *N*-Boc-Protected Imines

A solution of the imine (1 equiv) and PBAM or PBAM·TfOH (0.01 or 0.05 equiv) in toluene (0.3 M) was cooled to -20 °C and treated with bromonitromethane (1.2 equiv). The reaction was stirred at -20 °C for 24 hours. The solvent was removed *in vacuo*, and

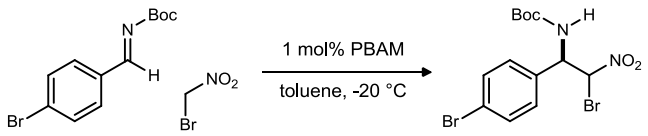
the crude reaction mixture purified by column chromatography to give the α-bromonitro adduct as a mixture of inseparable diastereomers.

General Procedure D: Amide Synthesis Using an Amine (Free Base)

The amine (1.2 equiv) was added drop wise to a solution of α-bromo nitroalkane (1.0 equiv, 0.2 M) and NIS (1.0 equiv) in THF and H_2O (5.0 equiv) at 0 °C, or rt, followed by K_2CO_3 (2.0 equiv). The reaction mixture was stirred at 0 °C, or rt, 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.

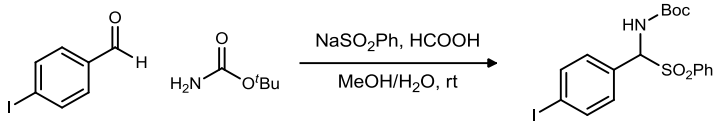
General Procedure E: Amide Synthesis Using an Ammonium Salt

K_2CO_3 (3.2 equiv) was added to the suspension of the ammonium salt (1.2 equiv) and the α-bromo nitroalkane (1.0 equiv, 0.2 M) in THF and H_2O (5.0 equiv) at 0 °C, or rt, followed by NIS (1.0 equiv). The reaction mixture was stirred at 0 °C, or rt, 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.

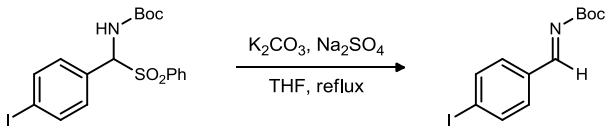


***tert*-Butyl (1*R*)-2-bromo-1-(4-bromophenyl)-2-nitroethylcarbamate (90).** Following General Procedure C, the *N*-Boc-imine (200 mg, 704 μmol) and bromonitromethane (65.0 μl, 845 μmol) provided the α-bromo nitroalkane (1:1 mixture of diastereomers), after flash column chromatography (SiO_2, 100% ethyl acetate), as a white solid (280 mg, 94%). The enantiomeric excess of each diastereomer was determined to be 95% ee by

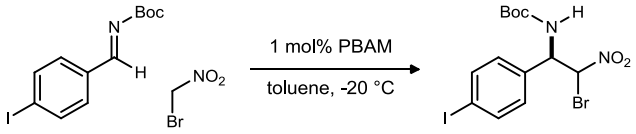
chiral HPLC analysis (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(major) = 20.5, 27.2 min, t_r(minor) = 16.0, 17.5 min). R_f = 0.42 (20% EtOAc/hexanes); mp = 184-185 °C (decomposition); IR (film) 3355, 2979, 1686, 1567, 1523, 1350, 1159 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 7.53 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.31 (br s, 1H), 6.29 (br s, 1H), 5.71 (d, *J* = 8.8 Hz, 1H), 5.61 (br s, 1H), 5.43 (br s, 1H), 5.41 (d, *J* = 9.0 Hz, 1H), 1.45 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.6, 154.3, 134.3, 133.7, 132.3, 132.2, 128.6, 128.4, 123.5, 123.3, 84.6, 81.4, 81.3, 81.1, 57.5 (2C), 28.2, 28.1; HRMS (ESI): Exact mass calcd for $C_{13}H_{16}Br_2N_2NaO_4$ $[M+Na]^+$ 444.9369, found 444.9377.



***Tert*-butyl (4-iodophenyl)(phenylsulfonyl)methylcarbamate (S-1).** Following the General Procedure A, *p*-iodobenzaldehyde (1.30 g, 5.60 mmol) gave the sulfone (280 mg, 11%), as a white powder. R_f = 0.57 (30% EtOAc/hexanes); mp = 175-176 °C; IR (film) 3184, 3066, 1702, 1584, 1444, 1222, 1175 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.7 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.68 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.58 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 5.89 (d, *J* = 10.8 Hz, 1H), 5.72 (d, *J* = 10.3 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 153.3, 137.9 (2C), 136.5, 134.1, 130.5, 129.4, 129.1, 96.3, 81.5, 73.3, 28.0; HRMS (ESI): Exact mass calcd for $C_{18}H_{20}INNaO_4S$ $[M+Na]^+$ 496.0050, found 496.0038.



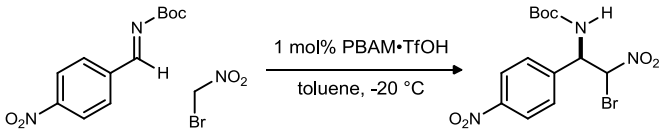
(*E*)-*tert*-Butyl-4-iodobenzylidenecarbamate (S-2). Following General Procedure B, the sulfone (250 mg, 530 μmol) provided the imine (170 mg, 98%) as a white paste. R_f = 0.40 (30% EtOAc/hexanes); IR (film) 2977, 1716, 1626, 1585, 1255, 1153 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.85 (d, *J* = 12.6 Hz, 2H), 7.64 (d, *J* = 12.6 Hz, 2H), 1.60 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 168.6, 162.3, 138.2, 133.4, 131.3, 101.2, 82.5, 27.9; HRMS (ESI): Exact mass calcd for C_7H_7IN $[M\text{-}C_5H_7O_2]^+$ 231.9618, found 231.9591.[154]



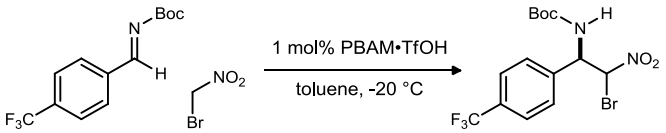
***tert*-Butyl (1*R*)-2-bromo-1-(4-iodophenyl)-2-nitroethylcarbamate (91).** Following General Procedure C, the *N*-Boc-imine (80.0 mg, 242 μmol) and bromonitromethane (22.0 μL, 280 μmol) provided the α-bromo nitroalkane (2.6:1 mixture of diastereomers), after flash column chromatography (SiO_2, 100% ethyl acetate), as a white solid (101 mg, 90%). The enantiomeric excess of the major and minor diastereomers was determined to be 93 and 85% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(major) = 22.0, 31.9 min, t_r(minor) = 18.6, 20.3 min). R_f = 0.57 (30% EtOAc/hexanes); mp = 180-181 °C (decomposition); IR (film) 3373, 1684, 1560, 1524, 1167 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, 2.6:1 mixture of diastereomers) δ 7.73 (d, *J* = 8.5 Hz, 2 H), 7.72 (d, *J* = 9.7 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 6.30 (br s, 1H), 6.27 (br s, 1H), 5.67 (br s, 1H), 5.59 (br s, 1H), 5.40 (br s,

[154] Boc group fragmented.

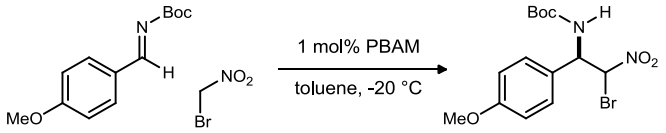
1H), 5.35 (br s, 1H), 1.45 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.3 (2C), 138.3, 138.2, 135.0 (2C), 128.8, 128.6, 95.3, 95.0, 84.7, 81.1, 79.9 (2C), 57.7 (2C), 28.2, 28.2; HRMS (ESI): Exact mass calcd for $C_{13}H_{16}BrIN_2NaO_4$ $[M+Na]^+$ 492.9230, found 492.9225.



***tert*-Butyl (1*R*)-2-bromo-2-nitro-1-(4-nitrophenyl)ethylcarbamate (92).** Following General Procedure C, the *N*-Boc-imine (200 mg, 800 μmol) and bromonitromethane (75.0 μL, 960 μmol) provided the α-bromo nitroalkane (1.5:1 mixture of diastereomers), after flash column chromatography (SiO_2, 20% ethyl acetate in hexanes), as a white solid (159 mg, 51%). The enantiomeric excess of both the major and minor diastereomers was determined to be 93% ee by chiral HPLC analysis (Chiralcel IA, 10% ^{i}PrOH/hexanes, 1.0 mL/min, t_r(major) = 25.7, 33.6 min, t_r(minor) = 15.7, 18.6 min). R_f = 0.33 (20% EtOAc/hexanes); mp = 144-148 °C (decomposition); IR (film) 3351, 2999, 1681, 1562, 1518, 1352, 1155 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.5:1 mixture of diastereomers) δ 8.27 (d, *J* = 8.8 Hz, 2H), 8.26 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 6.39 (br s, 1H), 6.35 (br s, 1H), 5.78 (d, *J* = 8.6 Hz, 2H), 5.57 (br s, 1H), 5.49 (d, *J* = 8.9 Hz, 1H), 1.46 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.7 (2C), 148.3, 148.2, 142.3, 141.6, 128.2, 127.9, 124.3, 124.2, 84.1, 81.7 (2C), 80.5, 57.5 (2C), 28.1 (2C); HRMS (CI): Exact mass calcd for $C_{13}H_{17}BrN_3O_6$ $[M+H]^+$ 390.0295, found 390.0273.

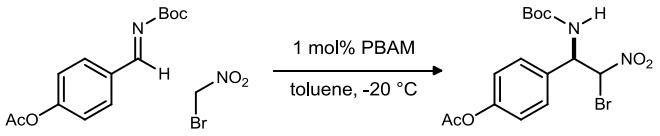


***tert*-Butyl (1*R*)-2-bromo-1-(4-(trifluoromethyl)phenyl)-2-nitroethylcarbamate (93).** Following General Procedure C, the *N*-Boc-imine (200 mg, 730 μmol) and bromonitromethane (70.0 μL, 880 μmol) provided the α-bromo nitroalkane (1.8:1 mixture of diastereomers), after flash column chromatography (SiO_2, 100% ethyl acetate), as a white solid (277 mg, 92%). The enantiomeric excess of the major and minor diastereomers was determined to be 93 and 82% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 1 mL/min, t_r(major) = 15.3, 19.8 min, t_r(minor) = 10.5, 11.9 min). R_f = 0.57 (30% EtOAc/hexanes); mp = 175-176 °C (decomposition); IR (film) 3373, 1686, 1561, 1525, 1330, 1167, 1127 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.8:1 mixture of diastereomers) δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 10.1 Hz, 2 H), 7.48 (d, *J* = 8.2 Hz, 2 H), 7.44 (d, *J* = 8.2 Hz, 2 H), 6.36 (br s, 1 H), 6.32 (br s, 1 H), 5.74 (br s, 2 H), 5.53 (br s, 1 H), 5.43 (br s, 1 H), 1.46 (s, 9 H), 1.44 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.6, 154.3, 139.2, 138.6, 131.3 (q, $^2J_{CF}$ = 32.8 Hz, 2C), 127.5, 127.3, 126.1 (m, 2C), 125.4 (q, $^1J_{CF}$ = 272.4 Hz, 2C), 84.6, 81.6, 81.4, 80.9, 57.6 (2C), 28.2, 28.1; HRMS (ESI): Exact mass calcd for $C_{14}H_{16}BrF_3N_2NaO_4$ $[M+Na]^+$ 435.0138, found 435.0126.



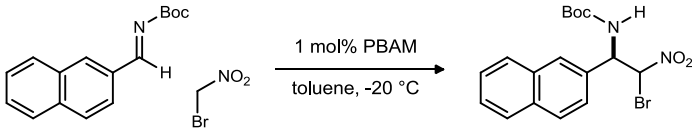
***tert*-Butyl (1*R*)-2-bromo-1-(4-methoxyphenyl)-2-nitroethylcarbamate (94).** Following General Procedure C, the *N*-Boc-imine (200 mg, 850 μmol) and bromonitromethane (80.0 μL, 1.02 mmol) provided the α-bromo nitroalkane (1:1 mixture of diastereomers),

after flash column chromatography (SiO_2, 100% ethyl acetate), as a white solid (301 mg, 95%). The enantiomeric excess of each diastereomer was determined to be 90 and 91% ee by chiral HPLC analysis (Chiralcel AD-H, 20% ^{i}PrOH/hexanes, 0.7 mL/min, t_r(major) = 13.6, 22.3 min, t_r(minor) = 16.3, 18.1 min). R_f = 0.33 (20% EtOAc/hexanes); mp = 161-162 °C (decomposition); IR (film) 3367, 2977, 1681, 1561, 1251, 1169, 1027 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 7.24 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.31 (br s, 1H), 6.27 (br s, 1H), 5.63 (br s, 1H), 5.57 (d, *J* = 4.2 Hz, 1H), 5.41 (br s, 1H), 5.30 (d, *J* = 9.0 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 1.45 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 160.1, 160.0, 154.5 (2C), 128.2, 128.1, 126.5 (2C), 114.4 (2C), 85.1, 82.0, 81.1, 80.9, 57.7 (2C), 55.2 (2C), 28.2, 28.1; HRMS (ESI): Exact mass calcd for $C_{14}H_{19}BrN_2NaO_5$ $[M+Na]^+$ 397.0370, found 397.0362.

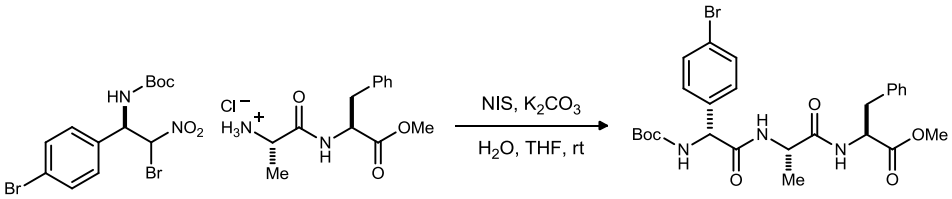


4-((1*R*)-2-Bromo-1-(*tert*-butoxycarbonylamino)-2-nitroethyl)phenyl acetate (95). Following General Procedure C, the *N*-Boc-imine (200 mg, 760 μmol) and bromonitromethane (71.0 μL, 910 μmol) provided the α-bromo nitroalkane (1:1 mixture of diastereomers), after flash column chromatography (SiO_2, 100% ethyl acetate), as a white solid (287 mg, 94%). The enantiomeric excess of each diastereomer was determined to be 85% ee by chiral HPLC analysis (Chiralcel AD-H, 20% ^{i}PrOH/hexanes, 0.7 mL/min, t_r(major) = 13.2, 28.2 min, t_r(minor) = 14.9, 16.2 min). R_f = 0.33 (30% EtOAc/hexanes); mp = 162 °C (decomposition); IR (film) 3372, 3010, 1754, 1682, 1563, 1372, 1223, 1170 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 7.35

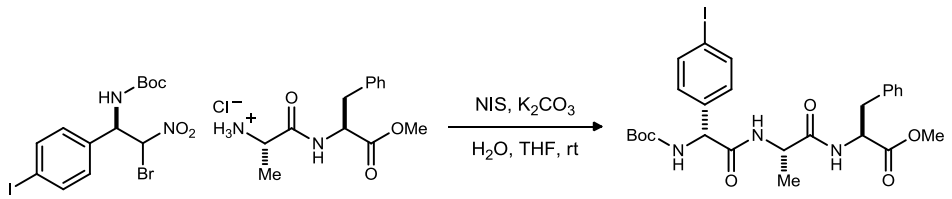
(d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 8.5 Hz, 2H), 6.32 (br s, 2H), 5.82 (br s, 1H), 5.66 (br s, 1H), 5.53 (br s, 1H), 5.49 (br s, 1H), 2.30 (s, 3H), 2.29 (s, 3H), 1.45 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 169.2, 169.1, 154.6, 154.4, 151.1, 151.0, 132.8, 132.3, 128.3, 128.1, 122.2 (2C), 84.8, 81.2, 81.0 (2C), 57.6, 57.4, 28.2 (2C), 21.1 (2C); HRMS (ESI): Exact mass calcd for $C_{15}H_{19}BrN_2NaO_6$ $[M+Na]^+$ 425.0319, found 425.0318.



***tert*-Butyl (1*R*)-2-bromo-1-(naphthalen-2-yl)-2-nitroethylcarbamate (96).** Following General Procedure C, the *N*-Boc-imine (200 mg, 780 μmol) and bromonitromethane (70.0 μL, 940 μmol) provided the α-bromo nitroalkane (1:1 mixture of diastereomers), after flash column chromatography (SiO_2, 100% ethyl acetate), as a white solid (282 mg, 92%). The enantiomeric excess of each diastereomer was determined to be 94 and 92% ee as determined by chiral HPLC analysis (Chiralcel AD-H, 20% ^{i}PrOH/hexanes, 0.7 mL/min, t_r(major) = 14.8, 30.7 min, t_r(minor) = 18.7, 20.8 min). R_f = 0.5 (30% EtOAc/hexanes); mp = 168-169 °C (decomposition); IR (film) 3373, 2979, 1688, 1562, 1516, 1165 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 7.88 (m, 6H), 7.82 (s, 1H), 7.80 (s, 1H), 7.55 (m, 4H), 7.43 (dd, J = 8.5, 1.8 Hz, 1H), 7.39 (dd, J = 8.5, 1.7 Hz, 1H), 6.44 (br s, 2H), 5.87 (br s, 2H), 5.67 (br s, 1H), 5.54 (d, J = 9.2 Hz, 1H), 1.48 (s, 9H), 1.47 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.8, 154.5, 133.4, 133.3, 133.1, 133.0, 132.5, 132.0, 129.2, 129.1, 128.1 (2C), 127.7 (2C), 126.9 (2C), 126.8 (2C), 126.7, 126.4, 123.8, 123.7, 85.2, 81.4, 81.1 (2C), 58.2 (2C), 28.2 (2C); HRMS (ESI): Exact mass calcd for $C_{17}H_{19}BrN_2NaO_4$ $[M+Na]^+$ 417.0420, found 417.0416.

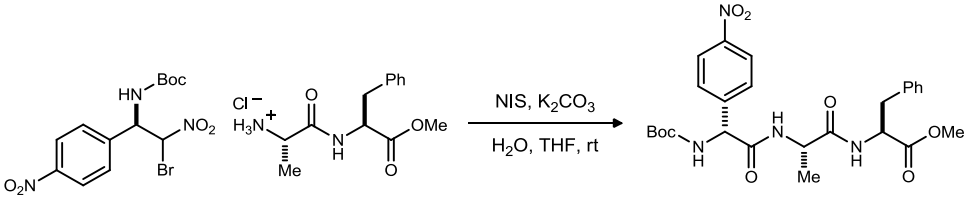


***N*-Boc-4-Br-Phenylglycine-Ala-Phe-OMe (101).** Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 50.0 μmol) and ammonium salt of the Ala-Phe dipeptide (16.0 mg, 60.0 μmol) provided the tripeptide (single diastereomer), after flash column chromatography (SiO_2, 30% ethyl acetate in hexanes), as a white solid (23.0 mg, 87% yield). $[\alpha]_D^{20}$ -32.0 (*c* 1.0, $CHCl_3$); R_f = 0.10 (30% EtOAc/hexanes); mp = 195-197 °C; IR (film) 3373, 1686, 1561, 1523, 1329, 1167, 1127 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.9 Hz, 2 H), 7.27 (m, 5 H), 7.10 (d, *J* = 6.6 Hz, 2 H), 6.49 (br s, 2 H), 5.80 (br s, 1 H), 5.11 (br s, 1 H), 4.82 (ddd, *J* = 6.1, 6.1, 6.1 Hz, 1 H), 4.44 (dq, *J* = 6.8, 6.8 Hz, 1 H), 3.74 (s, 3 H), 3.15 (dd, *J* = 13.7, 5.3 Hz, 1 H), 3.07 (dd, *J* = 13.7, 6.2 Hz, 1 H), 1.43 (s, 9 H), 1.23 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.6, 171.2, 169.3, 154.9, 137.2, 135.5, 132.1, 129.2, 128.9, 128.6, 127.2, 122.5, 80.4, 58.0, 53.3, 52.5, 48.9, 37.7, 28.3, 18.0; HRMS (ESI): Exact mass calcd for $C_{26}H_{33}BrN_3O_6$ $[M+H]^+$ 562.1547, found 562.1556.



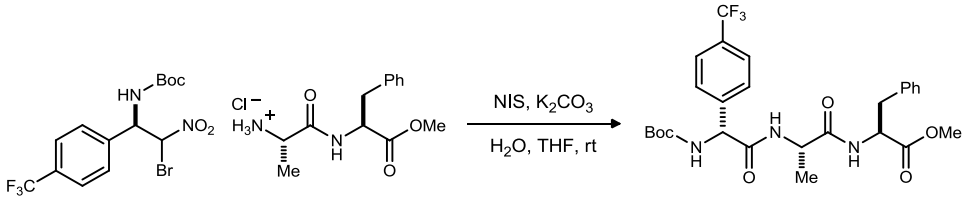
***N*-Boc-4-I-Phenylglycine-Ala-Phe-OMe (102).** Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 40.0 μmol) and the ammonium salt of the Ala-Phe dipeptide (15.0 mg, 50.0 μmol) provided the tripeptide (single diastereomer), after flash column chromatography (SiO_2, 40% ethyl acetate in hexanes), as a white solid (14.7 mg, 58%

yield). $[\alpha]_D^{20}$ -32.6 (*c* 2.5, $CHCl_3$); R_f = 0.10 (30% EtOAc/hexanes); mp = 169-171 °C; IR (film) 3279, 2932, 1645, 1538, 1367, 1167 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.28 (m, 3H), 7.11 (d, *J* = 4.4 Hz, 2H), 7.10 (d, *J* = 2.9 Hz, 2H), 6.46 (br s, 1H), 6.42 (br s, 1H), 5.75 (br s, 1H), 5.07 (br s, 1H), 4.82 (ddd, *J* = 6.2, 6.2, 6.2 Hz, 1H), 4.43 (dq, *J* = 7.1, 7.1 Hz, 1H), 3.74 (s, 3H), 3.15 (dd, *J* = 14.0, 5.7 Hz, 1H), 3.07 (dd, *J* = 14.0, 6.5 Hz, 1H), 1.43 (s, 9H), 1.24 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.6, 171.2, 169.3, 154.9, 137.2, 135.5, 132.1, 129.2, 128.9, 128.6, 127.2, 122.5, 80.4, 58.0, 53.3, 52.5, 48.9, 37.7, 28.3, 18.0; HRMS (ESI): Exact mass calcd for $C_{26}H_{33}IN_3O_6$ $[M+H]^+$ 610.1409, found 610.1423.

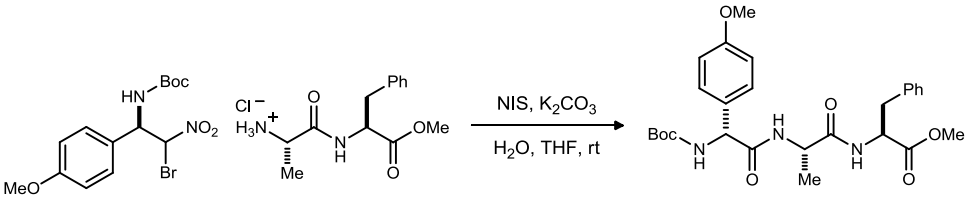


***N*-Boc-4-NO_2-Phenylglycine-Ala-Phe-OMe (103).** Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 50.0 μmol) and ammonium salt of the Ala-Phe dipeptide (18.0 mg, 60.0 μmol) provided the tripeptide (single diastereomer), after flash column chromatography (SiO_2, 40% ethyl acetate in hexanes), as a white solid (12.6 mg, 47% yield). $[\alpha]_D^{20}$ -23.6 (*c* 2.5, $CHCl_3$); R_f = 0.13 (40% EtOAc/hexanes); mp = 79-80 °C; IR (film) 3341, 2927, 1745, 1686, 1640, 1524, 1350, 1171 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.7 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.30 (m, 3H), 7.11 (d, *J* = 6.9 Hz, 2H), 6.58 (br s, 1H), 6.33 (d, *J* = 5.1 Hz, 1H), 5.89 (br s, 1H), 5.35 (br s, 1H), 4.85 (ddd, *J* = 6.1, 6.1, 6.1 Hz, 1H), 4.41 (dq, *J* = 7.1, 7.1 Hz, 1H), 3.76 (s, 3H), 3.18 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.10 (dd, *J* = 14.0, 6.4 Hz, 1H), 1.44 (s, 9H), 1.25 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.5, 171.0, 168.3, 154.8, 147.8, 145.3, 135.4, 129.2,

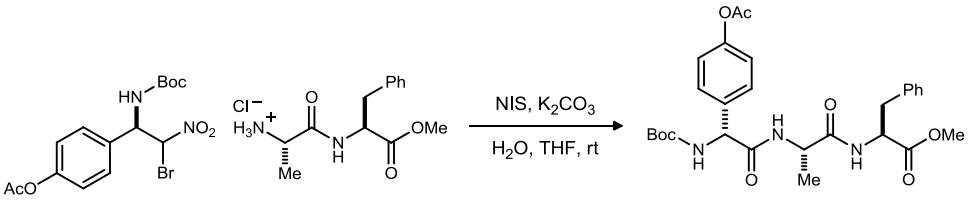
128.7, 128.1, 127.3, 124.2, 80.7, 58.0, 53.3, 52.5, 49.0, 37.7, 28.2, 18.1; HRMS (ESI): Exact mass calcd for $C_{26}H_{33}N_4O_8$ $[M+H]^+$ 529.2293, found 529.2294.



***N*-Boc-4-CF_3-Phenylglycine-Ala-Phe-OMe (104).** Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 50.0 μmol) and ammonium salt of the Ala-Phe dipeptide (17.0 mg, 60.0 μmol) provided the tripeptide (single diastereomer), after flash column chromatography (SiO_2, 40% ethyl acetate in hexanes), as a white solid (15.8 mg, 60% yield). $[\alpha]_D^{20}$ -20.6 (*c* 1.6, $CHCl_3$); R_f = 0.23 (40% EtOAc/hexanes); mp = 175-176 °C; IR (film) 3283, 3260, 1645, 1532, 1326, 1166, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.31 (m, 3H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.40 (d, *J* = 6.8 Hz, 1H), 6.34 (br s, 1H), 5.78 (br s, 1H), 5.19 (br s, 1H), 4.85 (ddd, *J* = 6.1, 6.1, 6.1 Hz, 1H), 4.42 (dq, *J* = 7.2, 7.2 Hz, 1H), 3.75 (s, 3H), 3.18 (dd, *J* = 14.0, 4.0 Hz, 1H), 3.10 (dd, *J* = 13.6, 6.4 Hz, 1H), 1.44 (s, 9H), 1.25 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.5, 171.2, 168.9, 154.9, 135.5, 130.6 (q, $^2J_{CF}$ = 32.3 Hz), 129.2, 128.6, 128.0, 127.5, 127.2, 126.0 (q, $^3J_{CF}$ = 3.5 Hz), 123.8 (q, $^1J_{CF}$ = 272.1 Hz), 80.5, 58.2, 53.3, 52.4, 49.0, 37.7, 28.2, 15.2; HRMS (ESI): Exact mass calcd for $C_{27}H_{33}F_3N_3O_6$ $[M+H]^+$ 552.2316, found 552.2322.

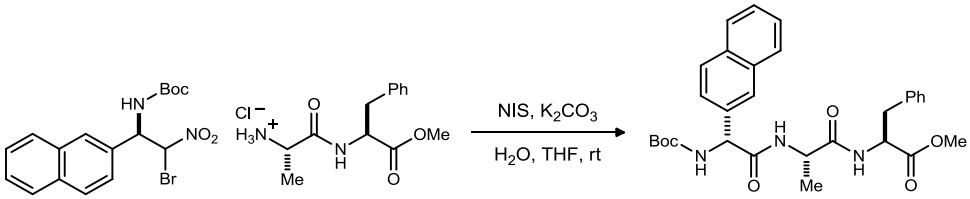


***N*-Boc-4-OMe-Phenylglycine-Ala-Phe-OMe (105).** Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 50.0 μmol) and the ammonium salt of the Ala-Phe dipeptide (18.0 mg, 60.0 μmol) provided the tripeptide (single diastereomer), after flash column chromatography (SiO_2, 40% ethyl acetate in hexanes), as a white solid (19.7 mg, 72% yield). $[\alpha]_D^{20}$ -38.1 (*c* 2.2, $CHCl_3$); R_f = 0.17 (40% EtOAc/hexanes); mp =179-180 °C; IR (film) 3282, 2927, 1651, 1512, 1247, 1169 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.25 (m, 5H), 7.09 (d, *J* = 6.6 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 6.60 (br s, 1H), 6.36 (d, *J* = 7.8 Hz, 1H), 5.66 (br s, 1H), 5.06 (br s, 1H), 4.80 (ddd, *J* = 6.6, 6.6, 6.6 Hz, 1H), 4.45 (dq, *J* = 6.6, 6.6 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.12 (dd, *J* = 13.8, 6.0 Hz, 1H), 3.03 (dd, *J* = 13.8, 6.6 Hz, 1H), 1.42 (s, 9H), 1.22 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.6, 171.4, 170.2, 159.6, 155.1, 135.7, 130.0, 129.2, 128.6, 128.5, 127.2, 114.4, 80.1, 58.2, 55.3, 53.3, 52.3, 48.8, 37.7, 28.3, 17.9; HRMS (ESI): Exact mass calcd for $C_{27}H_{36}N_3O_7$ $[M+H]^+$ 514.2548, found 514.2552.



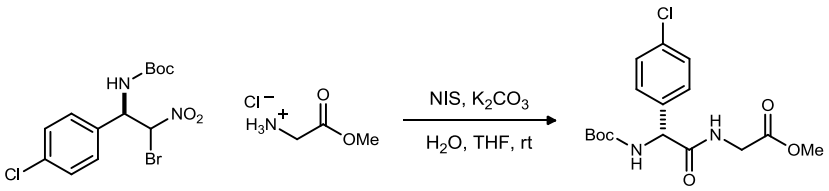
***N*-Boc-4-OAc-Phenylglycine-Ala-Phe-OMe (106).** Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 50.0 μmol) and ammonium salt of the Ala-Phe dipeptide (17.0 mg, 60.0 μmol) provided the tripeptide (single diastereomer), after column chromatography (SiO_2, 40% ethyl acetate in hexanes), as a white solid (13.2 mg, 49%

yield). $[\alpha]_D^{20}$ -34.3 (*c* 1.8, $CHCl_3$); R_f = 0.23 (40% EtOAc/hexanes); mp = 178-179 °C; IR (film) 3284, 2924, 1651, 1505, 1367, 1205, 1166 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.29 (m, 3H), 7.10 (m, 4H), 6.57 (br s, 1H), 6.39 (d, *J* = 7.4 Hz, 1H), 5.68 (br s, 1H), 5.12 (br s, 1H), 4.84 (ddd, *J* = 12.5, 6.3, 6.3 Hz, 1H), 4.44 (dq, *J* = 7.1, 7.1 Hz, 1H), 3.73 (s, 3H), 3.16 (dd, *J* = 13.9, 5.7 Hz, 1H), 3.09 (dd, *J* = 13.9, 6.5 Hz, 1H), 2.30 (s, 3H), 1.44 (s, 9H), 1.24 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.5, 171.2, 169.6, 169.2, 154.9, 150.6, 135.6, 129.2 (2C), 128.6, 128.4, 127.2, 122.1, 80.3, 58.0, 53.3, 52.4, 48.9, 37.7, 28.2, 21.1, 17.8; HRMS (ESI): Exact mass calcd for $C_{28}H_{36}N_3O_8$ $[M+H]^+$ 542.2497, found 542.2507.

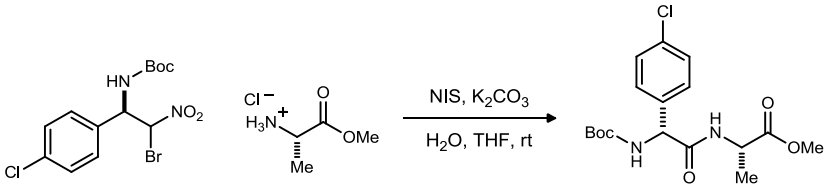


***N*-Boc-2-Naphylglycine-Ala-Phe-OMe (107).** Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 50.0 μmol) and ammonium salt of the Ala-Phe dipeptide (17.0 mg, 60.0 μmol) provided the tripeptide (single diastereomer), after flash column chromatography (SiO_2, 40% ethyl acetate in hexanes), as a white solid (15.5 mg, 57% yield). $[\alpha]_D^{20}$ -49.7 (*c* 1.9, $CHCl_3$); R_f = 0.20 (40% EtOAc/hexanes); mp = 183-185 °C; IR (film) 3286, 2977, 1749, 1645, 1531, 1166 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 4H), 7.51 (d, *J* = 3.8 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.29 (m, 3H), 7.36 (d, *J* = 6.4 Hz, 2H), 6.48 (br s, 1H), 6.31 (d, *J* = 7.0 Hz, 1H), 5.85 (br s, 1H), 5.27 (br s, 1H), 4.83 (ddd, *J* = 6.2, 6.2, 6.2 Hz, 1H), 4.46 (dq, *J* = 7.0, 7.0 Hz, 1H), 3.73 (s, 3H), 3.16 (dd, *J* = 13.6, 5.0 Hz, 1H), 3.08 (dd, *J* = 13.8, 6.4 Hz, 1H), 1.44 (s, 9H), 1.20 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.5, 171.3, 171.2, 155.0, 135.6, 133.3, 133.1,

129.2, 129.1, 128.6, 128.1, 127.7, 127.2, 127.2, 126.8, 126.5, 126.4, 124.3, 80.2, 58.9, 53.4, 52.4, 48.9, 37.7, 28.3, 17.8; HRMS (ESI): Exact mass calcd for $C_{30}H_{35}N_3NaO_6$ $[M+Na]^+$ 556.2418, found 556.2445.

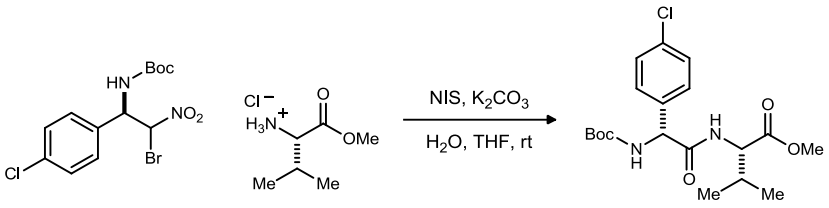


***N*-Boc-4-Cl-Phenylglycine-Gly-OMe (108a)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of glycine (8.00 mg, 63.6 μmol) provided the dipeptide after flash column chromatography (30% ethyl acetate in hexanes) as a white solid (14.9 mg, 79%). $[\alpha]_D^{20}$ -72.8 (*c* 0.13, $CHCl_3$); R_f = 0.08 (20% EtOAc/hexanes); mp 89-91 °C; IR (film) 3315, 2927, 1750, 1714, 1699, 1520, 1493, 1666 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35 (s, 4H), 6.39 (br s, 1H), 5.77 (br s, 1H), 5.21 (br s, 1H), 4.08 (dd, *J* = 18.5, 5.5 Hz, 1H), 3.99 (dd, *J* = 18.2, 4.6 Hz, 1H), 3.75 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 169.9, 169.8, 155.0, 136.5, 134.4, 129.2, 128.7, 80.4, 57.8, 52.4, 41.3, 28.2; HRMS (ESI): Exact mass calcd for $C_{16}H_{21}ClN_2NaO_5$ $[M+Na]^+$ 379.1031, found 379.1032.

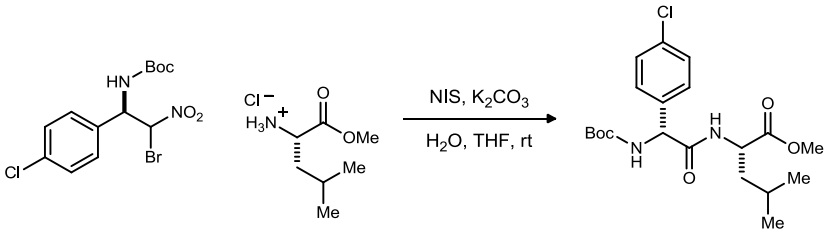


***N*-Boc-4-Cl-Phenylglycine-Ala-OMe (108b)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of L-alanine (9.00 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (20% ethyl acetate in hexanes) as a white solid (12.3 mg, 63%). $[\alpha]_D^{20}$ -57.7 (*c* 0.18,

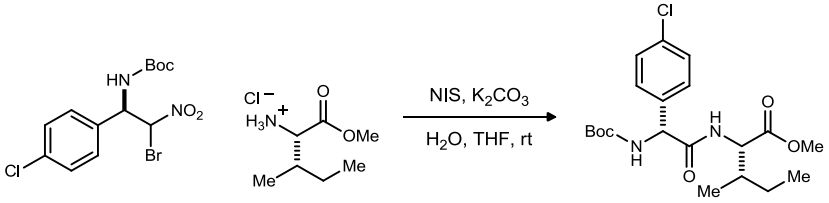
$CHCl_3$); R_f = 0.22 (30% EtOAc/hexanes); mp 122-125 °C; IR (film) 3314, 1745, 1716, 1662, 1492, 1366, 1163 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, *J* = 6.0 Hz, 2H), 7.32 (d, *J* = 4.8 Hz, 2H), 6.34 (d, *J* = 7.2 Hz, 1H), 5.72 (s, 1H), 5.14 (s, 1H), 4.56 (dq, *J* = 7.2, 7.2 Hz, 1H), 3.75 (s, 3H), 1.41 (s, 9H), 1.31 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 173.0, 169.1, 154.9, 136.7, 134.3, 129.2, 128.6, 80.3, 57.9, 52.6, 48.3, 28.2, 18.0; HRMS (ESI): Exact mass calcd for $C_{17}H_{23}ClN_2NaO_5$ $[M+Na]^+$ 393.1188, found 393.1211.



***N*-Boc-4-Cl-Phenylglycine-Val-OMe (108c)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of L-valine (11.0 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (20% ethyl acetate in hexanes) as a white solid (14.7 mg, 70%). $[\alpha]_D^{20}$ -54.4 (*c* 0.13, $CHCl_3$); R_f = 0.32 (30% EtOAc/hexanes); mp 105-108 °C; IR (film) 3318, 2967, 1742, 1716, 1661, 1524, 1492, 1168 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (s, 4H), 6.28 (d, *J* = 6.6 Hz, 1H), 5.74 (br s, 1H), 5.15 (br s, 1H), 4.53 (dd, *J* = 8.9, 4.9 Hz, 1H), 3.74 (s, 3H), 2.08 (qqd, *J* = 6.8, 6.8, 5.0 Hz, 1H), 1.41 (s, 9H), 0.76 (d, *J* = 6.6 Hz, 3H), 0.71 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 172.0, 169.4, 154.9, 137.0, 134.3, 129.2, 128.6, 80.3, 58.2, 57.0, 52.3, 31.3, 28.2, 18.7, 17.3; HRMS (ESI): Exact mass calcd for $C_{19}H_{28}ClN_2O_5$ $[M+H]^+$ 399.1681, found 399.1703.

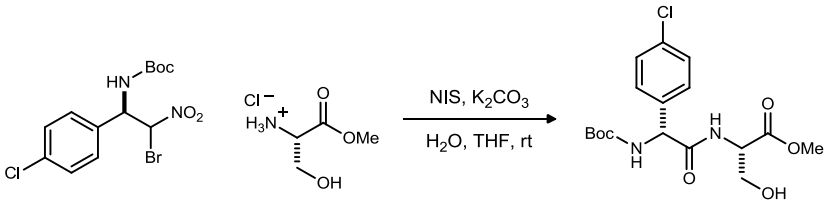


***N*-Boc-4-Cl-Phenylglycine-Leu-OMe (108d)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of L-leucine (12.0 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (20% ethyl acetate in hexanes) as a white solid (17.8 mg, 81%). $[\alpha]_D^{20}$ -58.1 (*c* 0.20, $CHCl_3$); R_f = 0.10 (10% EtOAc/hexanes); mp 79-81 °C; IR (film) 3313, 2958, 1747, 1716, 1661, 1539, 1493, 1167 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32 (s, 4H), 6.24 (d, *J* = 8.2 Hz, 1H), 5.74 (br s, 1H), 5.15 (br s, 1H), 4.59 (ddd, *J* = 8.9, 8.9, 5.1 Hz, 1H), 3.73 (s, 3H), 1.58 (ddd, *J* = 13.8, 8.5, 5.2 Hz, 1H), 1.44 (ddd, *J* = 14.8, 9.2, 5.8 Hz, 1H), 1.40 (s, 9H), 1.35 (m, 1H), 0.81 (d, *J* = 4.2 Hz, 3H), 0.80 (d, *J* = 4.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 173.1, 169.4, 154.9, 136.9, 134.3, 129.1, 128.6, 80.3, 58.0, 52.4, 50.9, 41.2, 28.2, 24.7, 22.7, 21.7; HRMS (ESI): Exact mass calcd for $C_{20}H_{29}ClN_2NaO_5$ $[M+Na]^+$ 435.1657, found 435.1673.

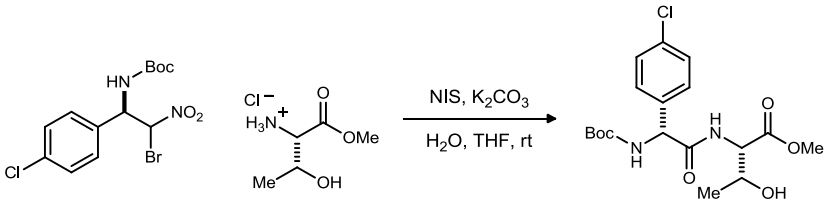


***N*-Boc-4-Cl-Phenylglycine-Ile-OMe (108e)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of L-isoleucine (12.0 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (20% ethyl acetate in hexanes) as a white solid (14.4 mg, 66%). $[\alpha]_D^{20}$ -

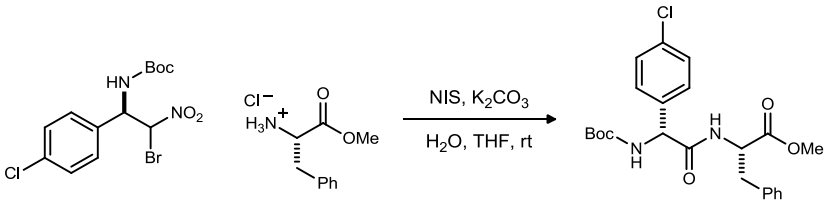
25.6 (*c* 0.32, $CHCl_3$); R_f = 0.32 (30% EtOAc/hexanes); mp 120-122 °C; IR (film) 3318, 1967, 1742, 1716, 1660, 1525, 1492, 1366, 1168 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, *J* = 3.0 Hz, 2H), 7.33 (d, *J* = 3.0 Hz, 2H), 6.27 (d, *J* = 6.0 Hz, 1H), 5.72 (br s, 1H), 5.14 (br s, 1H), 4.57 (dd, *J* = 8.8, 4.9 Hz, 1H), 3.74 (s, 3H), 1.81 (m, 1H), 1.41 (s, 9H), 0.96 (m, 1H), 0.88 (m, 1H), 0.82 (t, *J* = 7.4 Hz, 3H), 0.73 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 172.0, 169.3, 154.9, 136.9, 134.3, 129.2, 128.6, 80.3, 58.2, 56.4, 52.2, 37.8, 28.2, 24.8, 15.2, 11.3; HRMS (ESI): Exact mass calcd for $C_{20}H_{29}ClN_2NaO_5$ $[M+Na]^+$ 435.1657, found 435.1670.



***N*-Boc-4-Cl-Phenylglycine-Ser-OMe (108f)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of L-serine (10.0 mg, 63.6 μmol), after stirring at rt for 5 h, provided the dipeptide (single diastereomer) after flash column chromatography (50% ethyl acetate in hexanes) as a white solid (13.0 mg, 64%). $[\alpha]_D^{20}$ -38.2 (*c* 0.46, $CHCl_3$); R_f = 0.10 (40% EtOAc/hexanes); mp 122-125 °C; IR (film) 3322, 2926, 1667, 1493, 1367, 1166 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 9.6 Hz, 2H), 7.33 (d, *J* = 9.0 Hz, 2H), 6.95 (br s, 1H), 5.61 (br s, 1H), 5.16 (br s, 1H), 4.62 (ddd, *J* = 6.6, 3.0, 3.0 Hz, 1H), 3.92 (br s, 2H), 3.79 (s, 3H), 2.52 (br s, 1H), 1.42, (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 170.6, 169.9, 155.4, 135.9, 134.6, 129.3, 128.7, 80.9, 62.5, 58.7, 54.8, 52.9, 28.2; HRMS (ESI): Exact mass calcd for $C_{17}H_{23}ClN_2NaO_6$ $[M+Na]^+$ 409.1137, found 409.1133.

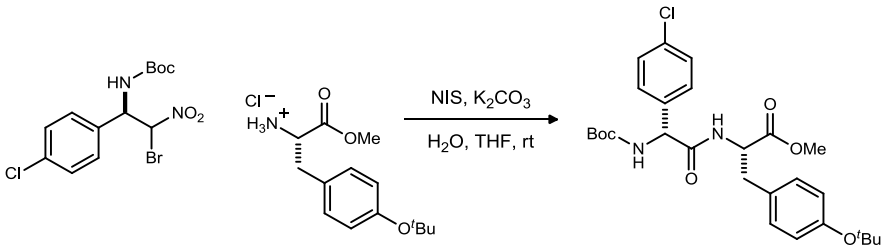


***N*-Boc-4-Cl-Phenylglycine-Thr-OMe (108g)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of L-threonine (11.0 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (40% ethyl acetate in hexanes) as a white solid (9.5 mg, 45%). $[\alpha]_D^{20}$ -48.1 (*c* 0.14, $CHCl_3$); R_f = 0.11 (40% EtOAc/hexanes); mp 130-133 °C; IR (film) 3332, 2926, 1715, 1665, 1516, 1492, 1367, 1166 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 9.0 Hz, 2H), 6.70 (br s, 1H), 5.73 (d, *J* = 5.4 Hz, 1H), 5.22 (br s, 1H), 4.58 (dd, *J* = 9.5, 2.2 Hz, 1H), 4.34 (qd, *J* = 6.6, 2.4 Hz, 1H), 3.79 (s, 3H), 2.04 (br s, 1H), 1.43 (s, 9H), 1.02 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.1, 70.1, 154.9, 136.6, 134.4, 129.2, 128.7, 80.5, 67.9, 58.3, 57.1, 52.7, 28.2, 19.7; HRMS (ESI): Exact mass calcd for $C_{18}H_{25}ClN_2NaO_6$ $[M+Na]^+$ 423.1293, found 423.1311.

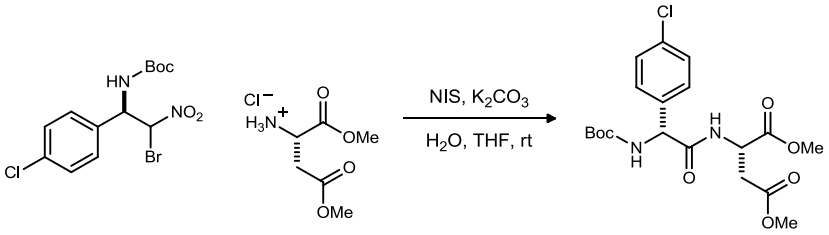


***N*-Boc-4-Cl-Phenylglycine-Phe-OMe (108h)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of L-phenylalanine (14.0 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (20% ethyl acetate in hexanes) as a white solid (15.2 mg, 64%). $[\alpha]_D^{20}$ -16.4 (*c* 0.1, $CHCl_3$); R_f = 0.13 (20% EtOAc/hexanes); mp 113-116 °C; IR (film) 3318,

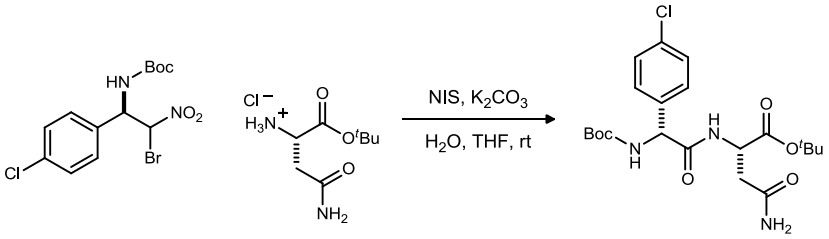
2926, 1742 (br), 1661, 1492, 1367, 1168 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1 H), 7.10 (t, *J* = 7.4 Hz, 2H), 6.67 (d, *J* = 5.1 Hz, 2H), 6.04 (br s, 1H), 5.82 (br s, 1H), 5.08 (br s, 1H), 4.87 (ddd, *J* = 7.8, 6.0, 6.0, Hz, 1H), 3.73 (s, 3H), 2.98 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.3, 168.9, 154.8, 137.0, 134.9, 134.3, 129.2, 128.9, 128.5 (2C), 127.1, 80.2, 57.9, 53.0, 52.5, 37.5, 28.2; HRMS (ESI): Exact mass calcd for $C_{23}H_{27}ClN_2NaO_5$ $[M+Na]^+$ 469.1501, found 469.1513.



***N*-Boc-4-Cl-Phenylglycine-Tyr(O^{t}Bu)-OMe (108i)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of *tert*-butyl protected L-tyrosine (18.0 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (20% ethyl acetate in hexanes) as a viscous oil (17.6 mg, 64%). $[\alpha]_D^{20}$ 16.9 (*c* 0.17, $CHCl_3$); R_f = 0.22 (30% EtOAc/hexanes); IR (film) 3319, 2978, 1743, 1663, 1506, 1492, 1366, 1163 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.53 (d, *J* = 5.4 Hz, 2H), 6.07 (br s, 1H), 5.85 (br s, 1H), 5.08 (br s, 1H), 4.84 (ddd, *J* = 10.9, 5.4, 5.4 Hz, 1H), 3.71 (s, 3H), 2.95 (dd, *J* = 14.1, 5.6 Hz, 1H), 2.90 (dd, *J* = 13.7, 4.5 Hz, 1H), 1.39 (br s, 9H), 1.31 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.3, 168.8, 154.8, 154.5, 137.1, 134.3, 129.6, 129.4, 129.3, 128.6, 124.0, 80.2, 78.4, 57.9, 53.1, 52.4, 36.9, 36.4, 28.8, 28.2; HRMS (ESI): Exact mass calcd for $C_{27}H_{35}ClN_2NaO_6$ $[M+Na]^+$ 541.2076, found 541.2078.

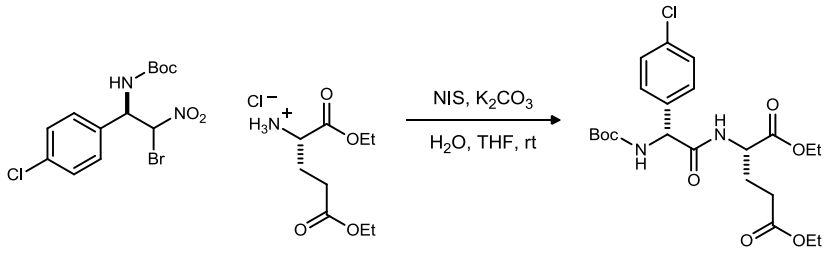


***N*-Boc-4-Cl-Phenylglycine-Asp(OMe)-OMe (108j)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of L-aspartic acid (13.0 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (30% ethyl acetate in hexanes) as a white solid (14.6 mg, 64%). $[\alpha]_D^{20}$ -32.0 (*c* 0.05, $CHCl_3$); R_f = 0.14 (30% ethyl EtOAc/hexanes); mp 110-113 °C; IR (film) 3320, 2928, 1734, 1718, 1684, 1670, 1507, 1490, 1368, 1219, 1168 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, *J* = 2.4 Hz, 2H), 7.33 (d, *J* = 3.6 Hz, 2H), 6.87 (br s, 1H), 5.67 (br s, 1H), 5.17 (br s, 1H), 4.83 (ddd, *J* = 8.5, 4.4, 4.4 Hz, 1H), 3.78 (s, 3H), 3.57 (s, 3H), 2.97 (dd, *J* = 17.2, 4.3 Hz, 1H), 2.74 (dd, *J* = 16.8, 3.2 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.1, 170.6, 169.4, 154.9, 136.6, 134.3, 129.2, 128.6, 80.4, 58.1, 53.0, 52.0, 48.7, 35.5, 28.2; HRMS (ESI): Exact mass calcd for $C_{19}H_{25}ClN_2NaO_7$ $[M+Na]^+$ 451.1242, found 451.1258.



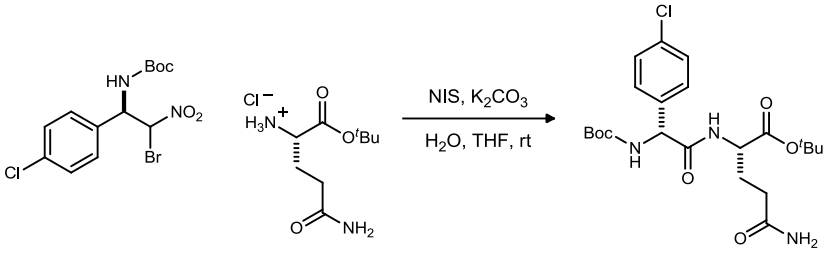
***N*-Boc-4-Cl-Phenylglycine-Asn-O^{t}Bu (108k)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of L-asparagine (14.0 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (60% ethyl acetate in hexanes) as a white solid (12.5 mg, 52%). $[\alpha]_D^{20}$ -

32.6 (*c* 0.33, $CHCl_3$); R_f = 0.03 (40% EtOAc/hexanes); mp 124-126 °C; IR (film) 3298, 2928, 1732, 1685, 1666, 1521, 1493, 1368, 1167 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.37 (br s, 1H), 7.36 (d, *J* = 9.6 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 5.76 (br s, 1H), 5.62 (br s, 1H), 5.56 (br s, 1H), 5.21 (br s, 1H), 4.66 (ddd, *J* = 8.3, 4.3, 4.3 Hz, 1H), 2.86 (dd, *J* = 16.2, 4.2 Hz, 1H), 2.63 (dd, *J* = 16.2, 4.2 Hz, 1H), 1.46 (s, 9H), 1.42 (br s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 172.0, 169.7, 169.3, 155.0, 136.5, 134.2, 129.0, 128.6, 82.7, 80.3, 58.1, 49.6, 36.7, 28.2, 27.8; HRMS (ESI): Exact mass calcd for $C_{21}H_{30}ClN_3NaO_6$ $[M+Na]^+$ 478.1715, found 478.1727.

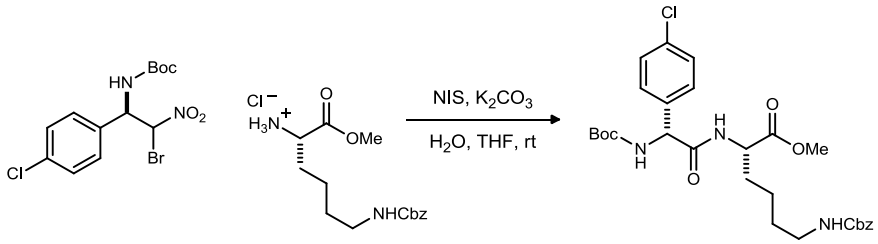


***N*-Boc-4-Cl-Phenylglycine-Glu(OEt)-OEt (108l)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of L-glutamic acid (15.0 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (20% ethyl acetate in hexanes) as a viscous oil (14.1 mg, 57%). $[\alpha]_D^{20}$ -53.3 (*c* 0.24, $CHCl_3$); R_f = 0.22 (30% EtOAc/hexanes); IR (film) 3327, 2980, 1736, 1665, 1510, 1492, 1386, 1247, 1168 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (s, 4H), 6.64, (d, *J* = 7.2 Hz, 1H), 5.75 (br s, 1H), 5.16 (br s, 1H), 4.56 (ddd, 7.9, 7.9, 4.6 Hz, 1H), 4.22 (dq, *J* = 10.7, 7.6 Hz, 1H), 4.21 (dq, *J* = 10.8, 7.5 Hz, 1H), 4.10 (dq, *J* = 10.9, 7.1 Hz, 1H), 4.07 (dq, *J* = 10.9, 7.9 Hz, 1H), 2.22 (m, 1H), 2.15 (m, 2H), 1.93 (m, 1H), 1.42 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 172.7, 171.3, 169.6, 154.9, 136.8, 134.3, 129.2, 128.6, 80.3, 61.8, 60.8, 58.0, 51.9, 29.8,

28.2, 26.8, 14.1 (2C); HRMS (ESI): Exact mass calcd for $C_{22}H_{32}ClN_2O_7$ $[M+H]^+$ 471.1893, found 471.1889.

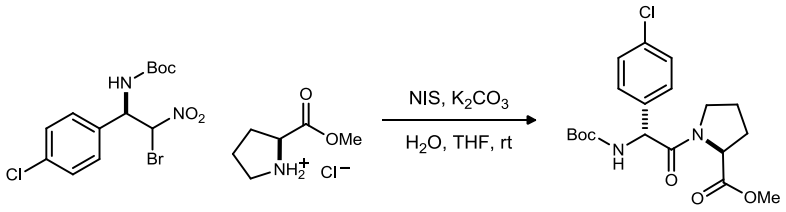


***N*-Boc-4-Cl-Phenylglycine-Gln-O^{t}Bu (108m)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of L-glutamine (15.0 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (70% ethyl acetate in hexanes) as a viscous oil (14.7 mg, 59%). $[\alpha]_D^{20}$ -54.7 (*c* 0.08, $CHCl_3$); R_f = 0.17 (70% EtOAc/hexanes); IR (film) 3322, 2930, 1732, 1652, 1522, 1492, 1368, 1161 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (s, 4H), 6.90 (d, *J* = 7.8 Hz, 1H), 5.79 (br s, 1H), 5.66 (br s, 1H), 5.40 (br s, 1H), 5.13 (br s, 1H), 4.42 (br s, 1H), 2.14 (m, 1H), 2.08 (m, 1H), 1.86 (m, 2H), 1.46 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 174.3, 170.6, 169.9, 155.0, 136.5, 134.4, 129.2, 128.6, 82.8, 80.5, 58.2, 52.4, 31.3, 29.7, 28.2, 27.9; HRMS (ESI): Exact mass calcd for $C_{22}H_{32}ClN_3NaO_6$ $[M+Na]^+$ 492.1872, found 492.1896.



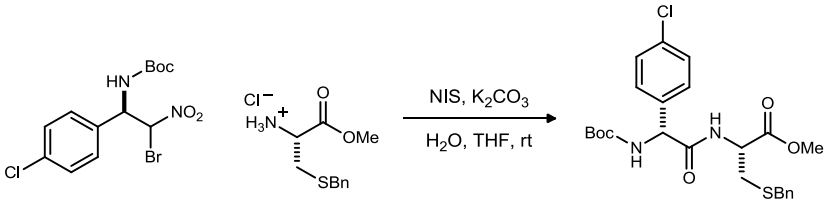
***N*-Boc-4-Cl-Phenylglycine-Lys(Cbz)-OMe (108n)** . Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of carboxybenzyl

protected L-lysine (22.0 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (30% ethyl acetate in hexanes) as an off-white solid (16.0 mg, 55%). $[\alpha]_D^{20}$ -54.5 (*c* 0.20, $CHCl_3$); R_f = 0.11 (30% EtOAc/hexanes); mp 93-95 °C; IR (film) 3318, 2925, 1702 (br), 1671, 1522, 1492, 1455, 1367, 1248, 1167 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, *J* = 4.2 Hz, 4H), 7.31 (s, 5H), 6.39 (br s, 1H), 5.70 (br s, 1H), 5.14 (br s, 1H), 5.10 (s, 2H), 4.80 (br s, 1H), 4.56 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1H), 3.74 (s, 3H), 3.08 (dddd, *J* = 12.8, 12.8, 6.4, 6.4 Hz, 2H), 1.80 (m, 2H), 1.61 (m, 2H), 1.40 (s, 9H), 1.14 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 172.3 (2C), 169.4, 156.5, 136.5, 134.3, 129.2, 128.6, 128.5 (2C), 128.1 (2C), 80.4, 66.6, 58.1, 52.5, 51.9, 40.4, 31.5, 29.7, 29.1, 28.2, 22.6, 21.8; HRMS (ESI): Exact mass calcd for $C_{28}H_{36}ClN_3NaO_7$ $[M+Na]^+$ 584.2134, found 584.2150.

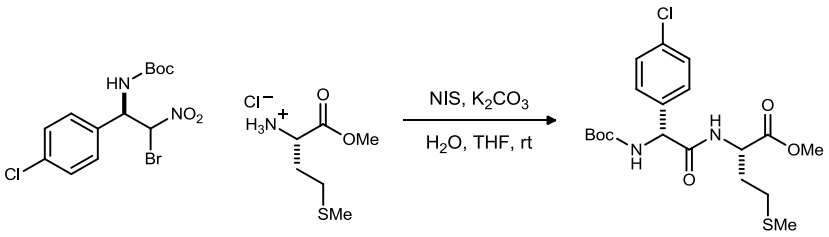


***N*-Boc-4-Cl-Phenylglycine-Pro-OMe (108o)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of L-proline (11.0 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (15-20% ethyl acetate in hexanes) as a viscous yellow oil (a mixture of two rotamers in approximately 5:1 ratio, 14.0 mg, 67%). $[\alpha]_D^{20}$ -152 (*c* 1.24, $CHCl_3$); R_f = 0.28 (20% EtOAc/hexanes); IR (neat) 3416, 3320, 2977, 1747, 1710, 1650, 1490, 1434, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) major rotamer: δ 7.35-7.28 (m, 4H), 6.10 (br d, *J* = 7.0 Hz, 1H), 5.37 (br d, *J* = 7.0 Hz, 1H), 4.42 (dd, *J* = 8.2, 3.4 Hz, 1H), 3.76 (s, 3H), 3.74-3.69 (m, 1H), 3.10 (td, *J* = 9.5, 7.4 Hz, 1H), 2.09-1.94 (m, 3H), 1.84-1.79 (m, 1H), 1.39 (s,

9H); ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer: ppm 172.3, 168.5, 154.8, 136.3, 134.3, 129.5, 129.2, 79.9, 59.4, 56.1, 52.5, 46.8, 29.0, 28.4, 24.6; HRMS (ESI): Exact mass calcd for $C_{19}H_{25}ClN_2NaO_5$ $[M+Na]^+$ 419.1350, found 419.1356.

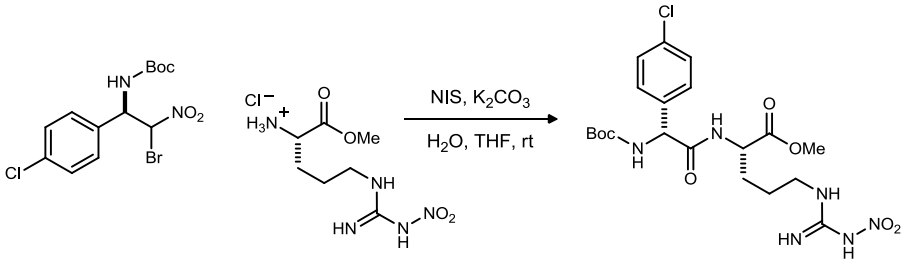


***N*-Boc-4-Cl-Phenylglycine-Cys(Bn)-OMe (108p)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of benzyl protected L-cysteine (8.00 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (30% ethyl acetate in hexanes) as a viscous oil (13.5 mg, 52%). $[\alpha]_D^{20}$ -59.2 (*c* 0.13, $CHCl_3$); R_f = 0.11 (20% EtOAc/hexanes); IR (film) 3318, 2925, 1748, 1668, 1559, 1540, 1507, 1367, 1219, 1167 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 7H), 7.18 (d, *J* = 7.8 Hz, 2H), 6.59 (br s, 1H), 5.73 (br s, 1H), 5.21 (br s, 1H), 4.77 (ddd, *J* = 5.4, 5.4, 5.4 Hz, 1H), 3.76 (s, 3H), 3.53 (d, *J* = 13.3 Hz, 1H), 3.48 (d, *J* = 13.3 Hz, 1H), 2.83 (dd, *J* = 14.0, 4.9 Hz, 1H), 2.78 (dd, *J* = 14.0, 5.8 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 170.8, 169.5, 154.9, 137.2, 136.5, 134.4, 129.2, 128.8, 128.7, 128.5, 127.3, 80.4, 58.0, 52.8, 51.8, 36.4, 33.1, 28.2; HRMS (ESI): Exact mass calcd for $C_{24}H_{29}ClN_2NaO_5S$ $[M+Na]^+$ 515.1378, found 515.1386.



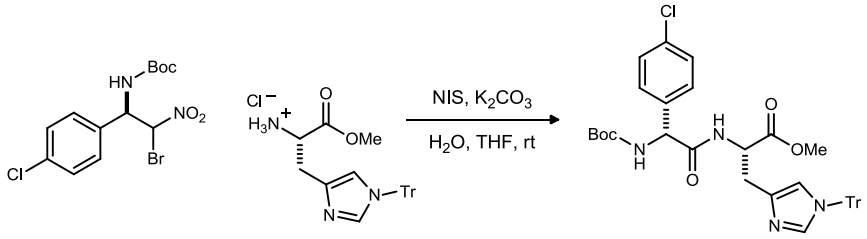
***N*-Boc-4-Cl-Phenylglycine-Met-OMe (108q)**. Following General Procedure E, the α-

bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of L-methionine (13.0 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (20% ethyl acetate in hexanes) as a viscous oil (9.9 mg, 43%). $[\alpha]_D^{20}$ -32.8 (*c* 0.20, $CHCl_3$); R_f = 0.24 (30% EtOAc/hexanes); IR (film) 3319, 2923, 1742, 1714, 1673, 1492, 1367, 1166 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.36 (s, 2H), 7.35 (s, 2H), 6.51 (d, *J* = 6.0 Hz, 1H), 5.74 (br s, 1H), 5.16 (br s, 1H), 4.72 (ddd, *J* = 7.4, 7.4, 4,9 Hz, 1H), 3.78 (s, 3H), 2.28 (m, 2H), 2.11 (m, 1H), 1.97 (s, 3H), 1.92 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.9, 169.4, 154.8, 134.4, 130.9, 129.2, 128.6, 80.4, 58.2, 52.7, 51.6, 31.0, 29.6, 28.2, 15.3; HRMS (ESI): Exact mass calcd for $C_{19}H_{27}ClN_2NaO_5S$ $[M+Na]^+$ 453.1221, found 453.1231.

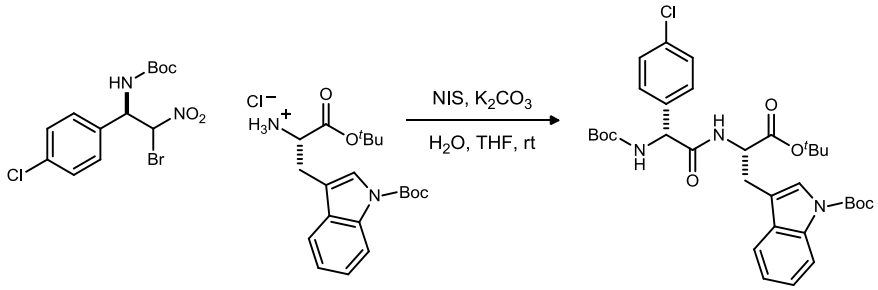


***N*-Boc-4-Cl-Phenylglycine-Arg(NO_2)-OMe (108r)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of nitro-protected L-arginine (17.0 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (80% ethyl acetate in hexanes) as a viscous oil (11.7 mg, 44%). $[\alpha]_D^{20}$ -37.3 (*c* 0.15, $CHCl_3$); R_f = 0.10 (70% EtOAc/hexanes); IR (film) 3309, 2927, 1667, 1629, 1560, 1492, 1367, 1268, 1163 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (s, 4H), 5.56 (br s, 1H), 5.26 (br s, 1H), 4.57 (br s, 1H), 3.78 (s, 3H), 3.41 (br s, 1H), 3.22 (br s, 1H), 1.93 (m, 1H), 1.66 (m, 1H), 1.60 (br s, 6H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 172.1, 170.9, 159.4, 155.2, 134.8, 130.9, 129.4, 128.5, 81.1, 58.6, 52.9,

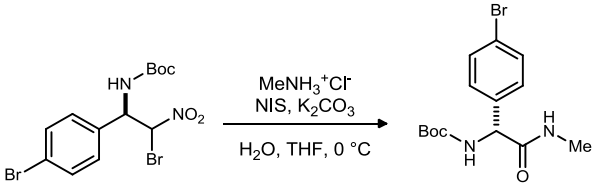
47.9, 40.4, 29.7, 28.2, 24.3; HRMS (ESI): Exact mass calcd for $C_{20}H_{29}ClN_6NaO_7$ $[M+Na]^+$ 523.1678, found 523.1691.



***N*-Boc-4-Cl-Phenylglycine-His(Tr)-OMe (108s)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of trityl-protected L-histidine (28.0 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (70% ethyl acetate in hexanes) as a white solid (14.1 mg, 41%). $[\alpha]_D^{20}$ -18.1 (*c* 0.22, $CHCl_3$); R_f = 0.03 (40% EtOAc/hexanes); mp 209-211 °C (decomp.); IR (film) 3313, 2925, 1746, 1715, 1677, 1491, 1446, 1366, 1168 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 6.0 Hz, 1H), 7.34 (m, 14 H), 7.23 (s, 1H), 7.22 (s, 1H), 7.08 (m, 4H), 6.48 (s, 1H), 5.98 (br s, 1H), 5.20 (br s, 1H), 4.63 (ddd, *J* = 7.2, 5.7, 4.5 Hz, 1H), 3.63 (s, 3H), 2.89 (dd, *J* = 14.7, 5.9 Hz, 1H) 2.86 (dd, *J* = 14.3, 3.6 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 177.2, 171.2, 154.8, 142.0 (3C), 138.5, 137.4, 136.0, 133.7, 129.7 (6C), 128.8, 128.5, 128.1 (9C), 119.5, 79.8, 75.4, 57.9, 53.1, 52.2, 29.0, 28.3; HRMS (ESI): Exact mass calcd for $C_{39}H_{40}ClN_4O_5$ $[M+H]^+$ 679.2682, found 679.2713.

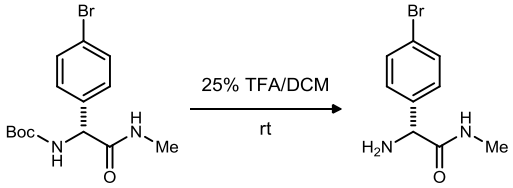


***N*-Boc-4-Cl-Phenylglycine-Trp(Boc)-O^{t}Bu (108t)**. Following General Procedure E, the α-bromo nitroalkane (20.0 mg, 52.7 μmol) and ammonium salt of boc-protected L-tryptophan (25.0 mg, 63.6 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (15% ethyl acetate in hexanes) as a viscous oil (14.5 mg, 44%). $[\alpha]_D^{20}$ -17.6 (*c* 0.25, $CHCl_3$); R_f = 0.43 (30% EtOAc/hexanes); IR (film) 3330, 2979, 1732 (br), 1667, 1492, 1454, 1369, 1254, 1159 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.31 (m, 2H), 7.28 (s, 1H), 7.25 (s, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.18 (br s, 1H), 5.79 (br s, 1H), 5.07 (br s, 1H), 4.82 (ddd, *J* = 6.0, 6.0, 6.0 Hz, 1H), 3.11 (d, *J* = 6.0 Hz, 2H), 1.67 (s, 9H), 1.42 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 170.2, 169.2, 154.8, 149.4, 136.6, 135.1, 134.1, 130.3, 129.0, 128.4, 124.5, 123.9, 122.6, 118.6, 115.2, 114.6, 83.6, 82.8, 80.1, 57.9, 53.0, 28.2, 28.1, 27.9, 27.2; HRMS (ESI): Exact mass calcd for $C_{33}H_{42}ClN_3NaO_7$ $[M+Na]^+$ 650.2603, found 650.2625.

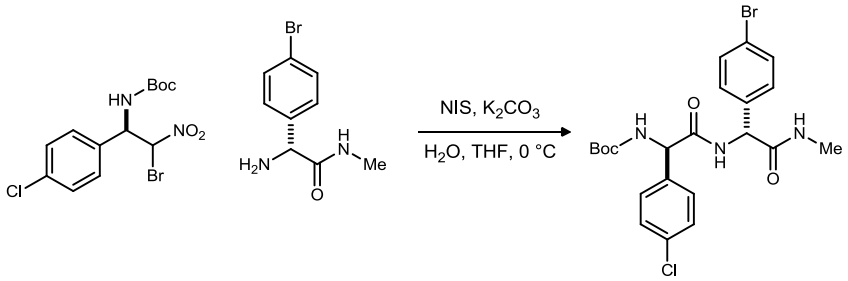


***N*-Boc-4-Br-Phenylglycine-*N*-Me (S-3).** Following General Procedure E, the α-bromo nitroalkane (100 mg, 240 μmol) and *N*-methylamine hydrochloride (19.0 mg, 280 μmol) gave the *N*-methyl phenylglycine (single diastereomer), after flash column

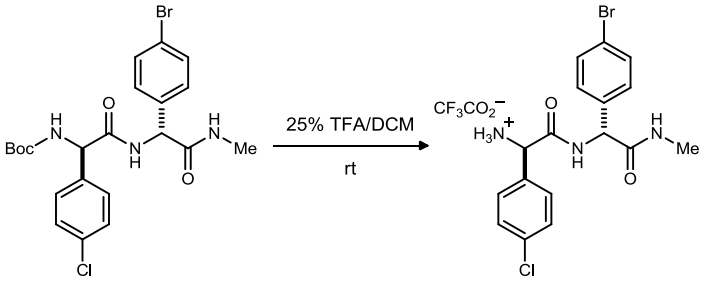
chromatography (SiO_2, 40% ethyl acetate in hexanes), as a white solid (50.7 mg, 63% yield). $[\alpha]_D^{20}$ -106.1 (*c* 0.33, $CHCl_3$); R_f = 0.24 (40% EtOAc/hexanes); mp = 179-181 °C; IR (neat) 3321, 2977, 1661, 1488, 1367, 1165, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 5.89 (br s, 2H), 5.11 (br s, 1H), 2.80 (d, *J* = 4.9 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 170.1, 155.1, 137.6, 132.1, 128.9, 122.3, 80.2, 57.9, 28.3, 26.6; HRMS (ESI): Exact mass calcd for $C_{14}H_{19}BrN_2NaO_3$ $[M+Na]^+$ 365.0471, found 365.0468.



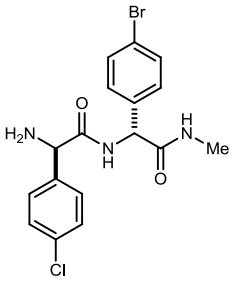
4-Br-Phenylglycine-*N*-Me (109). To a solution of the protected amine (136 mg, 400 μmol) in CH_2Cl_2 (5 ml), trifluoroacetic acid (1.25 ml) was added, and the reaction stirred for 2 hours at rt. It was then diluted with CH_2Cl_2, and washed with water. The aqueous layer was brought to a pH of 12 by addition of 1M KOH, and extracted with ethyl acetate. The organic layers were dried and condensed to give the free amine as an oil (69.3 mg, 72% yield). $[\alpha]_D^{20}$ -52.5 (*c* 0.04, $CHCl_3$); R_f = 0.14 (5% MeOH/CH_2Cl_2); IR (neat) 3299.9, 2927, 1652, 1592, 1488, 1409, 1011 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 4.44 (br s, 1H), 2.90 (br s, 1H), 2.77 (d, *J* = 4.8 Hz, 3H), [N*H*$_2$ not observed]; ^{13}C NMR (150 MHz, $CDCl_3$) ppm 173.2, 140.0, 131.8, 128.6, 121.8, 59.2, 26.0; HRMS (ESI): Exact mass calcd for $C_9H_{12}BrN_2O$ $[M+H]^+$ 243.0128, found 243.0124.



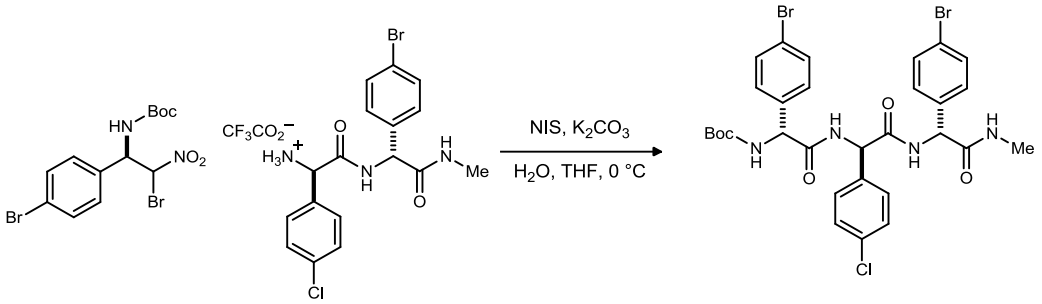
***N*-Boc-4-Cl-Phenylglycine-4-Br-Phenylglycine-*N*-Me (S-4).** Following General Procedure D, the α-bromo nitroalkane (88.0 mg, 230 μmol) and free amine (68.0 mg, 280 μmol) provided the dipeptide (single diastereomer), after trituration with CH_2Cl_2, as a white solid (83.0 mg, 70% yield), with some residual succinimide impurity (13%). An analytical sample was purified by column chromatography (SiO_2, 50% ethyl acetate in hexanes) for characterization. $[\alpha]_D^{20}$ -26.5 (*c* 0.17, $CHCl_3$); R_f = 0.11 (40% EtOAc/hexanes); mp = 250 °C (decomposition); IR (film) 3285, 2978, 1676, 1643, 1523, 1490 cm^{-1}; ^1H NMR (600 MHz, 5:1 $CDCl_3$:DMSO-d_6) δ 8.07 (d, *J* = 7.4 Hz, 1H), 7.38 (d, *J* = 4.0 Hz, 1H), 6.82 (d, *J* = 7.4 Hz, 2H), 6.79 (d, *J* = 7.4 Hz, 2H), 6.76 (d, *J* = 7.4 Hz, 2H), 6.70 (d, *J* = 7.6 Hz, 2H), 6.38 (d, *J* = 7.4 Hz, 1H), 4.87 (d, *J* = 7.1 Hz, 1H), 4.78 (d, *J* = 7.7 Hz, 1H), 2.07 (d, *J* = 4.6 Hz, 3H), 0.84 (s, 9H); ^{13}C NMR (150 MHz, 5:1 $CDCl_3$:DMSO-*d6*) ppm 168.3, 168.2, 153.7, 136.8, 136.3, 131.7, 129.9, 127.8, 127.5, 127.0, 120.0, 78.0, 56.1, 54.8, 27.0, 24.6; HRMS (ESI): Exact mass calcd for $C_{22}H_{25}BrClN_3NaO$ $[M+Na]^+$ 532.0609, found 532.0601.



4-Cl-Phenylglycine-4-Br-Phenylglycine-*N*-Me•CF_3CO_2H (110). To a solution of the protected amine (47.4 mg, 90.0 μmol) in CH_2Cl_2 (1.2 ml), trifluoroacetic acid (0.4 ml) was added, and the reaction stirred for 5 hours at rt. It was then concentrated *in vacuo*, and column chromatographed (2% MeOH/CH_2Cl_2), giving the pure trifluoroacetate salt of the deprotected dipeptide (36.5 mg, 75%).



For characterization, an analytical sample was diluted with CH_2Cl_2, and washed with water. The aqueous layer was brought to a pH of 12 by addition of 1M KOH, and extracted with ethyl acetate. The organic layers were dried and concentrated to give the free amine as an oil. $[\alpha]_D^{20}$ -16.7 (*c* 0.15, $CHCl_3$); R_f = 0.21 (5% MeOH/CH_2Cl_2); IR (film) 3291, 2924, 1641, 1489, 1091, 1011 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.40 (d, *J* = 6.7 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.30 (m, 6H), 7.19 (d, *J* = 8.3 Hz, 2H), 5.99 (d, *J* = 3.8 Hz, 1H), 5.36 (d, *J* = 7.1 Hz, 1H), 4.55 (br s, 1H), 2.78 (d, *J* = 4.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 172.4, 169.8, 136.7, 134.0, 132.1 (2C), 129.0, 128.8, 128.1, 122.5, 59.2, 56.3, 26.5; HRMS (ESI): Exact mass calcd for $C_{17}H_{18}BrClN_3O_2$ $[M+H]^+$ 410.0265, found 410.0274.



***N*-Boc-4-Br-Phenylglycine-4-Cl-Phenylglycine-4-Br-Phenylglycine-*N*-Me (111)**. Following General Procedure E, the α-bromo nitroalkane (13.0 mg, 31 μmol) and trifluoroacetate salt (20.0 mg, 38 μmol) provided the tripeptide (single diastereomer), after trituration with CH_2Cl_2, as a white solid (18.6 mg, 83% yield), with some residual succinimide impurity (10%). The desired compound was characterized with residual succinimide impurity. $[\alpha]_D^{20}$ -7.5 (*c* 0.16, $CHCl_3$); R_f = 0.16 (50% EtOAc/hexanes); mp = 235 °C (decomposition); IR (film) 3279, 1668, 1634, 1489, 1367, 1011 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.07 (d, *J* = 7.5 Hz, 1H), 8.75 (d, *J* = 7.5 Hz, 1H), 8.24 (d, *J* = 4.5 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 3H), 7.48 (d, *J* = 8.0 Hz, 5H), 7.42 (d, *J* = 8.0 Hz, 3H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.70 (d, *J* = 7.5 Hz, 1H), 5.31 (d, *J* = 7.0 Hz, 2H), 2.53 (d, *J* = 4.5 Hz, 3H), 1.36 (s, 9H); ^{13}C NMR (150 MHz, $DMSO_{d6}$) ppm 169.7, 169.5, 169.1, 155.3, 138.5, 132.7, 131.6, 131.5, 129.9, 129.6, 129.5, 129.4 (2C), 128.6, 128.5, 121.2, 79.0, 57.3, 56.3, 55.6, 28.5, 26.0; HRMS (ESI): Exact mass calcd for $C_{30}H_{32}Br_2ClN_4O_5$ $[M+H]^+$ 721.0422, found 721.0458.

Chapter III: Enantioselective aza-Henry Addition to Silyl Imines

General Procedure A: Synthesis of *N*-TMS-Protected Imines

According to the procedure of Collet and coworkers,[155] in a flame-dried round bottom flask under argon, *n*-butyl lithium (1 equiv) was added to hexamethyldisilazane (1.1 equiv) at 0 °C. After stirring for 10 m, the aldehyde (1 equiv), in THF (10 M), was added *via* cannula. The reaction was allowed to stir at rt for 1 h before the solvent was removed. The crude material was treated with TMSCl (1 equiv), and allowed to stir for 1 h at rt. The reaction was then diluted with hexanes and filtered under argon. The solvent was removed, giving the crude imine which was then purified via distillation.

General Procedure B: Bromonitromethane Addition to *N*-TMS-Protected Imines: Acetyl Bromide Quench

A solution of the imine (1 equiv) and PBAM[156] (0.10 equiv) in toluene (0.3 M) was cooled to -78 °C. Bromonitromethane was added to the reaction mixture in aliquots (0.2 equiv every 2 h) over 10 h. The reaction was then stirred at -78 °C for an additional 16 h before addition of acetyl bromide at -78 °C (1 equiv). The reaction was then stirred at -78 °C for 3 h and subsequently quenched at -78 °C by the addition of water (200 eq). The reaction mixture was diluted with CH_2Cl_2 and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the crude reaction mixture was purified by column chromatography to give the α-bromonitro adduct as a mixture of inseparable diastereomers.

General Procedure C: Bromonitromethane Addition to *N*-TMS-Protected Imines

[155] Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J. C.; Aubry, A.; Collet, A. *Chemistry-a European Journal* **1997**, *3*, 1691.
[156] Davis, T. A.; Wilt, J. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2010**, *132*, 2880.

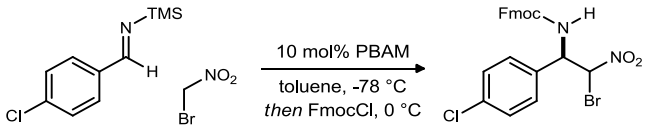
A solution of the imine (1 equiv) and PBAM (0.10 equiv) in toluene (0.3 M) was cooled to -78 °C. Bromonitromethane was added to the reaction mixture in aliquots (0.2 equiv every 2 h) over 10 h. The reaction was then stirred at -78 °C for an additional 16 h before its quench at -78 °C with an acylating reagent (1 equiv). The reaction was then warmed to 0 °C and stirred for 20 h. The solvent was removed *in vacuo*, and the crude reaction mixture was purified by column chromatography to give the α-bromonitro adduct as a mixture of inseparable diastereomers.

General Procedure D: 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_2O (5.0 equiv) at 0 °C, followed by K_2CO_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 E: Amide Synthesis Using an Ammonium Salt

K_2CO_3 (5.0 equiv) was added to the suspension of the ammonium salt (2.0 equiv) and the α-bromo nitroalkane (1.0 equiv, 0.2 M) in DME and H_2O (5.0 equiv) at 0 °C, followed by NIS (100 mol%). The reaction mixture was placed under an atmosphere of O_2 and stirred at 0 °C for 24 h. The resulting mixture was diluted with dichloromethane and then filtered. The filtrate was concentrated and subjected to purification by flash column chromatography on silica gel.

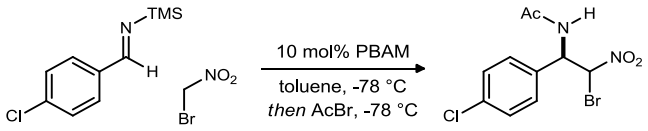


Fluorenylmethyl (1*R*)-2-bromo-1-(4-chlorophenyl)-2-nitroethylcarbamate (182). Following General Procedure C, the *N*-TMS-imine (20 mg, 94 μmol) and bromonitromethane (7.3 ml, 94 μmol), when quenched with fluorenylmethyl chloroformate (24.3 mg, 94 μmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a white solid (35.8 mg, 76%). The enantiomeric excess of both the major and minor diastereomers was determined to be 91% ee by chiral HPLC analysis (Chiralcel AD-H, 20% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 12.0 min, $t_r(d_1e_2$, major) = 38.8 min, $t_r(d_2e_1$, minor) = 13.3 min, $t_r(d_2e_2$, major) = 22.4 min). R_f = 0.29 (20% EtOAc/hexanes); mp = 154-156 °C (dec); IR (film) 3307, 1701, 1566, 1508, 1493, 1246 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.6 Hz, 4H), 7.58 (br s, 4H), 7.37 (m, 12H), 7.23 (br s, 4H), 6.30 (br s, 2H), 5.96 (br d, *J* = 8.4 Hz, 1H), 5.65 (br s, 1H), 5.57 (br s, 1H), 5.48 (br s, 1H), 4.57 (m, 2H), 4.46 (br s, 2H), 4.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.5, 155.3, 143.4 (2C), 141.3 (2C), 135.4, 135.3, 133.3, 132.8, 129.3 (2C), 128.3, 128.2, 127.8 (2C), 127.1 (2C), 124.9 (2C), 120.1 (2C), 83.9, 80.5, 67.3 (2C), 57.9 (2C), 47.0 (2C); HRMS (ESI): Exact mass calcd for $C_{23}H_{18}BrClN_2NaO_4$ $[M+Na]^+$ 523.0031, found 523.0057.

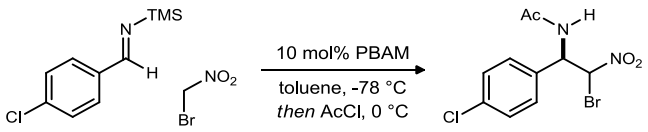
***N*-(2-Bromo-1-(4-chlorophenyl)-2-nitroethyl)-1,1,1-trimethylsilanamine (184).** The *N*-TMS-imine[157] (40.0 mg, 189 µmol) and bromonitromethane (16.0 µL, 227 µmol) were stirred at rt in $CDCl_3$ for 1 h and then analyzed directly by NMR. ^{1}H NMR indicated 81% conversion to the *N*-TMS-protected *α*-bromo nitroalkane (1.6:1 dr), with some *N*-TMS-imine and bromonitromethane remaining. Notably, the peaks seen at 1.43 and 1.22 ppm, corresponding to the *NH* protons of each diastereomer, appear as doublets which integrate to a single proton. The coupling constants for each peak (12.6 and 13.2 Hz, respectively) suggest the protons couple only to the neighboring benzylic methyne proton. These details indicate that the compound observed is the suggested *N*-TMS-protected adduct, and not the free amine which would result from deprotection of the TMS group.

N-TMS-protected *α*-bromo nitroalkane: ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.35 (m, 4H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.22 (d, *J* = 3.6 Hz, 1H), 5.82 (d, *J* = 9.0 Hz, 1H), 4.85 (dd, *J* = 12.6, 3.6 Hz, 1H), 4.49 (dd, *J* = 13.2, 9.0 Hz, 1H), 1.43 (d, *J* = 12.6 Hz, 1H), 1.22 (d, *J* = 13.2 Hz, 1H), 0.00 (s, 9H), -0.02 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 138.6, 138.3, 134.3, 134.1, 129.1, 128.9, 128.2, 127.8, 91.1, 83.5, 61.1, 59.8, 0.0, -0.1.

[157] Commercially available.

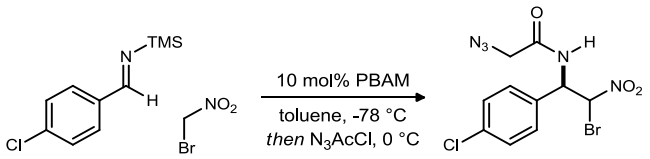


***N*-((1*R*)-2-Bromo-1-(4-chlorophenyl)-2-nitroethyl)acetamide (187).** Following General Procedure B, the *N*-TMS-imine (20 mg, 94 μmol) and bromonitromethane (7.3 μL, 94 μmol), when quenched with acetyl bromide (11.6 μL, 94 μmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 30% ethyl acetate in hexanes), as a viscous yellow oil (23.4 mg, 78%). The enantiomeric excess of the major and minor diastereomers were determined to be 93 and 91% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 10.2 min, $t_r(d_1e_2$, major) = 18.6 min, $t_r(d_2e_1$, minor) = 13.9 min, $t_r(d_2e_2$, major) = 16.0 min). R_f = 0.18 (30% EtOAc/hexanes); IR (film) 3266, 2925, 1661, 1566, 1538, 1373, 1094 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.39 (d, *J* = 6.4 Hz, 2H), 7.37 (d, *J* = 6.4 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 6.87 (br d, *J* = 8.5 Hz, 1H), 6.49 (br d, *J* = 8.0 Hz, 1H), 6.37 (d, *J* = 4.5 Hz, 1H), 6.35 (d, *J* = 5.6 Hz, 1H), 5.91 (dd, *J* = 8.6, 4.4 Hz, 1H), 5.78 (dd, *J* = 8.9, 5.6 Hz, 1H), 2.14 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 169.9, 169.7, 135.5, 135.4, 133.1, 132.7, 129.5, 129.4, 128.4 (2C), 83.9, 80.3, 56.0, 55.8, 23.1 (2C); HRMS (CI): Exact mass calcd for $C_{10}H_{11}BrClN_2O_3$ $[M+H]^+$ 320.9636, found 320.9628.



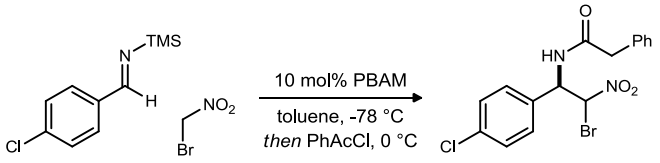
Following General Procedure C, the *N*-TMS-imine (20 mg, 94 μmol) and bromonitromethane (7.3 μL, 94 μmol), when quenched with acetyl chloride (6.7 μL, 94

μmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 30% ethyl acetate in hexanes), as a viscous yellow oil (25.0 mg, 83%). The enantiomeric excess of the major and minor diastereomers were determined to be 92 and 91% ee, respectively.

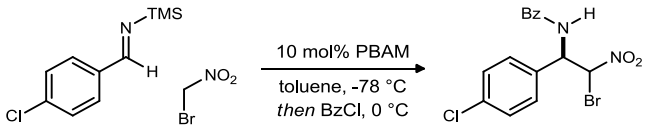


2-Azido-*N*-((1*R*)-2-bromo-1-(4-chlorophenyl)-2-nitroethyl)acetamide (199a). Following General Procedure C, the *N*-TMS-imine (50 mg, 236 μmol) and bromonitromethane (18.0 μL, 236 μmol), when quenched with azidoacetyl chloride (28.2 μL, 236 μmol), provided the α-bromo nitroalkane (1:1 mixture of diastereomers), after flash column chromatography (SiO_2, 15% ethyl acetate in hexanes), as a white solid (70.0 mg, 82%). The enantiomeric excess of both the major and minor diastereomers was determined to be 91% ee by chiral HPLC analysis (Chiralcel AD-H, 20% ^{i}PrOH/hexanes, 0.6 mL/min, $t_r(d_1e_1$, minor) = 10.5 min, $t_r(d_1e_2$, major) = 17.2 min, $t_r(d_2e_1$, minor) = 15.3 min, $t_r(d_2e_2$, major) = 18.5 min). R_f = 0.27 (30% EtOAc/hexanes); mp = 154-156 °C (dec); IR (film) 3290, 3026, 2116, 1662, 1553, 1537, 1317, 1287 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.61 (br d, *J* = 8.9 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.22 (br d, *J* = 8.6 Hz, 1H), 6.35 (d, *J* = 4.1 Hz, 1H), 6.34 (d, *J* = 5.1 Hz, 1H), 5.91 (dd, *J* = 8.9, 4.4 Hz, 1H), 5.76 (dd, *J* = 9.1, 5.3 Hz, 1H), 4.18 (d, *J* = 16.9 Hz, 1H), 4.15 (d, *J* = 17.0 Hz, 1H), 4.10 (d, *J* = 16.8 Hz, 1H), 4.09 (d, *J* = 16.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 166.5, 166.2, 135.8, 135.7, 132.6, 132.1, 129.6, 129.5, 128.3 (2C), 83.6,

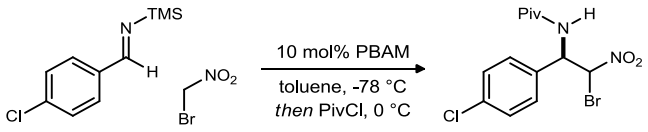
79.9, 55.7, 55.6, 52.4 (2C); HRMS (CI): Exact mass calcd for $C_{10}H_{10}BrClN_5O_3$ $[M+H]^+$ 363.9635, found 363.9638.



***N*-((1*R*)-2-Bromo-1-(4-chlorophenyl)-2-nitroethyl)-2-phenylacetamide (199b).** Following General Procedure B, the *N*-TMS-imine (20 mg, 94 μmol) and bromonitromethane (7.3 μL, 94 μmol), when quenched with phenylacetyl chloride (13 μL, 94 μmol), provided the α-bromo nitroalkane (2.4:1 mixture of diastereomers), after flash column chromatography (SiO_2, 20% ethyl acetate in hexanes), as a white solid (32 mg, 85%). The enantiomeric excess of the major and minor diastereomers were determined to be 93 and 94% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 20% ^{i}PrOH/hexanes, 1.0 mL/min, t_r(major) = 8.6, 15.3 min, t_r(minor) = 10.4, 17.1 min). R_f = 0.13 (15% EtOAc/hexanes); mp = 161-163 °C (decomposition); IR (film) 3277, 2922, 1653, 1563, 1531, 1494, 1353 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 2.4:1 mixture of diastereomers) δ 7.45 (m, 4H), 7.39 (m, 2H), 7.32 (m, 8H), 7.09 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.68 (br d, *J* = 8.8 Hz, 1H), 6.26 (d, *J* = 3.8 Hz, 1H), 6.25 (d, *J* = 5.0 Hz, 1H), 6.22 (br d, *J* = 8.5 Hz, 1H), 5.86 (dd, *J* = 8.8, 4.0 Hz, 1H), 5.71 (dd, *J* = 9.1, 5.1 Hz, 1H), 3.75 (d, *J* = 16.2 Hz, 1H), 3.70 (d, *J* = 16.4 Hz, 1H), 3.69 (d, *J* = 16.4 Hz, 1H), 3.66 (d, *J* = 16.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 170.7, 170.4, 135.4, 135.3, 133.8, 133.7, 133.1, 132.5, 129.5, 129.4 (3C), 129.3 (2C), 128.1 (2C), 127.9 (2C), 84.2, 80.2, 55.7, 55.6, 43.6, 43.5; HRMS (ESI): Exact mass calcd for $C_{16}H_{14}BrClN_2NaO_3$ $[M+Na]^+$ 418.9769, found 418.9795.

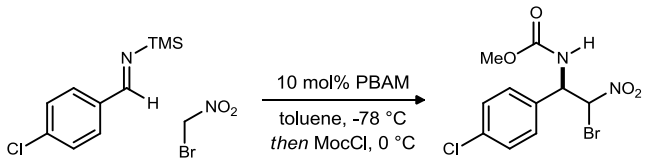


***N*-((1*R*)-2-Bromo-1-(4-chlorophenyl)-2-nitroethyl)benzamide (199c).** Following General Procedure C, the *N*-TMS-imine (20 mg, 94 μmol) and bromonitromethane (7.3 μL, 94 μmol), when quenched with benzoyl chloride (11 μL, 94 μmol), provided the α-bromo nitroalkane (1.4:1 mixture of diastereomers), after flash column chromatography (SiO_2, 15% ethyl acetate in hexanes), as a white solid (25.2 mg, 70%). The enantiomeric excess of the major and minor diastereomers were determined to be 94 and 95% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 20% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 8.6 min, $t_r(d_1e_2$, major) = 19.5 min, $t_r(d_2e_1$, minor) = 6.7 min, $t_r(d_2e_2$, major) = 14.1 min). R_f = 0.15 (15% EtOAc/hexanes); mp = 147-150 °C (dec); IR (film) 3299, 2923, 1641, 1564, 1521, 1343 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.87 (d, *J* = 7.3 Hz, 2H), 7.82 (d, *J* = 7.3 Hz, 2H), 7.59 (m, 2H), 7.56 (br d, *J* = 8.9 Hz, 1H), 7.50 (m, 4H), 7.38 (m, 6H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.03 (br d, *J* = 8.4 Hz, 1H), 6.48 (d, *J* = 4.3 Hz, 1H), 6.45 (d, *J* = 5.1 Hz, 1H), 6.10 (dd, *J* = 8.5, 4.2 Hz, 1H), 5.97 (dd, *J* = 8.9, 5.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 167.1, 166.9, 135.5, 135.4, 133.2, 133.0 (2C), 132.8, 132.4 (2C), 129.6, 129.4, 128.9, 128.4, 128.2, 127.2, 127.1, 84.2, 80.3, 56.3, 56.1; HRMS (ESI): Exact mass calcd for $C_{15}H_{12}BrClN_2NaO_3$ $[M+Na]^+$ 404.9612, found 404.9638.



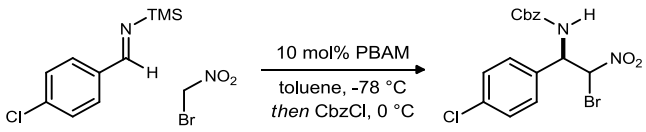
***N*-((1*R*)-2-Bromo-1-(4-chlorophenyl)-2-nitroethyl)pivalamide (199d).** Following General Procedure C, the *N*-TMS-imine (20 mg, 94 μmol) and bromonitromethane (7.3

μL, 94 μmol), when quenched with pivaloyl chloride (11.5 μL, 94 μmol), provided the α-bromo nitroalkane (1.4:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a white solid (22.7 mg, 67%). The enantiomeric excess of the major and minor diastereomers were determined to be 96 and 97% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 20% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 5.5 min, $t_r(d_1e_2$, major) = 9.5 min, $t_r(d_2e_1$, minor) = 4.8 min, $t_r(d_2e_2$, major) = 18.7 min). R_f = 0.21 (15% EtOAc/hexanes); mp = 142-146 °C (decomposition); IR (film) 3319, 2969, 1643, 1560, 1543, 1350, 1213 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.39 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.03 (br d, *J* = 8.5 Hz, 1H), 6.50 (br d, *J* = 8.0 Hz, 1H), 6.39 (d, *J* = 3.9 Hz, 1H), 6.37 (d, *J* = 4.9 Hz, 1H), 5.88 (dd, *J* = 8.4, 3.9 Hz, 1H), 5.74 (dd, *J* = 8.8, 5.0 Hz, 1H), 1.30 (s, 9H), 1.27 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 178.2, 177.9, 135.4, 135.3, 133.4, 133.0, 129.5, 129.4, 128.2, 128.1, 84.4, 80.5, 55.5, 55.4, 39.1, 39.0, 27.4, 27.3; HRMS (ESI): Exact mass calcd for $C_{13}H_{16}BrClN_2NaO_3$ $[M+Na]^+$ 384.9925, found 384.9933.



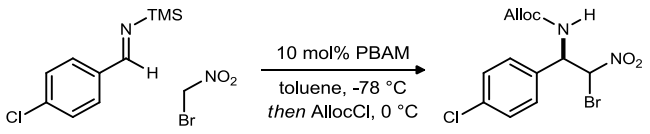
Methyl (1*R*)-2-bromo-1-(4-chlorophenyl)-2-nitroethylcarbamate (199e). Following General Procedure C, the *N*-TMS-imine (20 mg, 94 μmol) and bromonitromethane (7.3 μL, 94 μmol), when quenched with methyl chloroformate (7.3 μL, 94 μmol), provided the α-bromo nitroalkane (1.3:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a white solid (21 mg, 67%). The enantiomeric excess of both the major and minor diastereomers was determined to be

91% ee by chiral HPLC analysis (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 1.0 mL/min, t_r(major) = 12.1, 24.1 min, t_r(minor) = 14.5, 22.4 min). R_f = 0.14 (10% EtOAc/hexanes); mp = 121-125 °C; IR (film) 3301, 2922, 1701, 1567, 1534, 1494, 1351, 1252, 1093 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.3:1 mixture of diastereomers) δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 6.31 (br s, 2H), 5.93 (br s, 1H), 5.69 (br dd, *J* = 8.7, 3.8 Hz, 1H), 5.58 (br s, 1H), 5.49 (br s, 1H), 3.75 (s, 3H), 3,73 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 156.0, 155.7, 135.5, 135.4, 133.5, 132.9, 129.5, 129.4, 128.2, 128.1, 84.4, 80.6, 57.9 (2C), 53.0 (2C); HRMS (CI): Exact mass calcd for $C_9H_9ClNO_2$ $[M\text{-}CHBrNO_2]^+$ 198.0316, found 198.0309.

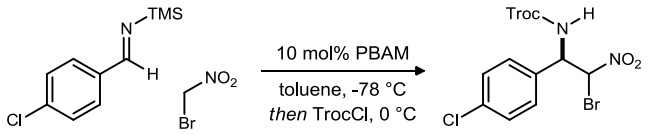


Benzyl (1*R*)-2-bromo-1-(4-chlorophenyl)-2-nitroethylcarbamate (199f). Following General Procedure C, the *N*-TMS-imine (20 mg, 94 μmol) and bromonitromethane (7.3 μL, 94 μmol), when quenched with benzyl chloroformate (13.2 μL, 94 μmol), provided the α-bromo nitroalkane (1.3:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a white solid (28.1 mg, 72%). The enantiomeric excess of the major and minor diastereomers were determined to be 91 and 90% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 15% ^{i}PrOH/hexanes, 0.7 mL/min, $t_r(d_1e_1$, minor) = 17.9 min, $t_r(d_1e_2$, major) = 31.3 min, $t_r(d_2e_1$, minor) = 19.3 min, $t_r(d_2e_2$, major) = 29.7 min). R_f = 0.19 (10% EtOAc/hexanes); mp = 112-115 °C; IR (film) 3308, 2924, 1699, 1567, 1532, 1494, 1350, 1249, 1093, 1015 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.38 (m, 14H), 7.28 (d, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 6.31 (br s, 2H), 6.01 (br d, *J* = 6.8 Hz, 1H), 5.70 (br

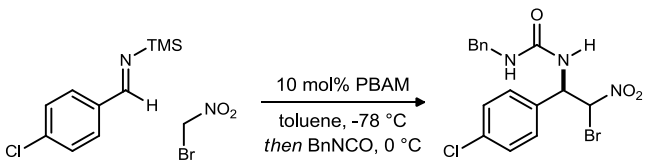
s, 1H), 5.65 (br s, 1H), 5.52 (br s, 1H), 5.16 (s, 2H), 5.14 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.4, 155.1, 135.5 (2C), 135.4 (2C), 133.4, 132.8, 129.4 (3C), 128.6 (2C), 128.5, 128.3 (2C), 128.2 (2C), 84.3, 80.7, 67.8 (2C), 57.9 (2C); HRMS (ESI): Exact mass calcd for $C_{16}H_{14}BrClN_2NaO_4$ $[M+Na]^+$ 434.9718, found 434.9708.



Allyl (1*R*)-2-bromo-1-(4-chlorophenyl)-2-nitroethylcarbamate (199g). Following General Procedure C, the *N*-TMS-imine (20 mg, 94 μmol) and bromonitromethane (7.3 μL, 94 μmol), when quenched with allyl chloroformate (10 μL, 94 μmol), provided the α-bromo nitroalkane (1:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a viscous white paste (27.8 mg, 85%). The enantiomeric excess of both the major and minor diastereomers was determined to be 91% ee by chiral HPLC analysis (Chiralcel AD-H, 8% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 17.1 min, $t_r(d_1e_2$, major) = 30.8 min, $t_r(d_2e_1$, minor) = 16.2 min, $t_r(d_2e_2$, major) = 33.4 min). R_f = 0.13 (10% EtOAc/hexanes); IR (film) 3307, 2925, 1699, 1568, 1532, 1494, 1352, 1278, 1250, 1093 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 9.0 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 9.0 Hz, 2H), 6.32 (br s, 2H), 6.00 (br d, *J* = 9.7 Hz, 1H), 5.93 (m, 2H), 5.69 (dd, *J* = 9.1, 4.3 Hz, 1H), 5.63 (br d, *J* = 8.8 Hz, 1H), 5.50 (br dd, *J* = 8.0, 5.9 Hz, 1H), 5.34 (d, *J* = 16.5 Hz, 2H), 5.27 (d, *J* = 10.5 Hz, 2H), 4.62 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.2, 155.0, 135.5, 135.4, 132.8, 132.0, 131.9, 129.5, 129.4, 128.3, 128.1, 118.6, 118.5, 84.3, 80.6, 66.6 (2C), 57.8 (2C); HRMS (ESI): Exact mass calcd for $C_{12}H_{12}BrClN_2NaO_4$ $[M+Na]^+$ 384.9561, found 384.9581.



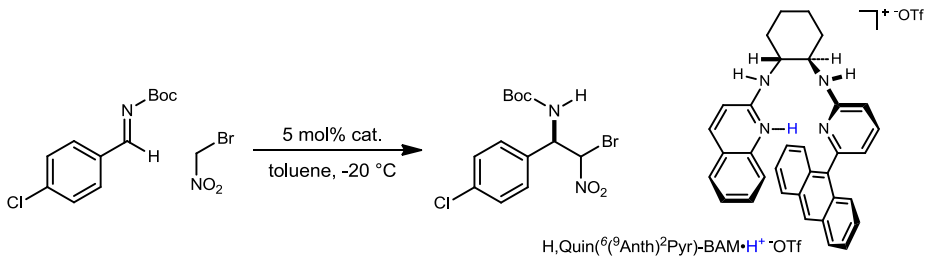
2,2,2-Trichloroethyl (1*R*)-2-bromo-1-(4-chlorophenyl)-2-nitroethylcarbamate (199h). Following General Procedure c, the *N*-TMS-imine (20 mg, 94 μmol) and bromonitromethane (7.3 μL, 94 μmol), when quenched with trichloroethyl chloroformate (13 μL, 94 μmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a viscous yellow oil (36 mg, 83%). The enantiomeric excess of the major and minor diastereomers were determined to be 92 and 91% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 8% ^{i}PrOH/hexanes, 1.0 mL/min, t_r(major) = 12.5, 19.2 min, t_r(minor) = 14.9, 17.9 min). R_f = 0.13 (10% EtOAc/hexanes); IR (film) 3307, 2921, 1717, 1568, 1520, 1494, 1229, 1093, 1015 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.42 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.34 (br s, 2H), 6.27 (br d, *J* = 8.9 Hz, 1H), 5.85 (br s, 1H), 5.72 (dd, *J* = 9.0, 4.4 Hz, 1H), 5.52 (br dd, *J* = 8.8, 5.5 Hz, 1H), 4.78 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 153.9, 153.5, 135.8, 135.7, 132.8, 132.2, 129.6, 129.5, 128.2, 128.1, 94.9 (2C), 83.9, 80.0, 74.9 (2C), 58.0 (2C); HRMS (CI): Exact mass calcd for $C_{11}H_{10}BrCl_4N_2O_4$ $[M+H]^+$ 454.8549, found 454.8533.



1-Benzyl-3-((1*R*)-2-bromo-1-(4-chlorophenyl)-2-nitroethyl)urea (199i). Following General Procedure C, the *N*-TMS-imine (20 mg, 94 μmol) and bromonitromethane (7.3

μL, 94 μmol), when quenched with benzyl isocyanate (12 μL, 94 μmol), provided the α-bromo nitroalkane (1.1:1 mixture of diastereomers), after flash column chromatography (SiO_2, 20% ethyl acetate in hexanes), as a viscous yellow oil (13 mg, 33%). The enantiomeric excess of the major and minor diastereomers were determined to be 92 and 86% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 20% ^{i}PrOH/hexanes, 1.0 mL/min, t_r(major) = 10.0, 21.4 min, t_r(minor) = 12.6, 23.7 min). R_f = 0.21 (30% EtOAc/hexanes); IR (film) 2926, 1727, 1582, 1495, 1455, 1365, 1233, 1092 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.1:1 mixture of diastereomers) δ 7.37 (m, 6H), 7.30 (d, *J* = 8.6 Hz, 4H), 7.27 (d, *J* = 9.9 Hz, 4H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.28 (d, *J* = 4.0 Hz, 1H), 6.26 (d, *J* = 5.8 Hz, 1H), 5.95 (br d, *J* = 9.1 Hz, 1H), 5.84 (dd, *J* = 8.9, 4.0 Hz, 1H), 5.64 (dd, *J* = 9.1, 5.8 Hz, 2H), 5.31 (m, 2H), 4.35 (d, *J* = 5.7 Hz, 2H), 4.32 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 156.7, 156.5, 138.2 (2C), 135.1, 135.0, 134.0, 133.5, 129.3, 129.2, 128.8 (2C), 128.3, 128.2, 127.6, 127.4 (3C), 85.2, 81.3, 57.0, 56.9, 44.6 (2C); HRMS (ESI): Exact mass calcd for $C_{16}H_{16}BrClN_3O_3$ $[M+H]^+$ 412.0058, found 412.0074.

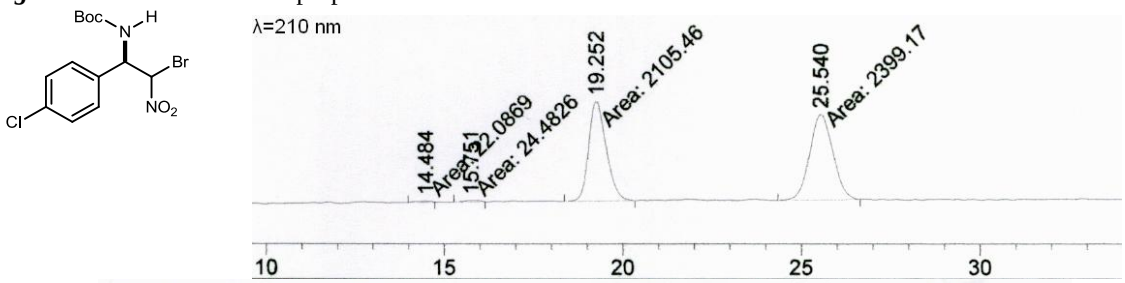
Assignment of Absolute Configuration for *N*-TMS Imine Adducts by Chemical Correlation



(*R*)-*tert*-Butyl 2-bromo-1-(4-chlorophenyl)-2-nitroethylcarbamate (84). As reported previously,[159] a solution of the imine (81.0 mg, 338 μmol) and H,Quin(^{6}(^{9}Anth)^{2}Pyr)-

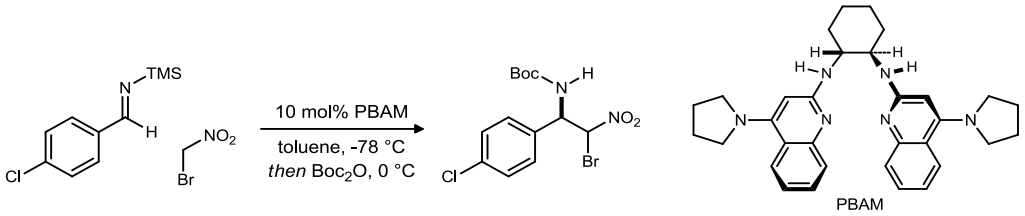
BAM•HOTf[158] (10.9 mg, 16.9 μmol) in toluene (1.1 mL) was cooled to -20 °C and treated with bromonitromethane (63.0 mg, 406 μmol). The reaction mixture was stirred at -20 °C for 2 d, and then concentrated and directly subjected to purification by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to give the α-bromo nitroalkane as a white solid (111 mg, 87%), which was determined to be 98% ee (each diastereomer) and 1:1 dr by chiral HPLC analysis (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 1 mL/min, $t_r(d_1e_1$, minor) = 14.5 min, $t_r(d_1e_2$, major) = 19.3 min, $t_r(d_2e_1$, minor) = 15.7 min, $t_r(d_2e_2$, major) = 25.5 min t_r(major) = 14.5, 19.3 min, t_r(major) = 15.7, 25.5 min. Figure 1).

Figure 1: HPLC trace of **xx** prepared *via* known method.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.484	MM	0.4860	22.08687	7.57472e-1	0.4853
2	15.751	MM	0.4726	24.48265	8.63374e-1	0.5379
3	19.252	MM	0.5702	2105.46411	61.53852	46.2617
4	25.540	MM	0.7524	2399.17090	53.14659	52.7151

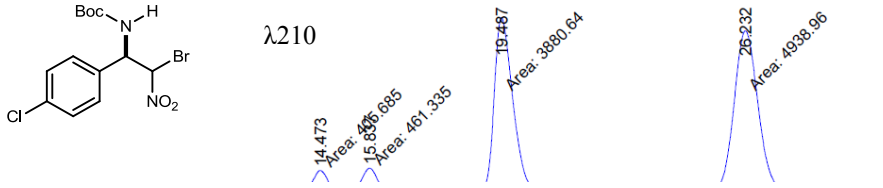
[158] Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466-3467Shen, B.; Johnston, J. N. *Org. Lett.* **2008**, *10*, 4397-4400.



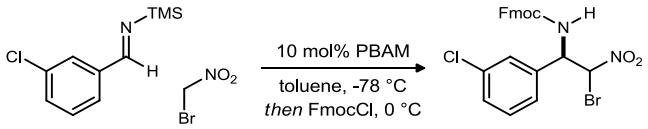
Following General Procedure C, the *N*-TMS-imine (20 mg, 94 μmol) and bromonitromethane (7.3 μL, 94 μmol), when quenched with Boc anhydride (20.5 mg, 94 μmol), provided the α-bromo nitroalkane (1:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a white solid (12.9 mg, 36%). The enantiomeric excess of both the major and minor diastereomers was determined to be 80 and 81% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 1 mL/min, $t_r(d_1e_1$, minor) = 14.5 min, $t_r(d_1e_2$, major) = 19.5 min, $t_r(d_2e_1$, minor) = 15.8 min, $t_r(d_2e_2$, major) = 26.2 min. Figure 2). R_f = 0.49 (20% EtOAc/hexanes); spectroscopic data (^{1}H NMR) was in complete accord with that previously reported.[159] The absolute configuration at the benzylic carbon was therefore determined by chemical correlation.

[159] Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, *465*, 1027.

Figure 2. HPLC trace of **xx** prepared from *N*-TMS imine, BNM and Boc_2O, in the presence of PBAM.

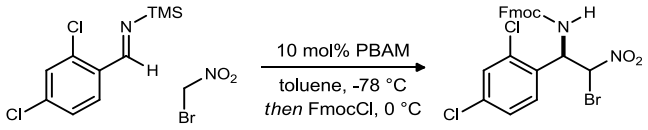


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.473	MM	0.4915	405.68488	13.75732	4.1881
2	15.837	MM	0.5064	461.33539	15.18413	4.7626
3	19.487	MM	0.5982	3880.64160	108.11904	40.0618
4	26.232	MM	0.8118	4938.96484	101.39876	50.9875



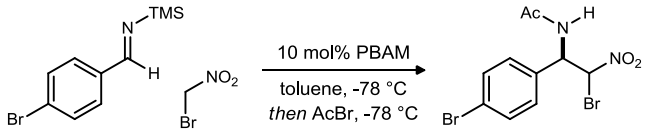
Fluorenylmethyl (1*R*)-2-bromo-1-(3-chlorophenyl)-2-nitroethylcarbamate (201a). Following General Procedure C, the *N*-TMS-imine[155] (40.0 mg, 190 µmol) and bromonitromethane (15.0 µL, 190 µmol), when quenched with fluorenylmethyl chloroformate (49.0 mg, 190 µmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a white foam (59.8 mg, 63%). The enantiomeric excess of the major and minor diastereomers were determined to be 82 and 83% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 15% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 13.9 min, $t_r(d_1e_2$, major) = 26.2 min, $t_r(d_2e_1$, minor) = 13.2 min, $t_r(d_2e_2$, major) = 26.1 min). R_f = 0.29 (20% EtOAc/hexanes); IR (film) 3309, 2923, 1704, 1567, 1514, 1333, 1248, 739 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.77 (d, *J* = 7.8 Hz, 4H), 7.58 (br s, 4H), 7.41 (dd, *J* = 7.2, 7.2 Hz, 4H), 7.31 (m, 10H), 7.17 (br s, 2H), 6.29

(br s, 2H), 6.05 (br d, J = 6.6 Hz, 1H), 5.69 (br s, 1H), 5.65 (br d, J = 9.0 Hz, 1H), 5.50 (br s, 1H), 4.55 (m, 2H), 4.44 (br s, 2H), 4.23 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.5, 155.1, 143.4 (2C), 143.3, 141.3 (2C), 136.3, 135.2 (2C), 130.5 (2C), 129.6, 129.5, 127.8 (2C), 127.1 (3C), 127.0, 125.1, 124.9 (2C), 120.1 (3C); HRMS (ESI): Exact mass calcd for $C_{23}H_{18}BrClN_2NaO_4$ $[M+Na]^+$ 523.0031, found 523.0024.

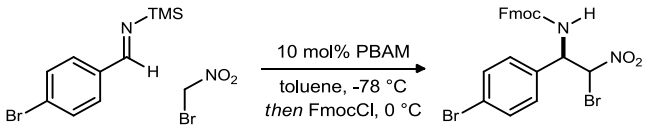


Fluorenylmethyl (1*R*)-2-bromo-1-(2,4-dichlorophenyl)-2-nitroethylcarbamate (201b). Following General Procedure C, the *N*-TMS-imine[155] (20 mg, 81 μmol) and bromonitromethane (6.3 μL, 81 μmol), when quenched with fluorenylmethyl chloroformate (21 mg, 81 μmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a yellow viscous oil (30.2 mg, 70%). The enantiomeric excess of the major and minor diastereomers were determined to be 90 and 91% ee, respectively, by chiral HPLC analysis (Chiralcel IA, 8% ^{i}PrOH/hexanes, 0.7 mL/min, $t_r(d_1e_1$, minor) = 41.2 min, $t_r(d_1e_2$, major) = 44.4 min, $t_r(d_2e_1$, minor) = 43.3 min, $t_r(d_2e_2$, major) = 54.0 min). R_f = 0.42 (30% EtOAc/hexanes); IR (film) 3316, 2925, 1713, 1568, 1515, 1477, 1451, 1256, 1248 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.79 (br d, J = 7.0 Hz, 4H), 7.55 (br m, 4H), 7.47 (br s, 2H), 7.42 (br t, J = 7.2 Hz, 6H), 7.30 (br m, 6H), 6.51 (br s, 1H), 6.47 (br d, J = 4.7 Hz, 1H), 6.25 (br d, J = 8.8 Hz, 1H), 6.04 (br s, 1H). 5.76 (br s, 1H), 5.72 (br s, 1H), 4.56 (br m, 2H), 4.45 (br s, 2H), 4.25 (br m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.5 (2C), 143.4, 143.3, 141.3 (2C), 130.7, 130.2, 129.7, 128.1, 127.9, 127.8 (4C), 127.1 (4C), 124.9, 124.8, 124.7, 120.0 (4C), 82.3, 77.5, 67.5

(2C), 56.0, 55.6, 47.1 (2C); HRMS (ESI): Exact mass calcd for $C_{23}H_{17}BrCl_2N_2NaO_4$ $[M+Na]^+$ 556.9641, found 556.9644.

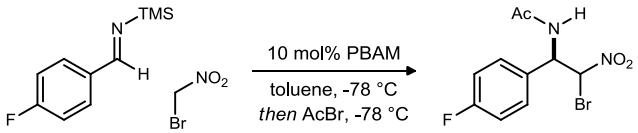


***N*-((1*R*)-2-Bromo-1-(4-bromophenyl)-2-nitroethyl)acetamide (S-5).** Following General Procedure B, the *N*-TMS-imine (40.0 mg, 160 µmol) and bromonitromethane (12.0 µL, 160 µmol), when quenched with acetyl bromide (12.0 µL, 160 µmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 30% ethyl acetate in hexanes), as a yellow viscous oil (27.1 mg, 46%). The enantiomeric excess of the major and minor diastereomers were determined to be 92 and 94% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 1.0 mL/min, t_r(major) = 13.4, 16.2 min, t_r(minor) = 9.6, 18.6 min). R_f = 0.20 (40% EtOAc/hexanes); IR (film) 3287, 2925, 2853, 1667, 1586, 1568, 1531, 1490, 1282, 1012 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.54 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.90 (br d, *J* = 8.8 Hz, 1H), 6.51 (br d, *J* = 8.3 Hz, 1H), 6.36 (d, *J* = 4.5 Hz, 1H), 6.34 (d, *J* = 5.7 Hz, 1H), 5.90 (dd, *J* = 8.7, 4.4 Hz, 1H), 5.76 (dd, *J* = 8.9, 5.8 Hz, 1H), 2.14 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 169.9, 169.8, 133.7, 133.3, 132.4, 132.3, 128.7 (2C), 123.6, 123.5, 83.8, 80.2, 56.0, 55.9, 23.1 (2C); HRMS (CI): Exact mass calcd for $C_{10}H_{11}Br_2N_2O_3$ $[M+H]^+$ 364.9131, found 364.9146.

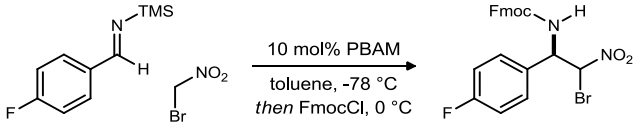


Fluorenylmethyl (1*R*)-2-bromo-1-(4-bromophenyl)-2-nitroethylcarbamate (201c). Following General Procedure C, the *N*-TMS-imine[160] (40 mg, 160 μmol) and bromonitromethane (12.0 μL, 160 μmol), when quenched with fluorenylmethyl chloroformate (41 mg, 160 μmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a yellow solid (55.5 mg, 64%). The enantiomeric excess of the major and minor diastereomers were determined to be 86 and 85% ee, respectively, by chiral HPLC analysis (Chiralcel IA, 20% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 13.6 min, $t_r(d_1e_2$, major) = 25.0 min, $t_r(d_2e_1$, minor) = 12.7 min, $t_r(d_2e_2$, major) = 44.9 min). R_f = 0.38 (30% EtOAc/hexanes); mp = 103-105 °C; IR (film) 3310, 3065, 1704, 1567, 1511, 1491, 1335, 1249, 1075, 739 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.79 (d, *J* = 7.2 Hz, 4H), 7.56 (br m, 6H), 7.43 (t, *J* = 7.8 Hz, 6H), 7.34 (br m, 4H), 7.17 (br m, 4H), 6.31 (br d, *J* = 5.4 Hz, 2H), 6.00 (br d, *J* = 9.0 Hz, 1H), 5.66 (br s, 1H), 5.61 (br s, 1H), 5.48 (br dd, *J* = 6.0, 6.0 Hz, 1H), 4.58 (br m, 2 H), 4.46 (br s, 2H), 4.24 (br m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.5, 155.1, 143.4 (2C), 141.3 (2C), 132.4, 132.3, 128.5, 128.4 127.8 (2C), 127.6, 127.1 (3C), 124.9 (2C), 123.7, 123.5, 120.1 (2C), 84.0, 80.4, 67.3 (2C), 57.8 (2C), 47.1 (2C); HRMS (ESI): Exact mass calcd for $C_{23}H_{18}Br_2N_2NaO_4$ $[M+Na]^+$ 566.9526, found 566.9528.

[160] Betschart, C.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1999-2021.

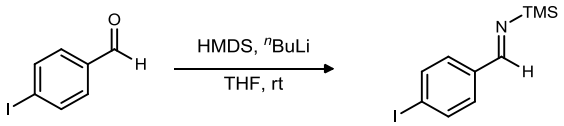


***N*-((1*R*)-2-Bromo-1-(4-fluorophenyl)-2-nitroethyl)acetamide (S-6).** Following General Procedure B, the *N*-TMS-imine (40.0 mg, 205 µmol) and bromonitromethane (16.0 µL, 205 µmol), when quenched with acetyl bromide (15.0 µL, 205 µmol), provided the α-bromo nitroalkane (1:1 mixture of diastereomers), after flash column chromatography (SiO_2, 50% ethyl acetate in hexanes), as a yellow paste (33.2 mg, 53%). The enantiomeric excess of both the major and minor diastereomers was determined to be 91% ee by chiral HPLC analysis (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 1.0 mL/min, t_r(major) = 11.1, 14.1 min, t_r(minor) = 9.1, 16.6 min). R_f = 0.06 (40% EtOAc/hexanes); IR (film) 3313, 2925, 2853, 1699 (br), 1601, 1579, 1510, 1235, 1156 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 7.35 (dd, *J* = 8.5, 5.1 Hz, 2H), 7.32 (dd, *J* = 8.6, 5.2 Hz, 2H), 7.09 (m, 4H), 6.95 (br d, *J*= 8.6 Hz, 1H), 6.59 (br d, *J* = 8.0 Hz, 1H), 6.36 (d, *J* = 4.8 Hz, 1H), 6.35 (dd, *J* = 5.7 Hz, 1H), 5.91 (dd, *J* = 8.6, 4.7 Hz, 1H), 5.80 (dd, *J* = 8.8, 5.8 Hz, 1H), 2.12 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 170.0, 169.9, 163.0 (d, $^1J_{CF}$ = 247.5 Hz, 2C), 130.4 (d, $^4J_{CF}$ = 3.0Hz), 130.1 (d, $^4J_{CF}$ = 4.5 Hz), 129.0 (d, $^3J_{CF}$ = 7.5 Hz), 128.9 (d, $^3J_{CF}$ = 7.5 Hz), 116.3 (d, $^2J_{CF}$ = 22.5 Hz), 116.2 (d, $^2J_{CF}$ = 22.5 Hz), 83.9, 80.6, 56.0, 55.8, 23.1 (2C); HRMS (CI): Exact mass calcd for $C_{10}H_{11}BrFN_2O_3$ $[M+H]^+$ 304.9932, found 304.9943.



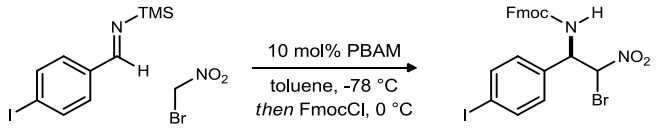
Fluorenylmethyl (1*R*)-2-bromo-1-(4-fluorophenyl)-2-nitroethylcarbamate (201d). Following General Procedure C, the *N*-TMS-imine[155] (40 mg, 205 µmol) and

bromonitromethane (16.0 µL, 205 µmol), when quenched with fluorenylmethyl chloroformate (53 mg, 205 µmol), provided the α-bromo nitroalkane (1.3:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a yellow solid (74.0 mg, 74%). The enantiomeric excess of both the major and minor diastereomers was determined to be 86% ee by chiral HPLC analysis (Chiralcel IA, 20% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 13.2 min, $t_r(d_1e_2$, major) = 20.0 min, $t_r(d_2e_1$, minor) = 11.4 min, $t_r(d_2e_2$, major) = 33.7 min). R_f = 0.35 (40% EtOAc/hexanes); mp = 98-101 °C; IR (film) 3315, 2925, 1713, 1607, 1568, 1511, 1352, 1230, 759, 740 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.79 (d, *J* = 7.8 Hz, 4H), 7.59 (br s, 4H), 7.43 (t, *J* = 7.5 Hz, 6H), 7.31 (m, 6H), 7.09 (br s, 4H), 6.32 (br s, 2H), 6.02 (br d, *J* = 8.8 Hz, 1H), 5.66 (br s, 2H), 5.52 (br s, 1H), 4.58 (br dd, *J* = 17.0, 10.1 Hz, 2H), 4.46 (br s, 2H), 4.24 (br m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 163.0 (d, $^1J_{CF}$ = 249.2 Hz, 2C), 155.5, 155.2, 143.4 (2C), 141.3 (2C), 130.1 (2C), 128.8 (2C), 127.8 (2C), 127.1 (d, $^3J_{CF}$ = 4.8 Hz, 2C), 124.9, 124.8, 120.1 (2C), 116.3 (d, $^2J_{CF}$ = 22.1 Hz), 116.2 (d, $^2J_{CF}$ = 22.9 Hz), 84.1, 80.8, 67.3 (2C), 57.9, 57.8, 47.1 (2C); HRMS (CI): Exact mass calcd for $C_{23}H_{19}BrFN_2O_4$ $[M+H]^+$ 485.0507, found 485.0518.



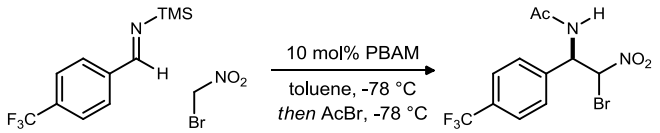
(*E*)-1,1,1-Trimethyl-*N*-(4-iodophenyl)silanamine (S-7). Following the General Procedure A, the aldehyde (2.0 g, 8.62 mmol) provided the imine (0.7 g, 27%) as a pale yellow oil. R_f = 0.27 (10% EtOAc/hexanes); bp = 85 °C/0.5 mm Hg; IR (film) 2952, 1642, 1585, 1481, 1394, 1250, 1094, 1006, 836 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.90

(s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 7.8 Hz, 2H), 0.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 167.2, 137.7, 137.4, 98.2, -1.23.[161]

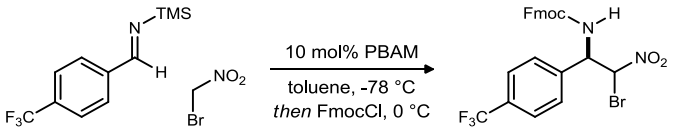


Fluorenylmethyl (1*R*)-2-bromo-1-(4-iodophenyl)-2-nitroethylcarbamate (201e). Following General Procedure C, the *N*-TMS-imine (40.0 mg, 132 μmol) and bromonitromethane (10.0 μL, 132 μmol), when quenched with fluorenylmethyl chloroformate (34.0 mg, 132 μmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a yellow solid (65.0 mg, 83%). The enantiomeric excess of both the major and minor diastereomers was determined to be 88% ee by chiral HPLC analysis (Chiralcel AD-H, 15% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 21.6 min, $t_r(d_1e_2$, major) = 80.5 min, $t_r(d_2e_1$, minor) = 20.5 min, $t_r(d_2e_2$, major) = 45.1 min). R_f = 0.29 (20% EtOAc/hexanes); mp = 175-177 °C; IR (film) 3309, 1703, 1566, 1512, 1246 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.77 (d, *J* = 7.2 Hz, 4H), 7.12 (br s, 4H), 7.57 (br s, 4H), 7.41 (dd, *J* = 7.8, 7.8 Hz, 4H), 7.31 (br m, 4H), 7.02 (br s, 4H), 6.28 (br s, 2H), 5.96 (br s, 1H), 5.62 (br s, 1H), 5.58 (br s, 1H), 5.44 (br s, 1H), 4.55 (br s, 2H), 4.44 (br s, 2H), 4.22 (br m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.4, 155.2, 143.4, 143.3, 141.3 (2C), 138.3 (2C), 133.9 (2C), 128.6, 128.5, 127.8 (2C), 127.1 (2C), 124.8 (2C), 120.1 (2C), 95.4, 95.3, 83.9, 80.3, 67.3 (2C), 58.0 (2C), 47.1 (2C); HRMS (ESI): Exact mass calcd for $C_{23}H_{18}BrIN_2NaO_4$ $[M+Na]^+$ 614.9387, found 614.9395.

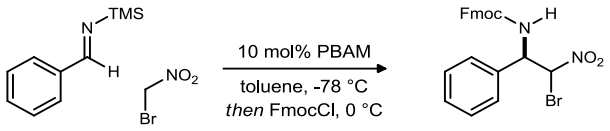
[161] HRMS was attempted, but the desired mass was not able to be detected. This is most likely due to the instability of the compound.



***N*-((1*R*)-2-Bromo-2-nitro-1-(4-(trifluoromethyl)phenyl)ethyl)acetamide (S-8).** Following General Procedure B, the *N*-TMS-imine (40.0 mg, 163 μmol) and bromonitromethane (13.0 μL, 163 μmol), when quenched with acetyl bromide (12.0 μL, 163 μmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 40% ethyl acetate in hexanes), as a yellow viscous oil (27.9 mg, 48%). The enantiomeric excess of both the major and minor diastereomers was determined to be 88% ee by chiral HPLC analysis (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 0.7 mL/min, t_r(major) = 17.9, 21.6 min, t_r(minor) = 13.7, 23.8 min). R_f = 0.10 (40% EtOAc/hexanes); IR (film) 3197, 2924, 2852, 1713, 1668, 1326, 1169, 1130, 1068 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.68 (d, *J* = 7.4 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.47 (d, *J* = 7.9 Hz, 2H), 6.89 (br d, *J* = 8.0 Hz, 1H), 6.46 (br d, *J* = 6.9 Hz, 1H), 6.40 (d, *J* = 3.6 Hz, 1H), 6.39 (d, *J* = 5.2 Hz, 1H), 6.03 (br d, *J* = 4.5 Hz, 1H), 5.87 (br dd, *J* = 8.2, 5.5 Hz, 1H), 2.16 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 169.9, 169.8, 138.6, 138.2, 131.7 (q, $^2J_{CF}$ = 11.9 Hz), 131.4 (q, $^2J_{CF}$ = 17.1 Hz), 127.6 (2C), 126.3 (q, $^3J_{CF}$ = 3.6 Hz), 126.2 (q, $^3J_{CF}$ = 3.7 Hz), 123.6 (q, $^1J_{CF}$ = 215.9 Hz), 123.5 (q, $^1J_{CF}$ = 215.5 Hz), 83.8, 80.0, 56.1, 56.0, 23.2 (2C); HRMS (CI): Exact mass calcd for $C_{11}H_{11}BrF_3N_2O_3$ $[M+H]^+$ 354.9900, found 301.0186.

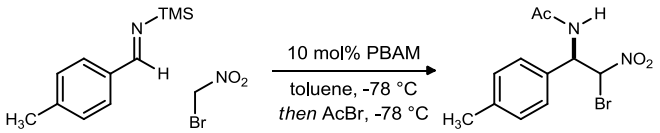


Fluorenylmethyl (1*R*)-2-bromo-1-(4-(trifluoromethyl)phenyl)-2-nitroethylcarbamate (201f). Following General Procedure C, the *N*-TMS-imine[155] (40 mg, 163 μmol) and bromonitromethane (13.0 μL, 163 μmol), when quenched with fluorenylmethyl chloroformate (42 mg, 163 μmol), provided the α-bromo nitroalkane (1.3:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a white solid (57.9 mg, 66%). The enantiomeric excess of the major and minor diastereomers were determined to be 80 and 76% ee, respectively, by chiral HPLC analysis (Chiralcel IA, 20% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 8.9 min, $t_r(d_1e_2$, major) = 30.7 min, $t_r(d_2e_1$, minor) = 9.8 min, $t_r(d_2e_2$, major) = 19.3 min). R_f = 0.37 (30% EtOAc/hexanes); mp = 180-182 °C (decomposition); IR (film) 3310, 2925, 1704, 1568, 1515, 1326, 1251, 1170, 1129, 1069, 740 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.89 (d, *J* = 6.6 Hz, 4H), 7.66 (br s, 4H), 7.59 (br m, 4H), 7.42 (t, *J* = 7.8 Hz, 8H), 4.33 (m, 4H), 6.35 (br s, 2H), 6.04 (br d, *J* = 5.4 Hz, 1H), 5.76 (br s, 1H), 5.67 (br d, *J* = 7.8 Hz, 1H), 5.57 (br s, 1H), 4.60 (br m, 2H), 4.49 (br s, 2H), 4.24 (br m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.4, 155.1, 144.4, 144.3, 143.3 (2C), 141.5, 141.3, 131.6 (m, 2C), 127.8 (2C), 127.6, 127.4, 127.1 (2C), 126.2 (br m, 2C), 124.8 (br m, 2C), 123.6 (q, $^1J_{CF}$ = 271.5 Hz), 123.5 (q, $^1J_{CF}$ = 271.5 Hz), 120.1, 120.0, 83.8, 80.2, 67.3 (2C), 58.0 (2C), 47.1 (2C); HRMS (ESI): Exact mass calcd for $C_{24}H_{18}BrF_3N_2NaO_4$ $[M+Na]^+$ 557.0294, found 557.0323.

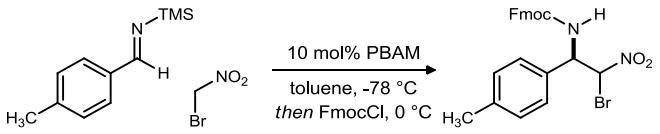


Fluorenylmethyl (1*R*)-2-bromo-1-phenyl-2-nitroethylcarbamate (201g). Following General Procedure C, the *N*-TMS-imine[162] (40.0 mg, 226 μmol) and bromonitromethane (17.5 μL, 226 μmol), when quenched with fluorenylmethyl chloroformate (58.0 mg, 226 μmol), provided the α-bromo nitroalkane (1:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a white solid (67.3 mg, 63%). The enantiomeric excess of both the major and minor diastereomers was determined to be 65 and 66% ee, respectively, by chiral HPLC analysis (Chiralcel IA, 20% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 14.9 min, $t_r(d_1e_2$, major) = 22.2 min, $t_r(d_2e_1$, minor) = 13.3 min, $t_r(d_2e_2$, major) = 32.6 min). R_f = 0.24 (20% EtOAc/hexanes); mp = 174-177 °C; IR (film) 3322, 1694, 1563, 1530, 1449, 1252 738 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.77 (d, J = 7.2 Hz, 4H), 7.59 (br s, 4H), 7.41 (m, 10H), 7.30 (m, 8H), 6.33 (br s, 2H), 5.99 (br d, J = 6.6 Hz, 1H), 5.70 (br s, 1H), 5.57 (br s, 1H), 5.52 (br s, 1H), 4.55 (m, 2H), 4.42 (br m, 2H), 4.24 (br m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.6, 155.3, 143.6, 143.5 (2C), 141.3 (2C), 134.7, 129.3, 129.2, 127.8 (2C), 127.2, 127.1, 126.8 (2C), 125.0, 124.9, 120.1 (4C), 84.6, 80.9, 67.4 (2C), 58.4 (2C), 47.1 (2C); HRMS (ESI): Exact mass calcd for $C_{23}H_{19}BrN_2O_4$ $[M]^+$ 466.0528, found 466.0515.

[162] Commercially available.

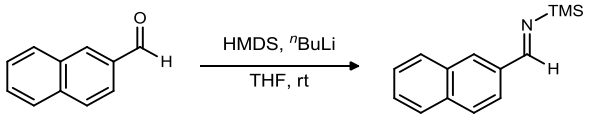


***N*-((1*R*)-2-Bromo-2-nitro-1-*p*-tolylethyl)acetamide (S-9).** Following General Procedure B, the *N*-TMS-imine[160] (40.0 mg, 209 μmol) and bromonitromethane (16.3 μL, 209 μmol), when quenched with acetyl bromide (15.0 μL, 209 μmol), provided the α-bromo nitroalkane (1.2:1mixture of diastereomers), after flash column chromatography (SiO_2, 40% ethyl acetate in hexanes), as a yellow viscous oil (26.9 mg, 43%). The enantiomeric excess of both the major and minor diastereomers was determined to be 75% ee by chiral HPLC analysis (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 0.7 mL/min, t_r(major) = 12.6, 21.2 min, t_r(minor) = 16.4, 19.9 min). R_f = 0.23 (40% EtOAc/hexanes); IR (film) 3300, 2924, 1667, 1607, 1574, 1532, 1516, 1324, 1267, 1178 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.22 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 10.0 Hz, 2H), 7.19 (s, 4H), 6.83 (br d, *J* = 7.9 Hz, 1H), 6.45 (br d, *J* = 7.3 Hz, 1H), 6.36 (d, *J* = 4.7 Hz, 1H), 6.34 (d, *J* = 5.6 Hz, 1H), 5.90 (dd, *J* = 8.8, 4.7 Hz, 1H), 5.78 (dd, *J* = 9.1, 5.6 Hz, 1H), 2.36 (s, 3H), 2.35 (s, 3H), 2.12 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 169.8, 169.7, 139.4, 139.3, 131.5, 131.2, 129.9, 129.8, 126.9, 126.8, 84.2, 80.9, 56.3, 56.1, 23.2, 23.1, 21.1 (2C); HRMS (CI): Exact mass calcd for $C_{11}H_{14}BrN_2O_3$ $[M]^+$ 301.0182, found 301.0186.



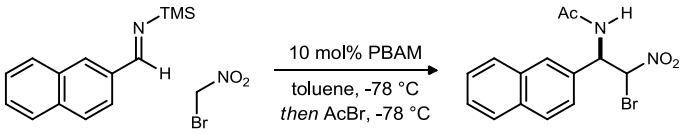
Fluorenylmethyl (1*R*)-2-bromo-2-nitro-1-(*p*-tolyl)ethylcarbamate (201h). Following General Procedure C, the *N*-TMS-imine[160] (40.0 mg, 209 μmol) and bromonitromethane (16.3 μL, 209 μmol), when quenched with fluorenylmethyl chloroformate (54.0 mg, 209

μmol), provided the α-bromo nitroalkane (1.1:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a yellow solid (63.2 mg, 63%). The enantiomeric excess of both the major and minor diastereomers was determined to be 70 and 71% ee, respectively, by chiral HPLC analysis (Chiralcel IA, 20% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 13.4 min, $t_r(d_1e_2$, major) = 38.4 min, $t_r(d_2e_1$, minor) = 15.6 min, $t_r(d_2e_2$, major) = 21.3 min). R_f = 0.24 (20% EtOAc/hexanes); mp = 105-108 °C; IR (film) 3311, 3021, 1705, 1565, 1512, 1450, 1349, 1249, 738 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.77 (d, *J* = 7.2 Hz, 4H), 7.58 (br s, 4H), 7.41 (dd, *J* = 7.8, 7.8 Hz, 4H), 7.30 (br m, 4H), 7.12 (br s, 8H), 6.31 (br s, 2H), 6.00 (br d, *J* = 7.8 Hz, 1H), 5.65 (br s, 1H), 5.59 (br d, *J* = 7.8 Hz, 1H), 5.49 (br s, 1H), 4.54 (dd, *J* = 10.7, 6.7 Hz, 1H), 4.53 (dd, *J* = 11.2, 6.8 Hz, 1H), 4.41 (br m, 2H), 4.23 (dd, *J* = 13.3, 6.7 Hz, 2H), 2.36 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.5, 155.2, 143.6, 143.5 (2C), 141.3, 139.4 (2C), 131.2, 129.9 (2C), 127.8 (2C), 127.1 (2C), 126.7, 126.6, 125.0, 124.9, 120.0 (2C), 84.5, 81.1, 67.4 (2C), 58.3, 58.2, 47.1 (2C), 21.1 (2C); HRMS (ESI): Exact mass calcd for $C_{24}H_{21}BrN_2O_4$ $[M]^+$ 480.0685, found 480.0675.



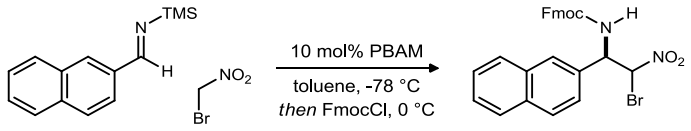
(*E*)-1,1,1-Trimethyl-*N*-(naphthalen-2-ylmethylene)silanamine (S-10). Following the General Procedure A, the aldehyde (2.7 g, 17.3 mmol) provided the imine (2.9 g, 73%) as a pale yellow solid. R_f = 0.23 (5% EtOAc/hexanes); bp = 168 °C/1.1 mm Hg; mp = 39-41 °C; IR (film) 2954, 1643, 1248, 859 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.18 (s, 1H), 8.07 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.95 (dd, *J* = 6.6, 2.4 Hz, 1H), 7.90 (m, 2H),

7.57 (ddd, *J* = 6.9, 6.9, 1.8 Hz, 1H), 7.54 (ddd, *J* = 6.9, 6.9, 1.7 Hz, 1H), 0.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 168.6, 136.4, 135.2, 133.1, 130.9, 128.9, 128.4, 127.9, 127.3, 126.4, 123.7, -1.09; HRMS (ESI): Exact mass calcd for $C_{11}H_9N$ $[M+H-C_3H_9Si]^+$ 155.0735, found 155.0696.

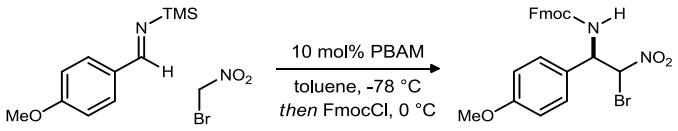


***N*-((1*R*)-2-Bromo-1-(naphthalen-2-yl)-2-nitroethyl)acetamide (S-11).** Following General Procedure B, the *N*-TMS-imine (40.0 mg, 176 μmol) and bromonitromethane (13.7 μL, 176 μmol), when quenched with acetyl bromide (13.0 μL, 176 μmol), provided the α-bromo nitroalkane (2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 30% ethyl acetate in hexanes), as a yellow solid (32.6 mg, 55%). The enantiomeric excess of both the major and minor diastereomers was determined to be 88% ee by chiral HPLC analysis (Chiralcel AD-H, 8% ^{i}PrOH/hexanes, 1.0 mL/min, t_r(major) = 27.2, 40.2 min, t_r(minor) = 22.2, 42.6 min). R_f = 0.23 (40% EtOAc/hexanes); mp = 125-129 °C (decomposition); IR (film) 3279, 2925, 1661, 1565, 1538, 1509, 1373, 1352 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 2:1 mixture of diastereomers) δ 7.87 (m, 6H), 7.82 (s, 1H), 7.80 (s, 1H), 7.55 (d, *J* = 6.0 Hz, 2H), 7.54 (d, *J* = 6.6 Hz, 2H), 7.44 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.39 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.95 (br d, *J* = 10.0 Hz, 1H), 6.52 (br s, 1H), 6.50 (d, *J* = 4.4 Hz, 1H), 6.48 (d, *J* = 5.5 Hz, 1H), 6.15 (dd, *J* = 8.8, 4.4 Hz, 1H), 6.00 (dd, *J* = 9.1, 5.5 Hz, 1H), 2.19 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 169.9, 169.7, 133.3 (2C), 133.0 (2C), 131.9, 131.5, 129.3, 129.2, 128.0 (2C), 127.7 (2C), 127.0 (2C), 126.9 (2C), 126.7, 126.6, 123.8, 123.7, 84.3, 80.5, 56.5, 56.4, 23.2 (2C); HRMS (ESI): Exact mass calcd for C14H13BrN2NaO3 $[M+Na]^+$ 359.0007, found

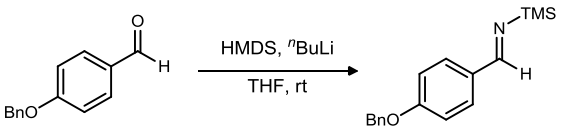
359.0025.



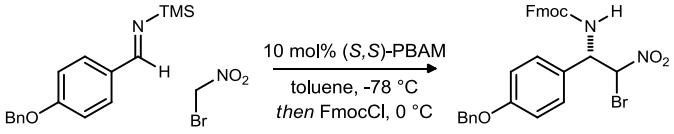
Fluorenylmethyl (1*R*)-2-bromo-1-(2-naphthalenyl)-2-nitroethylcarbamate (201i). Following General Procedure C, the *N*-TMS-imine (40.0 mg, 176 μmol) and bromonitromethane (13.7 μL, 176 μmol), when quenched with fluorenylmethyl chloroformate (46 mg, 176 μmol), provided the α-bromo nitroalkane (1.1:1 mixture of diastereomers), after flash column chromatography (SiO_2, 15% ethyl acetate in hexanes), as a yellow solid (57.0 mg, 63%). The enantiomeric excess of both the major and minor diastereomers was determined to be 83 and 84% ee, respectively, by chiral HPLC analysis (Chiralcel IA, 10% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 24.9 min, $t_r(d_1e_2$, major) = 57.7 min, $t_r(d_2e_1$, minor) = 23.7 min, $t_r(d_2e_2$, major) = 38.9 min). R_f = 0.19 (20% EtOAc/hexanes); mp = 176-179 °C (dec); IR (film) 3297, 2921, 2358, 1705, 1563, 1512, 1325, 1241, 1040 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.89 (m, 8H), 7.80 (m, 6H), 7.62 (br m, 2H), 7.56 (m, 4H), 7.43 (m, 6H), 7.33 (m, 4H), 6.45 (br s, 2H), 6.12 (br d, *J* = 7.2 Hz, 1H), 5.90 (br s, 1H), 5.71 (br s, 2H), 4.60 (dd, *J* = 10.8, 6.7 Hz, 1H), 4.57 (br m, 1H), 4.46 (br m, 2H), 4.27 (br s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.6, 155.3, 143.5, 143.4, 141.3 (3C), 133.4 (2C), 133.1, 133.0, 131.5, 129.3 (2C), 128.1, 127.8 (4C), 127.1 (5C), 126.9, 126.6, 126.4, 125.0, 124.9, 123.6, 120.0 (4C), 84.6, 80.7, 67.4 (2C), 58.6 (2C), 47.1 (2C); HRMS (ESI): Exact mass calcd for $C_{27}H_{21}BrN_2O_4$ $[M]^+$ 516.0685, found 516.0678.



Fluorenylmethyl (1*R*)-2-bromo-1-(4-methoxyphenyl)-2-nitroethylcarbamate (201j). Following General Procedure C, the *N*-TMS-imine[160] (40 mg, 193 μmol) and bromonitromethane (15.0 μL, 193 μmol), when quenched with fluorenylmethyl chloroformate (50 mg, 193 mmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 15% ethyl acetate in hexanes), as a yellow solid (73.2 mg, 76%). The enantiomeric excess of the major and minor diastereomers were determined to be 59 and 62% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 20% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 16.9 min, $t_r(d_1e_2$, major) = 52.2 min, $t_r(d_2e_1$, minor) = 18.3 min, $t_r(d_2e_2$, major) = 27.3 min) = 18.3, 27.3 min). R_f = 0.22 30% EtOAc/hexanes); mp = 109-112 °C; IR (film) 3309, 2927, 1704, 1566, 1514, 1251, 740 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.79 (d, *J* = 7.2 Hz, 4H), 7.60 (br s, 4H), 7.42 (t, *J* = 7.2 Hz, 6H), 7.32 (br s, 4H), 7.23 (br s, 2H), 6.91 (br d, *J* = 7.4 Hz, 4H), 6.31 (br s, 2H), 6.01 (br s, 1H), 5.62 (br s, 2H), 5.49 (br s, 1H), 5.56 (m, 2H), 4.43 (br s, 2H), 4.25 (dd, *J* = 13.2, 6.7 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 160.2 (2C), 155.5, 155.3, 143.5 (2C), 141.3 (4C), 128.1 (2C), 127.8, (2C), 127.1 (2C), 125.0, 124.9, 120.0 (2C), 114.6, 114.5, 84.3, 81.3, 67.4 (2C), 58.1, 57.9, 55.3 (2C), 47.1 (2C); HRMS (ESI): Exact mass calcd for $C_{24}H_{21}BrN_2NaO_5$ $[M+Na]^+$ 519.0526, found 519.0540.



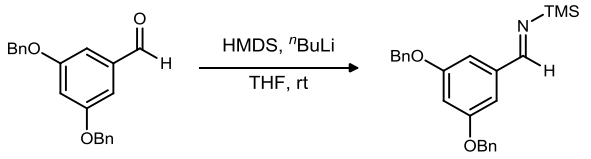
(*E*)-*N*-(4-(Benzyloxy)benzylidene)-1,1,1-trimethylsilanamine (S-12). Following General Procedure A, the aldehyde (5.0 g, 23.4 mmol) provided the imine (4.9 g, 74%) as a pale yellow solid. R_f = 0.13 (5% EtOAc/hexanes); bp = 185 °C/1.1 mmHg; mp = 38-39 °C; IR (film) 2955, 1645, 1602, 1578, 1509, 1248 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 7.5 Hz, 2H), 7.41 (dd, *J* = 7.4. 7.4 Hz, 2H), 7.36 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 5.14 (s, 2H), 0.27 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 167.7, 161.4, 136.6, 132.4, 130.2, 128.6, 128.1, 127.5, 114.8, 70.0, -1.0; HRMS (CI): Exact mass calcd For $C_{14}H_{12}NO$ $[M\text{-}C_3H_9Si]^+$ 210.0919, found 210.0902.[163]



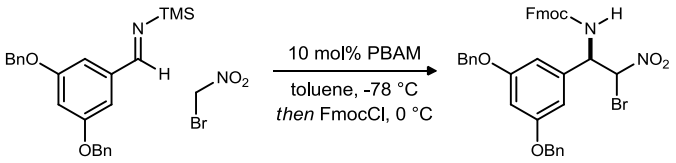
Fluorenylmethyl(1*R*)-1-(4(benzyloxy)phenyl)-2-bromo-2-nitroethylcarbamate (201k). Following General Procedure C, the *N*-TMS-imine (40.0 mg, 141 μmol) and bromonitromethane (11.0 μL, 141 μmol), when quenched with fluorenylmethyl chloroformate (36.0 mg, 141 mmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 15% ethyl acetate in hexanes), as a white solid (52.6 mg, 66%). The enantiomeric excess of the major and minor diastereomers were determined to be 72 and 74% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 1.0 mL/min, t_r(major) = 37.3, 70.9 min, t_r(minor) = 33.9, 106.6 min). R_f = 0.33 (30% EtOAc/hexanes); mp = 170-173 °C

[163] Trimethylsilyl group fragmented during MS analysis.

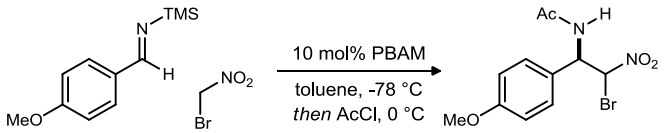
(decomposition); IR (film) 3322, 3038, 2922, 1704, 1698, 1451, 1243, 1180 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.79 (d, *J* = 7.2 Hz, 4H), 7.60 (br m, 4H), 7.42 (br m, 12H), 7.35 (br m, 6H), 7.23 (br m, 4H), 6.99 (br d, *J* = 6.7 Hz, 4H), 6.32 (br d, *J* = 5.2 Hz, 2H), 5.99 (br d, *J* = 8.3 Hz, 1H), 5.62 (br s, 1H), 5.57 (br s, 1H), 5.49 (br dd, *J* = 5.3, 5.3 Hz, 1H), 5.08 (s, 2H), 5.57 (s, 2H), 4.55 (dd, *J* = 10.7, 6.6 Hz, 2H), 4.43 (br m, 2H), 4.25 (br dd, *J* = 13.7, 6.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 159.4 (2C), 155.5, 155.2, 143.5, 143.4, 141.3 (4C), 136.4 (2C), 128.7 (2C), 128.2 (2C), 128.1 (2C), 127.8 (2C), 127.5 (2C), 127.1 (2C), 125.0, 124.9, 120.1 (2C), 115.4 (2C), 84.4, 81.2, 70.0 (2C), 67.3 (2C), 58.1, 57.9, 47.1 (2C); HRMS (ESI): Exact mass calcd for $C_{30}H_{25}BrN_2NaO_5$ $[M+Na]^+$ 595.0845, found 595.0831.



(*E*)-*N*-(3,5-(Dibenzyloxy)benzylidene)-1,1,1-trimethylsilanamine (S-13). Following General Procedure A, the aldehyde (1.52 g, 4.77 mmol) provided the imine (1.40 g, 76%) as a yellow solid. R_f = 0.36 (20% EtOAc/hexanes); bp = 210 °C/1.1 mmHg; IR (film) 1594, 1447, 1294, 1156, 1054 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.46 (d, *J* = 10.8 Hz, 4H), 7.41 (t, *J* = 11.4 Hz, 4H), 7.35 (t, *J* = 10.2 Hz, 2H), 7.10 (d, *J* = 3.6 Hz, 2H), 6.74 (*J* = 3.6 Hz, 1H), 5.11 (s, 4H), 0.28 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 161.1, 137.9, 136.8, 136.7, 135.8, 128.8, 128.6, 128.4, 128.0, 127.9, 127.7, 127.6, 127.5, 111.0, 107.7 (2C), 70.2, 70.1, 2.0; HRMS (ESI): Exact mass calcd for $C_{24}H_{27}NO_2Si$ $[M]^+$ 389.1811, found 389.1798.

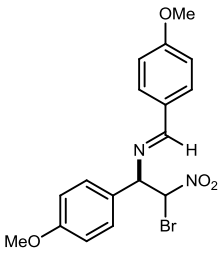


Fluorenylmethyl(1*R*)-1-(3,5-(dibenzyloxy)phenyl)-2-bromo-2-nitroethylcarbamate (201l). Following General Procedure C, the *N*-TMS imine (400 mg, 1.03 mmol) and bromonitromethane (80.0 µL, 1.03 µmol), when quenched with fluorenylmethyl chloroformate (270 mg, 1.03 mmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 20% ethyl acetate in hexanes), as a white solid (427 mg, 61%). The enantiomeric excess of the major and minor diastereomers were determined to be 79 and 82% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 20% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 21.3 min, $t_r(d_1e_2$, major) = 34.9 min, $t_r(d_2e_1$, minor) = 24.1 min, $t_r(d_2e_2$, major) = 41.0 min). R_f = 0.21 (20% EtOAc/hexanes); mp = 181-183 °C (dec); IR (film) 3321, 1697, 1598, 1565, 1450, 1162, 739 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.78 (br d, *J* = 7.2 Hz, 4H), 7.61 (br d, *J* = 4.8 Hz, 4H), 7.44-7.33 (m, 28H), 6.63 (br s, 1H), 6.62 (t, *J* = 1.8 Hz, 1H), 6.56 (br s, 2H), 6.53 (br s, 2H), 6.29 (br s, 2H), 5.98 (br d, *J* = 6.6 Hz, 1H), 5.66 (br s, 1H), 5.54 (br s, 1H), 5.46 (br s, 1H), 5.04 (s, 4H), 5.03 (s, 4H), 5.57 (dd, *J* = 10.8, 6.6 Hz, 1H), 5.43 (br s, 1H), 4.42 (br dd, *J* = 9.6, 7.8 Hz, 2H), 4.26 (br m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 160.4 (2C), 144.3, 143.4, 141.5, 141.3 (4C), 136.5, 136.24 (2C), 136.22 (4C), 128.6, 128.5 (4C), 128.2, 127.8, 127.6 (4C), 127.1, 127.08, 127.05, 127.0, 124.9, 124.7 (2C), 120.0, 106.2 (4C), 102.5 (2C), 84.4, 80.5, 70.3 (4C), 67.5, 65.2, 58.4, 58.1, 50.3, 47.1; HRMS (ESI): Exact mass calcd for $C_{37}H_{31}BrN_2O_6$ $[M]^+$ 678.1365, found 678.1346.

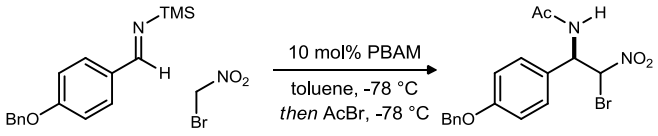


***N*-((1*R*)-2-Bromo-1-(4-methoxyphenyl)-2-nitroethyl)acetamide (202j).** Following General Procedure B, the *N*-TMS-imine (40.0 mg, 193 μmol) and bromonitromethane (15.0 μL, 193 μmol), when quenched with acetyl bromide (14.0 μL, 193 μmol), provided the α-bromo nitroalkane (1.1:1 mixture of diastereomers), after flash column chromatography (SiO_2, 30% ethyl acetate in hexanes), as a white solid (37.5 mg, 61%). The enantiomeric excess of the major and minor diastereomers were determined to be 70 and 69% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 1.0 mL/min, t_r(major) = 14.3, 19.4 min, t_r(minor) = 11.2, 21.5 min). R_f = 0.17 (40% EtOAc/hexanes); mp = 87-92 °C; IR (film) 3278, 2926, 1661, 1612, 1567, 1515, 1373, 1254, 1181, 1031 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.1:1 mixture of diastereomers) δ 7.25 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 5.4 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 6.80 (br d, *J* = 8.5 Hz, 1H), 6.42 (br d, *J* = 8.0 Hz, 1H), 6.34 (d, *J* = 4.8 Hz, 1H), 6.31 (d, *J* = 5.6 Hz, 1H), 5.84 (dd, *J* = 8.4, 4.8 Hz, 1H), 5.74 (dd, *J* = 8.7, 5.7 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 169,8, 169.7, 160.2 (2C), 128.4, 128.3, 126.4, 126.1, 114.6, 114.5, 84.2, 81.1, 56.2, 55.9, 55.3 (2C), 23.2 (2C); HRMS (ESI): Exact mass calcd for $C_{11}H_{13}BrN_2NaO_4$ $[M+Na]^+$ 338.9956, found 338.9962.

Also observed was the trans-imination dimer side product (**S-14**), isolated as a 1.5:1 mixture of diastereomers after column chromatography (100 % hexanes), as a viscous yellow oil (trace amounts). The enantiomeric excess of both the major and minor

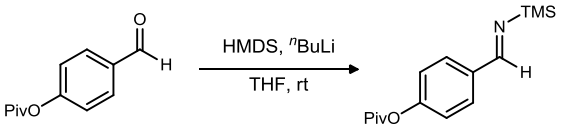


diastereomers was determined to be 22% ee, by chiral HPLC analysis (Chiralcel AD-H, 3% ^{i}PrOH/hexanes, 0.6 mL/min, t_r(major) = 50.0, 53.5 min, t_r(minor) = 40.9, 47.6 min). R_f = 0.11 (5% EtOAc/hexanes); IR (film) 3010, 2934, 2839, 1636, 1606, 1563, 1512, 1305, 1252, 1305, 1252, 1167, 832 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 1.5L1 mixture of diastereomers) δ 8.33 (s, 1H), 8.17 (s, 1H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 10.3 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.27 (d, *J* = 8.7 Hz, 1H), 6.23 (d, *J* = 9.7 Hz, 1H), 4.95 (d, *J* = 9.7 Hz, 1H), 4.93 (d, *J* = 8.7 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 163.9, 163.7, 162.4, 162.3, 160.0, 159.9, 130.4 (2C), 129.4, 128.9, 128.2, 128.1, 114.7 (2C), 114.3, 114.2, 114.0, 113.9, 84.0, 82.2, 55.4, 55.3, 55.2 (4C); HRMS (ESI): Exact mass calcd for $C_{17}H_{18}BrN_2O_4$ $[M+H]^+$ 393.0450, found 393.0445.

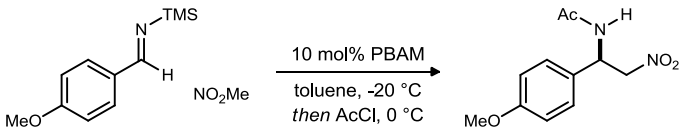


***N*-((1*R*)-1-(4-(Benzyloxy)phenyl)-2-bromo-2-nitroethyl)acetamide (202k).** Following General Procedure B, the *N*-TMS-imine (40.0 mg, 141 μmol) and bromonitromethane (11.0 μL, 141 μmol), when quenched with acetyl bromide (10.0 μL, 141 μmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 30% ethyl acetate in hexanes), as a white solid (24.3 mg, 44%). The enantiomeric excess of the major and minor diastereomers were determined to be 61 and 67% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 1.0 mL/min, t_r(major) = 16.2, 30.0 min, t_r(minor) = 19.3, 33.2 min). R_f = 0.20 (40% EtOAc/hexanes); mp = 119-121 °C (decomposition); IR (film) 3277, 2925,

1661, 1607, 1566, 1513, 1374, 1250, 1180, 737 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.39 (m, 10H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.23 (*J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.70 (br d, *J* = 8.5 Hz, 1H), 6.36 (d, *J* = 4.6 Hz, 1H), 6.34 (d, *J* = 5.4 Hz, 1H), 6.27 (br d, *J* = 6.0 Hz, 1H), 5.86 (dd, *J* = 8.6, 4.6 Hz, 1H), 5.76 (dd, *J* = 8.9, 5.3 Hz, 1H), 5.08 (s, 2H), 5.07 (s, 2H), 2.13 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 169.7, 169.5, 159.4 (2C), 136.4 (2C), 128.6 (2C), 128.3, 128.2, 128.1, 127.4 (3C), 126.7, 126.3, 155.5, 155.4, 84.3, 81.0, 70.1 (2C), 56.2, 55.8, 23.2 (2C); HRMS (ESI): Exact mass calcd for $C_{17}H_{17}BrN_2NaO_4$ $[M+Na]^+$ 415.0269, found 415.0257.

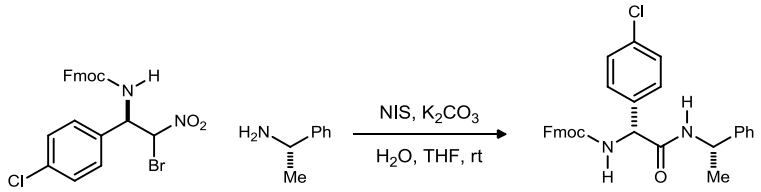


(*E*)-4-((Trimethylsilylimino)methyl)phenyl pivalate (S-15). Following General Procedure A, the aldehyde (3.0 g, 14.5 mmol) provided the imine (1.4 g, 34%) as a clear viscous oil. R_f = 0.17 (5% EtOAc/hexanes); bp = 130 °C/1.1 mmHg; IR (film) 2973, 1754, 1699, 1603, 1276, 1202, 1114, 849 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.07 (d, *J* = 8.7 Hz, 2H), 7.83 (d, *J* = 8.5 Hz, 2H), 1.38 (s, 9H), 0.27 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 176.5, 167.2, 154.9, 136.2, 131.6, 121.4, 39.2, 27.1, -0.2; HRMS (ESI): Exact mass calcd for C_7H_7NO $[M-C_8H_{16}OSi]^+$ 121.0528, found 121.0323.



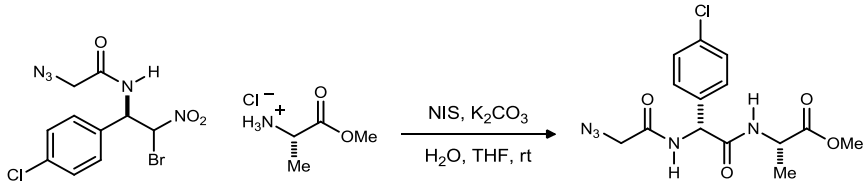
(*R*)-*N*-(1-(4-methoxyphenyl)-2-nitroethyl)acetamide (211). Following General Procedure C, the *N*-TMS-imine (40.0 mg, 193 μmol) and nitromethane (10.0 μL, 193 μmol), when stirred at -20 °C for 5 d and quenched with acetyl chloride (14.0 μL, 193

μmol), provided the nitroalkane, after flash column chromatography (SiO_2, 30% ethyl acetate in hexanes), as a yellow oil (10.1 mg, 22%). The enantiomeric excess of the product was determined to be 19% ee by chiral HPLC analysis (Chiralcel AD-H, 12% ^{i}PrOH/hexanes, 1.0 mL/min, t_r(major) = 8.8 min, t_r(minor) = 6.5 min). $[\alpha]_D^{20}$ +10.0 (*c* 0.08, $CHCl_3$); R_f = 0.1 (30% EtOAc/hexanes); IR (film) 3296, 2923, 1658, 1554, 1514, 1252 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.11 (br d, *J* = 6.0 Hz, 1H), 5.60 (dd, *J* = 6.0, 6.0 Hz, 1H), 4.91 (dd, *J* = 12.6, 6.0 Hz, 1H), 4.70 (dd, *J* = 12.6, 6.0 Hz, 1H), 3.80 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 169.6, 159.9, 128.2, 127.7, 114.6, 78.1, 55.3, 50.9, 23.2; HRMS (ESI): Exact mass calcd for $C_{11}H_{14}N_2NaO_4$ $[M+Na]^+$ 261.0851, found 261.0844.

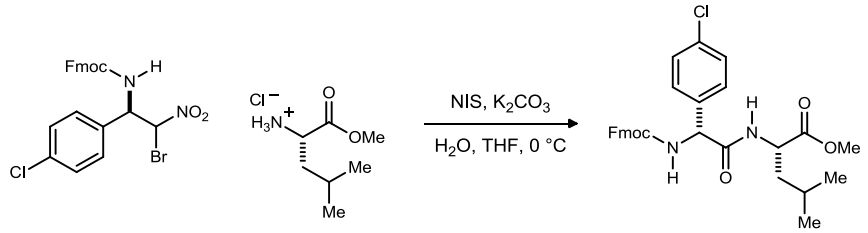


***N*-Fmoc-4-Cl-Phenylglycine-*N*-α-MeBn (212).** Following General Procedure D, the α-bromo nitroalkane (10 mg, 20 μmol) and α-methyl benzyl amine (97% ee, 3.0 μL, 20 μmol) provided the amide (single diastereomer), after column chromatography (SiO_2, 20% ethyl acetate in hexanes), as a white solid (6.7 mg, 66% yield). $[\alpha]_D^{20}$ -20.0 (*c* 0.04, $CHCl_3$); R_f = 0.10 (20% EtOAc/hexanes); mp = 224-226 °C; IR (film) 3298, 2923, 1684, 1647, 1540 cm^{-1}; ^{1}H NMR (600 MHz) δ 7.76 (d, *J* = 7.2 Hz, 2H), 7.55 (br s, 2H), 7.40 (t, *J* = 7.8 Hz, 3H), 7.35 (m, 6H), 7.30 (m, 4H), 6.22 (br s, 1H), 5.84 (br s, 1H), 5.15 (br s, 1H), 5.10 (br s, 1H), 4.35 (br s, 2H), 4.18 (br s, 1H), 1.39 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz) ppm 168.2, 155.5, 143.7, 143.6, 142.1, 141.2, 136.7, 129.3, 128.8, 128.6,

127.7 (2C), 127.0, 126.1, 125.0, 119.9, 67.1, 58.1, 49.4, 47.1, 21.1; HRMS (ESI): Exact mass calcd for $C_{31}H_{28}ClN_2O_3$ $[M+H]^+$ 511.1783, found 511.1807.

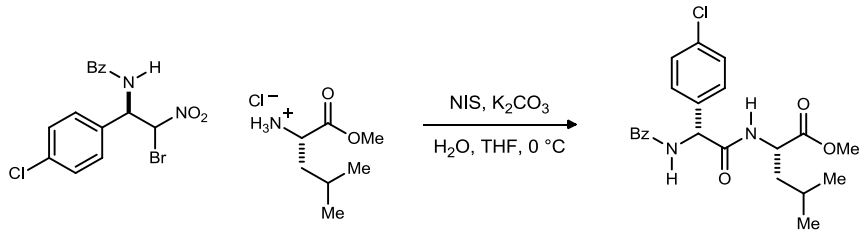


***N*-N_3Ac-4-Cl-Phenylglycine-Ala-OMe (215).** Following a modified General Procedure E, the α-bromo nitroalkane (40.0 mg, 110 μmol) and the ammonium salt of L-alanine (18.5 mg, 130 μmol), when stirred at 0 °C for 4 h, provided the dipeptide (single diastereomer), after column chromatography (SiO_2, 50% ethyl acetate in hexanes), as a white solid (19.3 mg, 50% yield). $[\alpha]_D^{20}$ -86.7 (*c* 0.03, $CHCl_3$); R_f = 0.06 (30% EtOAc/hexanes); mp = 165-168 °C (dec); IR (film) 3293, 2923, 2105, 1738, 1645, 1544, 1492, 1222 cm^{-1}; ^1H NMR (600 MHz) δ 7.70 (d, *J* = 6.9 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 7.3 Hz, 1H), 5.61 (d, *J* = 7.0 Hz, 1H), 4.56 (dq, *J* = 7.2, 7.2 Hz, 1H), 4.06 (d, *J* = 16.6 Hz, 1H), 4.01 (d, *J* = 16.6 Hz, 1H), 3.77 (s, 3H), 1.31 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz) ppm 173.0, 168.6, 166.5, 135.8, 134.6, 129.2, 128.6, 55.9, 52.6, 52.4, 48.3, 17.9; HRMS (ESI): Exact mass calcd for $C_{14}H_{16}ClN_5NaO_4$ $[M+Na]^+$ 376.0783, found 376.0784.



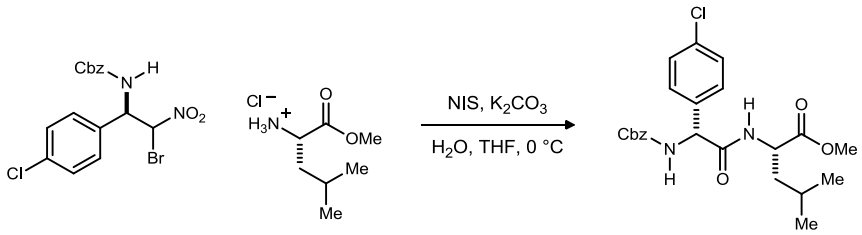
***N*-Fmoc-4-Cl-Phenylglycine-Leu-OMe (216).** Following General Procedure E, the α-bromo nitroalkane (55.0 mg, 110 μmol) and the ammonium salt of L-leucine (24.0 mg,

132 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (15% ethyl acetate in hexanes) as a white solid (32.1 mg, 55%). $[\alpha]_D^{20}$ -35.1 (*c* 0.61, $CHCl_3$); R_f = 0.26 (30% EtOAc/hexanes); mp 146-148 °C; IR (film) 3318, 2957, 2926, 1736, 1666, 1535, 1242, 739 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.8 Hz, 2H), 7.55 (br s, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.30 (br m, 6H), 6.27 (br d, *J* = 6.0 Hz, 1H), 6.22 (br s, 1H), 5.26 (br d, *J* = 4.2 Hz, 1H), 4.59 (br d, *J* = 4.8 Hz, 1H), 4.36 (br m, 2H), 4.18 (br m, 1H), 3.73 (s, 3H), 1.55 (br m, 2H), 1.40 (br m, 1H), 0.77 (br s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 174.7, 173.0, 156.8, 143.7, 141.2, 136.6, 134.5, 129.2 (2C), 127.7, 127.0, 125.0, 199.9, 67.2, 58.0, 52.5, 51.0, 47.0, 41.2, 24.7, 22.6, 21.6; HRMS (ESI): Exact mass calcd for $C_{30}H_{31}ClN_2NaO_5$ $[M+Na]^+$ 557.1819, found 557.1842.

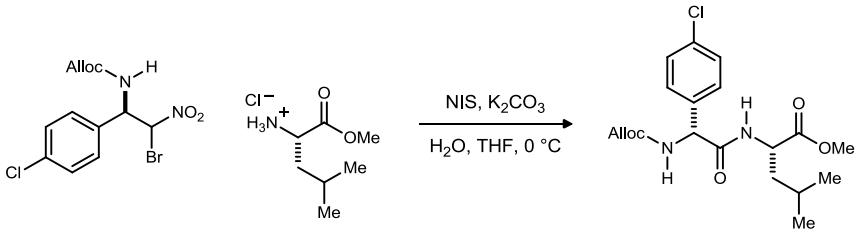


***N*-Bz-4-Cl-Phenylglycine-Leu-OMe (217).** Following General Procedure E, the α-bromo nitroalkane (42.0 mg, 110 μmol) and the ammonium salt of L-leucine (24.0 mg, 132 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (20% ethyl acetate in hexanes) as a white solid (31.0 mg, 65%). $[\alpha]_D^{20}$ -21.3 (*c* 0.16, $CHCl_3$); R_f = 0.14 (30% EtOAc/hexanes); mp 123-125 °C; IR (film) 3294, 2924, 1742, 1640, 1530, 1209 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.2 Hz, 2H), 7.64 (d, *J* = 6.0 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.42 (m, 4H), 7.33 (d, *J* = 8.4 Hz, 2H), 6.42 (d, *J* = 8.4 Hz, 1H), 5.69 (d, *J* = 6.0 Hz, 1H), 4.62 (ddd, *J* = 9.0, 9.0, 5.4 Hz,

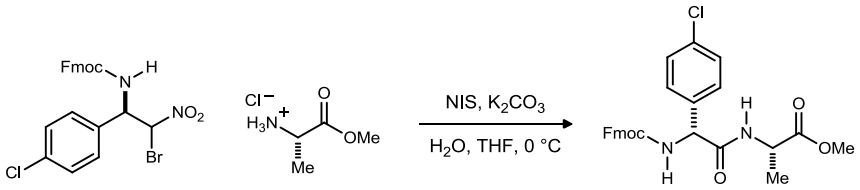
1H), 3.73 (s, 3H), 1.59 (ddd, *J* = 13.8, 8.4, 5.4 Hz, 1H), 1.46 (ddd, *J* = 14.4, 9.0, 6.0 Hz, 1H), 1.31 (m, 1H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 173.0, 169.4, 166.6, 136.5, 134.4, 133.4, 131.9, 129.2, 128.7, 128.6, 127.1, 56.8, 52.5, 51.1, 41.2, 24.7, 22.6, 21.6; HRMS (ESI): Exact mass calcd for $C_{22}H_{25}ClN_2NaO_4$ $[M+Na]^+$ 439.1401, found 439.1416.



***N*-Cbz-4-Cl-Phenylglycine-Leu-OMe (218).** Following General Procedure E, the α-bromo nitroalkane (46.0 mg, 110 μmol) and the ammonium salt of L-leucine (24.0 mg, 132 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (15% ethyl acetate in hexanes) as a white paste (25.4 mg, 53%). $[\alpha]_D^{20}$ -41.4 (*c* 0.51, $CHCl_3$); R_f = 0.22 (30% EtOAc/hexanes); IR (film) 3321, 2925, 2854, 1736, 1667, 1495, 1237, 699 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (br s, 9H), 6.30 (br s, 1H), 6.17 (br s, 1H), 5.26 (br s, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 5.03 (d, *J* = 12.6 Hz, 1H), 4.58 (ddd, *J* = 9.0, 9.0, 5.4 Hz, 1H), 3.72 (s, 3H), 1.56 (br m, 2H), 1.44 (br m, 1H), 0.78 (d, *J* = 8.4 Hz, 3H), 0.76 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 174.8, 173.0, 155.5, 136.6, 136.0, 134.5, 129.1, 128.6, 128.5, 128.2, 67.0, 58.1, 52.4, 50.9, 41.1, 24.7, 22.6, 21.6; HRMS (ESI): Exact mass calcd for $C_{23}H_{27}ClN_2NaO_5$ $[M+Na]^+$ 469.1506, found 469.1486.

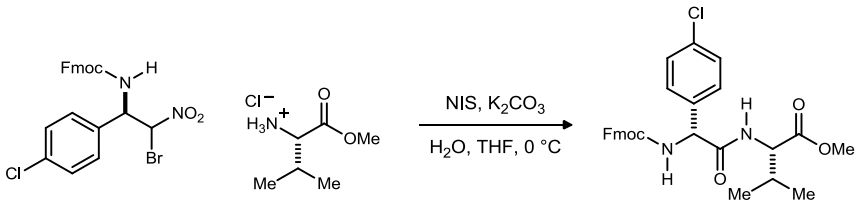


***N*-Alloc-4-Cl-Phenylglycine-Leu-OMe (219).** Following General Procedure E, the α-bromo nitroalkane (40.0 mg, 110 μmol) and the ammonium salt of L-leucine (24.0 mg, 132 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (15% ethyl acetate in hexanes) as a white solid (25.1 mg, 57%). $[\alpha]_D^{20}$ -49.1 (*c* 0.63, $CHCl_3$); R_f = 0.24 (30% EtOAc/hexanes); mp 102-104 °C; IR (film) 3318, 2957, 1737, 1666, 1534, 1237 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32 (br s, 4H), 6.32 (br d, *J* = 7.2 Hz, 1H), 6.14 (br s, 1H), 5.87 (br m, 1H), 5.27 (br m, 2H), 5.15 (d, *J* = 10.2 Hz, 1H), 4.52 (m, 3H), 3.73 (s, 3H), 1.56 (ddd, *J* = 13.8, 8.4, 5.4 Hz, 1H), 1.42 (ddd, *J* = 14.4, 9.0, 5.4 Hz, 1H), 1.29 (m, 1H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 173.0, 169.1, 155.4, 136.6, 134.4, 132.4, 129.1, 128.5, 117.9, 66.0, 58.0, 52.4, 50.9, 41.1, 24.7, 22.6, 21.6; HRMS (ESI): Exact mass calcd for $C_{19}H_{25}ClN_2NaO_5$ $[M+Na]^+$ 419.1350, found 419.1344.

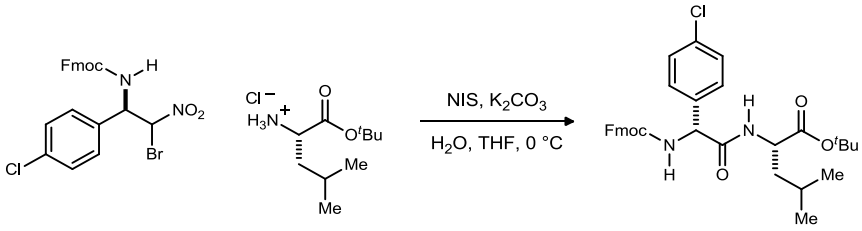


***N*-Fmoc-4-Cl-Phenylglycine-Ala-OMe (220).** Following General Procedure E, the α-bromo nitroalkane (40.0 mg, 80 μmol) and the ammonium salt of L-alanine (13.0 mg, 96 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (30% ethyl acetate in hexanes) as a white solid (18.3 mg, 46%). $[\alpha]_D^{20}$ -26.3 (*c* 0.32,

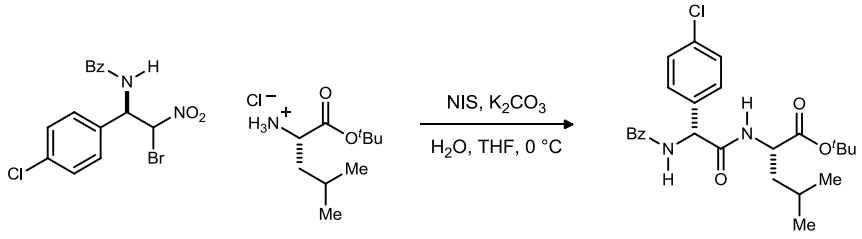
$CHCl_3$); R_f = 0.13 (30% EtOAc/hexanes); mp 158-160 °C (dec); IR (film) 3311, 2963, 1737, 1664, 1534, 1338, 1250, 739 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.8 Hz, 2H), 7.53 (br s, 2H), 7.36 (m, 8H), 6.24 (br s, 1H), 6.11 (br s, 1H), 5.2 (br s, 1H), 4.72 (br s, 1H), 4.37 (br m, 2H), 4.22 (br m, 1H), 3.75 (s, 3H), 1.31 (br s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 172.8, 168.7, 156.6, 143.8, 141.2, 136.0, 134.7, 129.8, 129.3, 127.7, 127.0, 125.0, 120.0, 66.9, 58.1, 52.7, 48.4, 18.0; HRMS (ESI): Exact mass calcd for $C_{27}H_{25}ClN_2NaO_5$ $[M+Na]^+$ 515.1350, found 515.1362.



***N*-Fmoc-4-Cl-Phenylglycine-Val-OMe (221).** Following General Procedure E, the α-bromo nitroalkane (40.0 mg, 80 μmol) and the ammonium salt of L-valine (16.0 mg, 96 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (15% ethyl acetate in hexanes) as a white solid (18.5 mg, 44%). $[\alpha]_D^{20}$ -39.4 (*c* 0.34, $CHCl_3$); R_f = 0.27 (30% EtOAc/hexanes); mp 175-177 °C; IR (film) 3315, 2926, 1719, 1582, 1495, 1227, 738 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.8 Hz, 2H), 7.56 (br s, 2H), 7.35 (m, 8H), 6.21 (br s, 2H), 5.26 (br d, *J* = 3.6 Hz, 1H), 4.54 (br s, 1H), 4.38 (br m, 2H), 4.18 (br s, 1H), 3.74 (s, 3H), 2.06 (br m, 1H), 0.72 (d, *J* = 4.8 Hz, 3H), 0.67 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.9, 169.1, 155.5, 143.7, 141.2, 136.8, 134.5, 129.3, 128.5, 127.6, 127.0, 125.0, 120.0, 67.1, 58.2, 57.1, 52.3, 47.1, 31.4, 18.7, 17.3; HRMS (ESI): Exact mass calcd for $C_{29}H_{29}ClN_2NaO_5$ $[M+Na]^+$ 543.1663, found 543.1657.

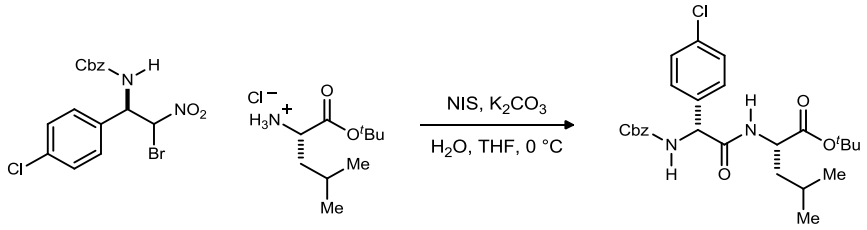


***N*-Fmoc-4-Cl-Phenylglycine-Leu-O^{t}Bu (223).** Following General Procedure E, the α-bromo nitroalkane (30.0 mg, 60.0 μmol) and the ammonium salt of L-leucine (27.0 mg, 120 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (15% ethyl acetate in hexanes) as a white solid (21.3 mg, 62%). $[\alpha]_D^{20}$ -34.2 (*c* 0.78, $CHCl_3$); R_f = 0.14 (20% EtOAc/hexanes); mp 146-149 °C; IR (film) 3312, 2958, 2925, 1727, 1662, 1531, 1367, 1245, 1149, 762 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.8 Hz, 2H), 7.56 (br s, 2H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.33 (br s, 4H), 7.29 (br s, 2H), 6.22 (br s, 1H), 6.09 (br d, *J* = 5.4 Hz, 1H), 5.20 (br d, *J* = 3.6 Hz, 1H), 4.47 (br s, 1H), 4.34 (br s, 2H), 4.18 (br s, 1H), 1.51 (br m, 2H), 1.46 (s, 9H), 1.30 (br m, 1H), 0.79 (br s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.6, 168.6, 155.4, 143.7, 141.2, 136.8, 134.4, 129.2, 128.6, 127.7, 127.0, 125.0, 119.9, 82.4, 67.1, 58.2, 51.6, 47.1, 41.5, 27.9, 24.8, 22.6, 21.9; HRMS (ESI): Exact mass calcd for $C_{33}H_{38}ClN_2O_5$ $[M+H]^+$ 577.2464, found 577.1032.



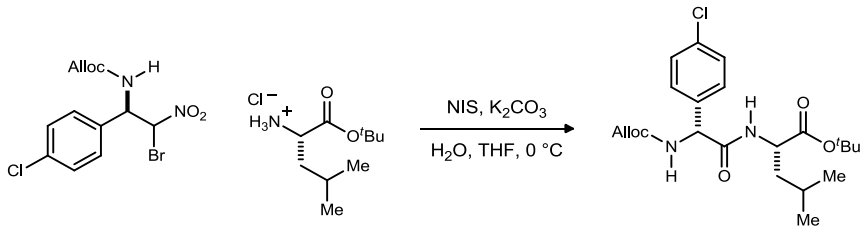
***N*-Bz-4-Cl-Phenylglycine-Leu-O^{t}Bu (S-16).** Following General Procedure E, the α-bromo nitroalkane (23.0 mg, 60.0 μmol) and the ammonium salt of L-leucine (27.0 mg, 120 μmol) provided the dipeptide (single diastereomer) after flash column

chromatography (15% ethyl acetate in hexanes) as a white solid (16.2 mg, 58%). $[\alpha]_D^{20}$ -22.6 (*c* 0.27, $CHCl_3$); R_f = 0.33 (30% EtOAc/hexanes); mp 116-118 °C; IR (film) 3299, 2927, 1735, 1640, 1530, 1489, 1150 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.2 Hz, 2H), 7.65 (d, *J* = 6.0 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 6.21 (d, *J* = 8.4 Hz, 1H), 5.63 (d, *J* = 6.0 Hz, 1H), 4.49 (ddd, *J* = 8.4, 8.4, 6.0 Hz, 1H), 1.54 (ddd, *J* = 13.8, 8.4, 5.4 Hz, 1H), 1.45 (s, 9H), 1.40 (ddd, *J* = 14.4, 8.4, 6.0 Hz, 1H), 1.33 (m, 1H), 0.81 (d, *J* = 7.2 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.5, 169.0, 166.5, 136.8, 134.4, 133.5, 131.8, 129.2, 128.7, 128.5, 127.1, 82.4, 56.9, 51.7, 41.5, 27.9, 24.8, 22.6, 21.9; HRMS (ESI): Exact mass calcd for $C_{25}H_{31}ClN_2NaO_4$ $[M+Na]^+$ 577.2464, found 577.1032.

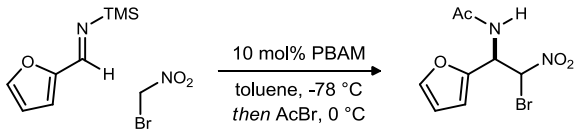


***N*-Cbz-4-Cl-Phenylglycine-Leu-O^{t}Bu (224).** Following General Procedure E, the α-bromo nitroalkane (25.0 mg, 60.0 μmol) and the ammonium salt of L-leucine (27.0 mg, 120 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (15% ethyl acetate in hexanes) as a white solid (18.4 mg, 63%). $[\alpha]_D^{20}$ -39.2 (*c* 0.77, $CHCl_3$); R_f = 0.19 (20% EtOAc/hexanes); mp 92-95 °C; IR (film) 3315, 2957, 2927, 1727, 1662, 1529, 1493, 1241, 1149 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.32 (br s, 9H), 6.16 (br s, 1H), 6.07 (br s, 1H), 5.19 (br s, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 5.02 (d, *J* = 12.6 Hz, 1H), 4.46 (ddd, *J* = 8.4, 8.4, 6.0 Hz, 1H), 1.49 (br m, 2H), 1.45 (s,

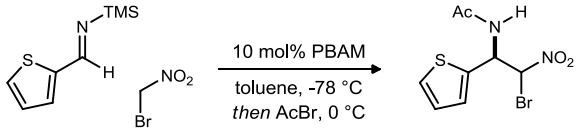
9H), 1.29 (br m, 1H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.6, 168.6, 155.4, 136.8, 136.1, 134.4, 129.2, 128.8, 128.5, 128.1, 128.0, 82.4, 67.1, 58.2, 51.6, 41.5, 27.9, 24.7, 22.6, 21.9; HRMS (ESI): Exact mass calcd for $C_{26}H_{33}ClN_2NaO_5$ $[M+Na]^+$ 481.1870, found 481.1872.



***N*-Alloc-4-Cl-Phenylglycine-Leu-O^{t}Bu (225).** Following General Procedure E, the α-bromo nitroalkane (22.0 mg, 60.0 μmol) and the ammonium salt of L-leucine (27.0 mg, 120 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (15% ethyl acetate in hexanes) as a white solid (17.9 mg, 68%). $[\alpha]_D^{20}$ -47.6 (*c* 0.86, $CHCl_3$); R_f = 0.14 (20% EtOAc/hexanes); mp 84-86 °C; IR (film) 3314, 2956, 2922, 1728, 1663, 1531, 1368, 1242, 1150 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (s, 4H), 6.15 (d, *J* = 7.8 Hz, 2H), 5.87 (br s, 1H), 5.28 (br d, *J* = 15.0 Hz, 1H), 5.19 (br d, *J* = 9.6 Hz, 2H), 4.55 (dd, *J* = 13.2, 5.4 Hz, 1H), 4.50 (dd, *J* = 13.8, 6.0 Hz, 1H), 4.46 (ddd, *J* = 8.4, 8.4, 5.4 Hz, 1H), 1.53 (dd, *J* = 8.2, 5.6 Hz, 1H), 1.50 (ddd, *J* = 8.2, 5.5 Hz, 1H), 1.45 (s, 9H), 1.31 (m, 1H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.77 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.7, 168.7, 155.3, 136.8, 134.4, 132.4, 129.1, 128.6, 117.9, 82.4, 65.9, 58.1, 51.6, 41.5, 27.9, 24.7, 22.6, 21.8; HRMS (ESI): Exact mass calcd for $C_{22}H_{31}ClN_2NaO_5$ $[M+Na]^+$ 461.1814, found 461.1797.



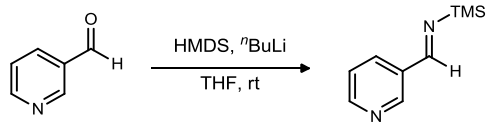
(*E*)-*N*-(furan-2-ylmethylene)-1,1,1-trimethylsilanamine (227). Following General Procedure B, the *N*-TMS imine[160] (40.0 mg, 239 μmol) and bromonitromethane (18.6 μL, 239 μmol), when quenched with acetyl bromide (17.7 μL, 239 mmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 15% ethyl acetate in hexanes), as a yellow oil (28.0 mg, 42%). The enantiomeric excess of the major and minor diastereomers were determined to be 48 and 36% ee, respectively, by chiral HPLC analysis (Chiralcel IA, 5% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 24.9 min, $t_r(d_1e_2$, major) = 28.2 min, $t_r(d_2e_1$, minor) = 26.2 min, $t_r(d_2e_2$, major) = 35.5 min). R_f = 0.28 (20% EtOAc/hexanes); IR (film) 2924, 2852, 1712, 1463 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.42 (dd, *J* = 7.2, 1.2 Hz, 2H), 6.54 (br d, *J* = 10.1, 1H), 6.43 (d, *J* = 3.4 Hz, 1H), 6.41-6.38 (m, 5H), 6.31 (br d, 1H), 6.03 (dd, *J* = 9.0, 4.6 Hz, 1H), 6.99 (dd, *J* = 9.2, 5.6 Hz, 1H), 2.13 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 169.59, 169.55, 146.9, 146.5, 143.46, 143.45, 110.84, 110.82, 109.8, 109.6, 81.4, 79.2, 51.5, 50.9, 23.01, 22.97; HRMS: Exact mass not observed.[164]



(*E*)-*N*-(thiophen-2-ylmethylene)-1,1,1-trimethylsilanamine (229). Following General Procedure B, the *N*-TMS-imine[155] (40.0 mg, 218 μmol) and bromonitromethane (17.0

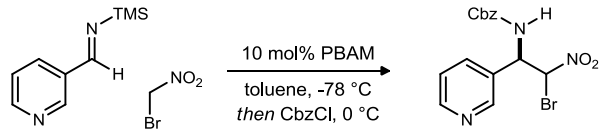
[164] Exact mass could not be observed under ESI or APCI conditions. This may be due to the instability of the product.

µL, 218 µmol), when quenched with acetyl bromide (16.0 µL, 218 mmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a yellow oil (13.5 mg, 21%). The enantiomeric excess of the major and minor diastereomers were determined to be 39 and 37% ee, respectively, by chiral HPLC analysis (Chiralcel IA, 10% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 10.2 min, $t_r(d_1e_2$, major) = 15.3 min, $t_r(d_2e_1$, minor) = 12.7 min, $t_r(d_2e_2$, major) = 13.8 min). R_f = 0.32 (20% EtOAc/hexanes); IR (film) 3329, 1728, 1660, 1662, 1515, 1410, 1237 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.34 (ddd, *J* = 7.4, 5.1, 1.1 Hz, 2H), 7.11 (d, *J* = 3.5 Hz, 1H), 7.08 (d, *J* = 2.8 Hz, 1H), 7.02 (m, 2 H), 6.60 (br d, *J* = 7.8 Hz, 1H), 6.47 (d, *J* = 5.0 Hz, 1H), 6.45 (d, *J* = 4.4 Hz, 1H), 6.26 (br d, *J* = 7.9 Hz, 1H), 6.17 (dd, *J* = 8.8, 4.4 Hz, 1H), 6.09 (dd, *J* = 8.8, 5.2 Hz, 1H), 2.14 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 169.6, 169.4, 136.9, 136.4, 127.3, 127.34, 127.25, 127.09, 127.06, 126.6, 126.5, 83.4, 80.6, 52.9, 52.5, 23.1, 23.0; HRMS (CI): Exact mass calcd for $C_8H_{10}BrN_2O_3S$ $[M+H]^+$ 292.9590, found 292.9604.



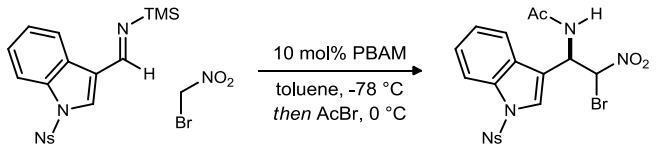
(*E*)-1,1,1-trimethyl-*N*-(pyridin-3-ylmethylene)silanamine (223). Following General Procedure A, but without filtering and distillation, the aldehyde (3.0 g, 28 mmol) provided a quantitative amount of the imine (5.9 g), as a crude mixture with LiCl. For characterization, a small amount of this crude mixture was dissolved in $CDCl_3$ and filtered to remove the LiCl. R_f = 0.1 (20% EtOAc/hexanes); IR (film) 1642, 1423, 1253, 1030, 842 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.91, (s, 1H), 8.66 (d, *J* = 4.8

Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.35 (dd, *J* = 7.8 Hz, 4.8 Hz, 1H), 0.26 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 165.4, 151.9, 151.1, 134.4, 133.8, 123.6, -1.3; HRMS (EI): Exact mass calcd for $C_9H_{14}N_2Si$ $[M]^+$ 178.0926, found 178.0918.

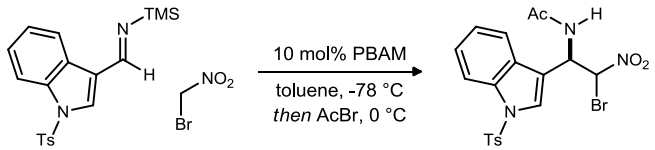


(*E*)-1,1,1-trimethyl-*N*-(pyridin-3-ylmethylene)silanamine (240). Following General Procedure C, the *N*-TMS-imine (78% pure, 100 mg, 450 µmol) and bromonitromethane (34 µL, 450 µmol), when quenched with carbobenzyloxy chloroformate (64 µL, 450 mmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 30% ethyl acetate in hexanes), as a yellow viscous oil (29 mg, 17%).[165] The enantiomeric excess of the major and minor diastereomers were determined to be 15 and 15% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 20% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 10.8 min, $t_r(d_1e_2$, major) = 18.9 min, $t_r(d_2e_1$, minor) = 12.4 min, $t_r(d_2e_2$, major) = 15.9 min). R_f = 0.13 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers, as a mixture with pyridine carboxaldehyde) δ 8.67 (br s, 4H), 7.52 (dd, *J* = 11.2, 8.4 Hz, 2H), 7.28 (br s, 12H), 6.38 (d, *J* = 8.8 Hz, 2H), 6.10 (d, *J* = 9.2 Hz, 2H), 5.79 (br m, 1H), 5.59 (br m, 1H), 5.17 (s, 2H), 5.14 (s, 2H); HRMS (ESI): Exact mass calcd for $C_{15}H_{15}BrN_3O_4$ $[M+H]^+$ 380.0240, found 380.0261.

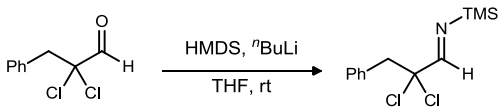
[165] Due to its instability, the product could only be isolated as a mixture with pyridine carboxaldehyde and was not able to be fully characterized.



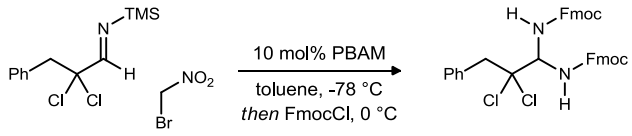
***N*-((1*R*)-2-Bromo-2-nitro-1-(1-((4-nitrophenyl)sulfonyl)-indol-3-yl)ethyl)acetamide (252).** Following General Procedure B, the *N*-TMS-imine (90% pure, 44 mg, 99 μmol) and bromonitromethane (8.0 μL, 99 μmol), when quenched with acetyl bromide (7.0 μL, 99 mmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 30% ethyl acetate in hexanes), as a yellow solid (7.5 mg, 15%). The enantiomeric excess of the major and minor diastereomers was determined to be 8 and 8% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 20% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 10.3 min, $t_r(d_1e_2$, major) = 12.3 min, $t_r(d_2e_1$, minor) = 14.6 min, $t_r(d_2e_2$, major) = 15.3 min). R_f = 0.11 (30% EtOAc/hexanes); mp = 129-131 °C; IR (film) 3281, 2924, 1663, 1567, 1533, 1350, 1181, 740 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 8.29 (m, 4H), 7.95 (m, 6H), 7.68 (s, 2H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.41 (m, 2H), 7.34 (m, 2H), 6.70 (d, *J* = 10.2 Hz, 1H), 6.54 (d, *J* = 4.8 Hz, 1H), 6.52 (d, *J* = 4.8 Hz, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 6.14 (dd, *J* = 9.0, 4.8 Hz, 1H), 6.10 (dd, *J* = 8.4, 5.4 Hz, 1H), 2.13 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 169.9, 169.7, 150.8 (2C), 142.7, 142.5, 134.6 (2C), 128.5, 128.1, 128.0, 126.4, 124.9, 124.8 (3C), 124.7, 124.6, 124.4, 124.3, 119.5, 118.2, 117.7, 113.8, 113.7, 82.0, 80.1, 49.7, 49.1, 23.1, 23.0; HRMS (ESI): Exact mass calcd for $C_{18}H_{15}BrN_4NaO_7S$ $[M+Na]^+$ 532.9743, found 532.9764.



***N*-((1R)-2-Bromo-2-nitro-1-(1-((4-methylhenyl)sulfonyl)-indol-3-yl)ethyl)acetamide (254).** Following General Procedure B, the *N*-TMS-imine (40 mg, 108 μmol) and bromonitromethane (8.4 μL, 108 μmol), when quenched with acetyl bromide (8.0 μL, 108 mmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 30% ethyl acetate in hexanes), as a yellow oil (15.0 mg, 29%). The enantiomeric excess of the major and minor diastereomers was determined to be 55 and 56% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 20% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 6.3 min, $t_r(d_1e_2$, major) = 8.4 min, $t_r(d_2e_1$, minor) = 6.8 min, $t_r(d_2e_2$, major) = 9.8 min). R_f = 0.13 (30% EtOAc/hexanes); IR (film) 3287, 2928, 1665, 1570, 1448, 1373, 1174, 1131, 1091, 910 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 8.26 (s, 1H), 8.24 (s, 1H), 7.96-7.58 (m, 8H), 6.33 (m, 8H), 7.09 (d, *J* = 4.8 Hz, 1H), 6.95 (d, *J* = 6.0 Hz, 1H), 6.58 (d, *J* = 6.0 Hz, 1H), 6.55 (d, *J* = 5.4 Hz, 1H), 6.26 (dd, *J* = 8.4, 4.8 Hz, 1H), 6.18 (dd, *J* = 9.0, 6.0 Hz, 1H), 2.35 (s, 3H), 2.34 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 170.6, 169.7, 145.6, 145.5, 134.6, 134.4, 134.3, 134.0, 130.3, 130.1 (3C), 126.8 (3C), 126.3, 125.7, 125.6, 125.2, 125.0, 199.9, 119.2, 116.8, 116.5, 113.7, 113.5, 82.4, 80.2, 55.8 (2C), 23.1, 22.9, 21.6 (2C); HRMS (ESI): Exact mass calcd for $C_{19}H_{18}BrN_3NaO_5S$ $[M+Na]^+$ 502.0048, found 502.0040.

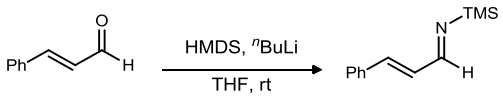


(*E*)-*N*-(2,2-dichloro-3-phenylpropylidene)-1,1,1-trimethylsilanamine (265). Following General Procedure A, the aldehyde (3.0 g, 15 mmol) provided the imine (1.2 g, 30%) as a while crystalline solid. R_f = 0.45 (20% EtOAc/hexanes); bp = 90 °C/0.6 mmHg; IR (film) 2958, 1683, 1252, 845 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.36 (d, *J* = 6.0 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 3H), 3.66 (s, 2H), 0.24 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 165.1, 134.3, 131.7, 127.8, 127.4, 89.6, 47.9, -1.5; HRMS (EI): Exact mass calcd for $C_{12}H_{17}C_{l2}NSi$ $[M]^+$ 273.0507, found 274.0570.

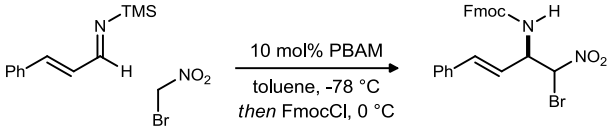


Bis((9H-fluoren-9-yl)methyl) (2,2-dichloro-3-phenylpropane-1,1-diyl)dicarbamate (267). Following General Procedure C, the *N*-TMS-imine (40.0 mg, 146 μmol) and bromonitromethane (11.0 μL, 146 μmol), when quenched with fluorenylmethyl chloroformate (38.0 mg, 146 μmol), did not provide the desired α-bromo nitroalkane. Instead, the doubly-Fmoc protected aminal side product was isolated, after flash column chromatography (SiO_2, 15% ethyl acetate in hexanes), as a white solid (41.8 mg, 86%). R_f = 0.18 (20% EtOAc/hexanes); mp = 139-141 °C; IR (film) 3291, 1706, 1509, 1242, 735 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.76 (br s, 4H), 7.59 (br d, *J* = 7.2 Hz, 4H), 7.40-7.29 (m, 13H), 5.97 (br s, 1H), 5.51 (br s, 2H), 4.59 (br s, 2H), 4.47 (br dd, *J* = 10.2, 6.6 Hz, 2H), 4.24 (br t, *J* = 6.0 Hz, 2H), 3.38 (br s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.5, 143.5, 141.3, 133.0, 131.6, 131.3, 128.2, 128.0, 127.9, 127.8, 127.7, 124.98, 124.88, 120.0, 76.6, 67.4, 67.2, 49.0, 47.1, 47.0; HRMS (ESI): Exact mass calcd for

$C_{39}H_{32}Cl_2N_2NaO_4$ $[M+Na]^+$ 685.1637, found 685.1614.



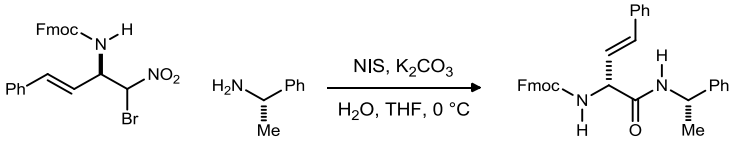
(*E*)-1,1,1-trimethyl-*N*-((*E*)-3-phenylallylidene)silanamine (275). Following General Procedure A, the aldehyde (5.0 g, 38 mmol) provided the imine (2.6 g, 34%) as a yellow viscous oil. R_f = 0.38 (20% EtOAc/hexanes); bp = 80 °C/0.6 mmHg; IR (film) 1677, 1632, 972, 749 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.72 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 5.4 Hz, 2H), 7.39 (m, 3H), 7.12 (d, *J* = 15.6 Hz, 1H), 6.85 (dd, *J* = 16.2, 8.4 Hz, 1 H), 0.25 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 170.4, 144.8, 135.6, 132.0, 129.4, 128.8, 127.5; HRMS (ESI): Exact mass calcd for C_9H_9N $[M-C_3H_8Si]^+$ 131.0735, found 131.0495.[166]



Fluorenylmethyl ((2*R*,*E*)-1-bromo-1-nitro-4-phenylbut-3-en-2-yl)carbamate (276). Following General Procedure C, the *N*-TMS-imine (600 mg, 2.94 mmol) and bromonitromethane (22.8 µL, 2.94 mmol), when quenched with fluorenylmethyl chloroformate (762 mg, 2.94 mmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a white solid (725 mg, 50%). The enantiomeric excess of the major and minor diastereomers were determined to be 64 and 63% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 20% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 10.9 min, $t_r(d_1e_2$, major) = 20.9 min, $t_r(d_2e_1$, minor) = 15.1 min, $t_r(d_2e_2$, major) = 32.2 min). R_f =

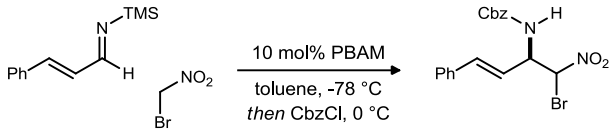
[166] Trimethylsilyl group fragmented during MS analysis.

0.37 (20% EtOAc/hexanes); mp = 162-164 °C; IR (film) 3317, 1710, 1564, 1508, 1243, 739 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.77 (d, *J* = 7.8 Hz, 4H), 7.59 (dd, *J* = 12.0, 6.6 Hz, 4H), 7.42-7.30 (m, 18H), 6.70 (br d, *J* = 15.6 Hz, 2H), 6.27 (br s, 2H), 6.16 (br dd, *J* = 15.0, 9.0 Hz, 1H), 6.11 (br dd, *J* = 15.6, 7.2 Hz, 1H), 5.47 (br d, *J* = 7.8 Hz, 1H), 5.34 (br d, *J* = 6.6 Hz, 1H), 5.11 (br s, 1H), 5.08 (br s, 1H), 4.56 (br m, 2H), 4.46 (br m, 2H), 4.25 (br s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.9, 143.7, 143.4, 141.3 (2C), 136.6, 136.2, 135.1, 135.0 128.9, 128.8, 128.7 (2C), 127.8 (2C), 127.1 (2C), 126.9 (2C), 125.0, 124.9, 120.6, 120.0; HRMS (ESI): Exact mass calcd for $C_{25}H_{21}BrN_2NaO_4$ $[M-Na]^+$ 515.0582, found 515.0580.

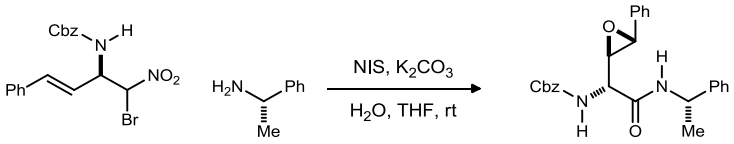


Fluorenylmethyl ((*R*,*E*)-1-oxo-4-phenyl-1-(*S*)-1-phenylethylamino but-3-en-2-yl) carbamate (277). Following General Procedure D, the α-bromo nitroalkane (30 mg, 61 μmol) and α-methyl benzyl amine (97% ee, 9.0 μL, 73 μmol) provided the amide (single diastereomer), after column chromatography (SiO_2, 15% ethyl acetate in hexanes), as a white solid (10 mg, 33% yield). $[\alpha]_D^{20}$ -28.5 (*c* 0.27, $CHCl_3$); R_f = 0.31 (30% EtOAc/hexanes); mp = 139-141 °C; IR (film) 3317, 3062, 1711, 1663, 1522, 1450, 1245, 1051, 739 cm^{-1}; ^1H NMR (600 MHz) δ 7.77 (d, *J* = 7.2 Hz, 2H), 7.39 (d, *J* = 6.6 Hz, 2H), 7.36 (m, 14 H), 6.42 (br s, 1H), 6.24 (br d, *J* = 7.8 Hz, 1H), 5.56 (br s, 1H), 5.16 (br m, 1H), 4.68 (br s, 1H), 4.49 (br d, *J* = 6.6 Hz, 2H), 4.40 (br s, 1H), 3.61 (br s, 1H), 1.54 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 167.0, 151.0, 143.8, 143.4, 141.3, 141.2, 128.8, 128.6, 128.5, 127.8, 127.7, 127.0, 126.7, 126.1, 125.8, 125.0, 124.9, 120.0,

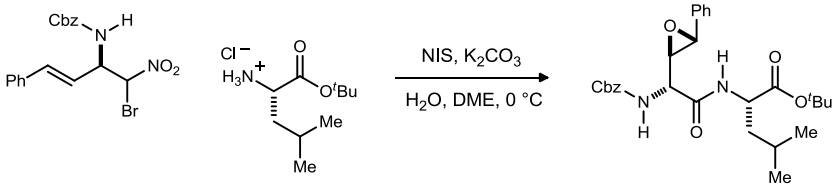
67.1, 60.0, 55.5, 47.1, 21.6; HRMS (ESI): Exact mass calcd for $C_{33}H_{30}N_2NaO_3$ $[M+Na]^+$ 525.2154, found 525.2175.



Benzyl ((2*R*,*E*)-1-bromo-1-nitro-4-phenylbut-3-en-2-yl)carbamate (280). Following General Procedure C, the *N*-TMS-imine (1.0 mg, 4.9 mmol) and bromonitromethane (380 µL, 4.9 mmol), when quenched with carboxybenzyl chloroformate (700 mL, 4.9 mmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as an orange solid (1.1 g, 55%). The enantiomeric excess of the major and minor diastereomers was determined to be 69 and 71% ee, respectively, by chiral HPLC analysis (Chiralcel OD-H, 10% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 22.5 min, $t_r(d_1e_2$, major) = 36.3 min, $t_r(d_2e_1$, minor) = 25.6 min, $t_r(d_2e_2$, major) = 34.3min). R_f = 0.38 (20% EtOAc/hexanes); mp = 96-98 °C; IR (film) 3310, 3030, 1704, 1564, 1510, 1349, 1240, 968, 741 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.35 (m, 20H), 6.74 (d, *J* = 15.6 Hz, 2H), 6.31 (d, *J* = 8.4 Hz, 2H), 6.18 (dd, *J* = 15.0, 5.4 Hz, 1H), 6.13 (dd, *J* = 15.6, 7.2 Hz, 1H), 5.50 (br s, 1H), 5.36 (br s, 1H), 5.19 (d, *J* = 4.8 Hz, 2H), 5.17 (d, *J* = 4.8 Hz, 2H), 5.12 (br m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.2, 136.5, 136.1, 135.6, 135.1, 135.0, 128.8 (2C), 128.7 (2C), 128.6 (2C), 128.4 (2C), 128.2 (2C), 126.9, 126.8, 120.7, 120.3, 82.7, 81.9, 67.7, 67.6, 57.4, 56.9; HRMS (ESI): Exact mass calcd for $C_{18}H_{17}BrN_2NaO_4$ $[M+Na]^+$ 427.0269, found: 427.0271.

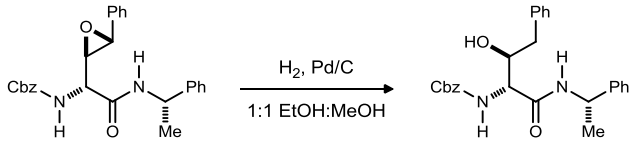


Benzyl ((*R*)-2-oxo-2-(((*S*)-1-phenylethyl) amino) -1-((2*R*,3*R*) -3-phenyloxiran-2-yl) ethyl) carbamate (282). Following General Procedure D, the α-bromo nitroalkane (30 mg, 74 μmol) and α-methyl benzyl amine (97% ee, 18 μL, 150 μmol) provided the amide (single diastereomer), after column chromatography (SiO_2, 15% ethyl acetate in hexanes), as a white solid (11 mg, 36% yield). $[\alpha]_D^{20}$ -58.5 (*c* 0.34, $CHCl_3$); R_f = 0.16 (20% EtOAc/hexanes); mp = 142-144 °C; IR (film) 3309, 2925, 1714, 1642, 1521, 1497, 1454, 1240, 698 cm^{-1}; ^1H NMR (600 MHz) δ 7.34 (m, 15H), 6.57 (d, *J* = 6.6 Hz, 1H), 5.98 (br s, 1H), 5.35 (dt, *J* = 6.6, 6.6 Hz, 1H), 5.13 (d, *J* = 12.0 Hz, 1H), 5.09 (d, *J* = 12.0 Hz, 1H), 4.22 (br s, 1H), 3.87 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.06 (d, *J* = 7.8 Hz, 1H), 1.61 (d, 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 166.9, 155.8, 142.5, 136.1, 128.8, 128.53, 128.48, 128.3, 128.1, 128.0, 127.6, 126.1, 125.7, 67.0, 61.5, 60.4, 56.3, 49.6, 22.0; HRMS (ESI): Exact mass calcd for $C_{26}H_{26}N_2NaO_4$ $[M+Na]^+$ 453.1790, found 453.1812.



(*S*)-*tert*-Butyl 2-((*R*)-2-(((benzyloxy) carbonyl) amino) -2-((2*R*,3*R*) -3-phenyloxiran-2-yl) acetamido)-4-methylpentanoate (284). Following General Procedure E, the α-bromo nitroalkane (30 mg, 74 μmol) and the ammonium salt of L-leucine (33 mg, 150 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (30%

ethyl acetate in hexanes) as a yellow oil (11 mg, 32%). $[\alpha]_D^{20}$ -34.7 (*c* 0.38, $CHCl_3$); R_f = 0.10 (30% EtOAc/hexanes); IR (film) 3321, 2958, 1728, 1670, 1501, 1241, 1150 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.36 (m, 10 H), 6.62 (d, *J* = 7.8 Hz, 1H), 5.94 (br s, 1H), 5.14 (d, *J* = 12.6 Hz, 1H), 5.10 (d, *J* = 12.6 Hz, 1H), 4.55 (ddd, *J* = 8.4, 8.4, 5.4 Hz, 1H), 4.24 (br s, 1H), 3.96 (dd, *J* = 7.8, 6.0 Hz, 1H), 2.99 (d, *J* = 7.8 Hz, 1H), 1.73 (m, 3H), 1.49 (s, 9H)1.01 (d, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.4, 155.7, 136.1, 135.8, 128.4 (2C), 128.1, 128.0, 125.6 (2C), 82.1, 67.0, 61.4, 60.1, 56.2, 51.9, 41.5, 27.9, 24.9, 22.8, 22.0; HRMS (ESI): Exact mass calcd for $C_{28}H_{37}N_2O_6$ $[M+H]^+$ 497.2646, found 497.2633.



Benzyl ((2*R*,3*S*) -3-hydroxy-1-oxo-4-phenyl-1-(((*S*) -1-phenylethyl) amino) butan-2-yl) carbamate (288). After stirring in a 1:1 mixture of EtOH:MeOH (0.01 M) for 5 hours at ambient temperature, in the presence of H_2 (balloon) and 10% Pd/C (10 mg), the epoxy amide (9.1 mg, 21 μmol) provided the alcohol (single diastereomer) as a yellow oil (9.0 mg, 99% yield). $[\alpha]_D^{20}$ +36.4 (*c* 0.11, $CHCl_3$); R_f = 0.11 (30% EtOAc/hexanes); IR (film) 3299, 2922, 1706, 1652, 1537, 1250, 698 cm^{-1}; ^1H NMR (600 MHz) δ 7.29 (m, 15H), 6.73 (d, *J* = 6.6 Hz, 1H), 5.83 (d, *J* = 7.8 Hz, 1H), 5.10 (m, 3H), 4.12 (dd, *J* = 8.4, 4.2 Hz, 1H), 3.98 (br s, 1H), 3.78 (br s, 1H), 3.02 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.93 (dd, *J* = 13.8, 6.0 Hz, 1H), 1.52 (d, 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 170.1, 156.6, 142.6, 137.3, 135.9, 129.2, 128.69, 128.66, 128.56, 128.3, 128.1, 127.4, 126.8, 125.8, 74.1, 67.3, 56.0, 49.1, 40.8, 22.2; HRMS (ESI): Exact mass calcd for $C_{26}H_{28}N_2NaO_4$ $[M+Na]^+$ 455.1947, found 455.1968.

Chapter IV: Application of UmAS to the Total Synthesis of Feglymycin

General Procedure A: Bromonitromethane Addition to *N*-TMS-Protected Imines

A solution of the imine (1 equiv) and PBAM (0.10 equiv) in toluene (0.3 M) was cooled to -78 °C. Bromonitromethane was added to the reaction mixture in aliquots (0.2 equiv every 2 h) over 10 h. The reaction was then stirred at -78 °C for an additional 16 h before its quench at -78 °C with an acylating reagent (1 equiv). The reaction was then warmed to 0 °C and stirred for 20 h. The solvent was removed *in vacuo*, and the crude reaction mixture was purified by column chromatography to give the α-bromonitro adduct as a mixture of inseparable diastereomers.

General Procedure B: Sulfone Synthesis

tert-Butyl carbamate (1 equiv) and benzene sulfinic acid (2 equiv) were dissolved in a 2:1 mixture of toluene and water (0.3 M). The aldehyde (1.2 equiv) and formic acid (2 equiv) were added and the reaction was then allowed to stir for a period of 11 to 15 days at rt. The mixture was filtered, and the resulting solid washed several times with ether to remove remaining aldehyde. The solid was then dried under vacuum at 60 °C to give the pure sulfone.

General Procedure C: Synthesis of *N*-Boc-Protected Imines

To a round bottom flask, potassium carbamate (6 equiv) and sodium sulfate (7 equiv) were added. The flask was then flame dried and the contents placed under argon. The sulfone (1 equiv.) was then added to the flask, and dissolved in THF (0.1 M). The reaction mixture was then allowed to reflux for 4-5 hours. The solid salts were then filtered off, and the resulting mixture was concentrated *in vacuo* to give the pure imine.

General Procedure D: Bromonitromethane Addition to *N*-Boc-Protected Imines

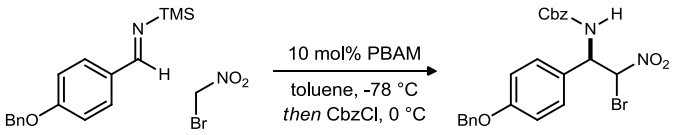
A solution of the imine (1 equiv) and PBAM or PBAM·TfOH (0.01 or 0.05 equiv) in toluene (0.3 M) was cooled to -20 °C and treated with bromonitromethane (1.2 equiv). The reaction was stirred at -20 °C for 24 hours. The solvent was removed *in vacuo*, and the crude reaction mixture purified by column chromatography to give the α-bromonitro adduct as a mixture of inseparable diastereomers.

General Procedure E: Amide Synthesis Using an Amine (Free Base)

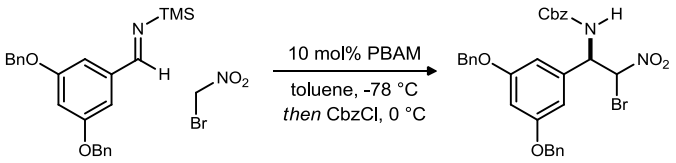
The amine (1.2 equiv) was added drop wise to a solution of α-bromo nitroalkane (1.0 equiv, 0.2 M) and NIS (1.0 equiv) in THF and H_2O (5.0 equiv) at 0 °C, or rt, followed by K_2CO_3 (2.0 equiv). The reaction mixture was stirred at 0 °C, or rt, for 2 d. The resulting mixture was diluted with dichloromethane, 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 F: Amide Synthesis Using an Ammonium Salt

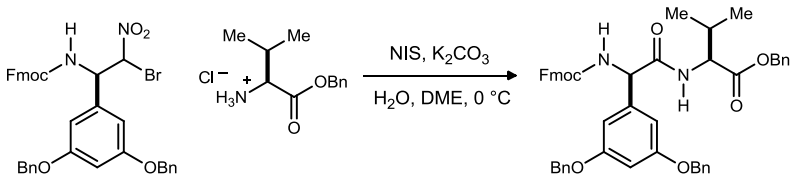
K_2CO_3 (3.2 equiv) was added to the suspension of the ammonium salt (1.2 equiv) and the α-bromo nitroalkane (1.0 equiv, 0.2 M) in THF and H_2O (5.0 equiv) at 0 °C, or rt, followed by NIS (1.0 equiv). The reaction mixture was stirred at 0 °C, or rt, for 2 d. The resulting mixture was diluted with dichloromethane, dried with $MgSO_4$ and then filtered through Celite. The filtrate was concentrated and subjected to purification by flash column chromatography on silica gel.



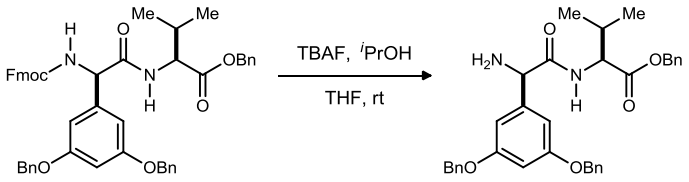
Carboxybenzyloxy (1*R*)-1- (4 (benzyloxy) phenyl) -2-bromo -2-nitroethyl carbamate (316). Following General Procedure A, the *N*-TMS-imine (40 mg, 140 μmol) and bromonitromethane (11 μL, 140 μmol), when quenched with benzyl chloroformate (20 μL, 140 mmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a white solid (38.4 mg, 56%). The enantiomeric excess of the major and minor diastereomers was determined to be 67 and 67% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 33.1 min, $t_r(d_1e_2$, major) = 43.5 min, $t_r(d_2e_1$, minor) = 35.7 min, $t_r(d_2e_2$, major) = 38.5 min). R_f = 0.25 (20% EtOAc/hexanes); mp = 119-121 °C IR (film) 3346, 3031, 1694, 1563, 1512, 1345, 1288, 1245, 738 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.40 (m, 20H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 6.6 Hz, 2H), 6.99 (d, *J* = 6.6 Hz, 2H), 6.31 (br s, 2H), 5.98 (br s, 1H), 5.65 (br m, 2H), 5.50 (br s, 1H), 5.16 (s, 2H), 5.14 (s, 2H), 5.08 (s, 2H), 5.07 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 159.5, 159.4, 155.5, 155.2, 136.4 (2C), 135.7 (2C), 135.6 (2C), 128.6 (4C), 128.5, 128.4, 128.2 (2C), 128.1 (2C), 127.4 (4C), 115.4, 115.3, 84.6, 81.3, 70.1 (2C), 67.7, 67.6, 58.1, 58.0; HRMS (EI): Exact mass calcd for $C_{23}H_{21}BrN_2O_5$ $[M]^+$ 484.0634, found 484.0647.



Carboxybenzyloxy (1*R*)-1-(3,5 (dibenzyloxy) phenyl) -2-bromo-2-nitroethyl carbamate (317). Following General Procedure A, the *N*-TMS-imine (40 mg, 100 µmol) and bromonitromethane (8.0 µL, 100 µmol), when quenched with benzyl chloroformate (15 µL, 100 mmol), provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate in hexanes), as a white solid (32 mg, 53%). The enantiomeric excess of the major and minor diastereomers was determined to be 71 and 71% ee, respectively, by chiral HPLC analysis (Chiralcel IA, 20% ^{i}PrOH/hexanes, 1.0 mL/min, t_r(minor) = 14.9 min, t_r(major) = 16.9 min). R_f = 0.30 (20% EtOAc/hexanes); mp = 126-128 °C; IR (film) 3326, 3032, 1691, 1599, 1563, 1452, 1264, 1160, 695 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.39 (m, 30H), 6.62 (dd, *J* = 4.2, 2.4 Hz, 1H), 6.61 (dd, *J* = 4.2, 2.4 Hz, 1H), 6.55 (d, *J* = 1.8 Hz, 2H), 6.52 (s, 2H), 6.27 (br s, 2H), 5.99 (d, *J* = 8.4 Hz, 1H), 5.68 (br s, 1H), 5.57 (d, *J* = 7.8 Hz, 1H), 5.46 (br s, 1H), 5.16 (s, 2H), 5.14 (s, 2H), 5.03 (s, 4H), 5.02 (s, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 160.41 (2C), 160.39 (2C), 155.4 (2C), 136.3 (2C), 136.2 (2C), 135.7 (2C), 128.62 (6C), 128.58 (2C), 128.4 (3C), 128.2 (3C), 127.6 (6C), 106.2 (2C), 106.1 (2C), 102.5, 102.4, 84.7, 80.6, 70.3 (4C), 67.7 (2C), 58.5, 58.2; HRMS (EI): Exact mass calcd for $C_{30}H_{27}BrN_2O_6$ $[M]^+$ 590.1052, found 590.1036.

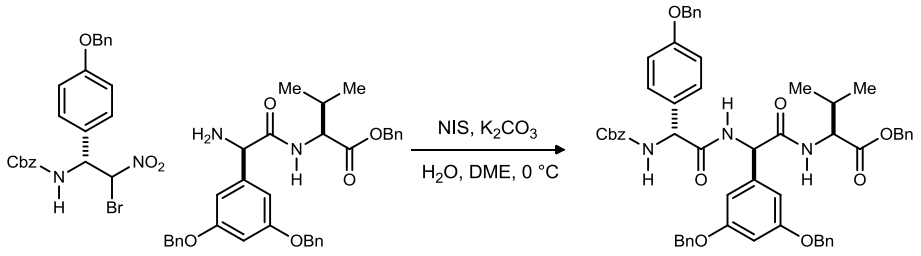


(*S*)-Benzyl 2-((*R*)-2-((((9H-fluoren-9-yl) methoxy) carbonyl) amino)-2-(3,5-bis (benzyloxy) phenyl) acetamido) -3-methylbutanoate (319). Following General Procedure F, the α-bromo nitroalkane (50 mg, 74 μmol) and the ammonium salt of L-valine (37 mg, 150 μmol) provided the dipeptide (single diastereomer) after flash column chromatography (15% ethyl acetate in hexanes) as a white solid (36 mg, 63%). $[\alpha]_D^{20}$ -31.1 (*c* 0.24, $CHCl_3$); R_f = 0.22 (30% EtOAc/hexanes); mp 165-167 °C; IR (film) 3302, 2961, 1738, 1657, 1600, 1533, 1451, 1250, 1158 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.2 Hz, 2H), 7.61 (br s, 2H), 7.34 (m, 19H), 6.74 (br s, 2H), 6.58 (br s, 1H), 6.48 (br s, 1H), 6.32 (br s, 1H), 5.32 (br s, 1H), 5.16 (br m, 2H), 4.98 (br m, 4H), 4.60 (br m, 1H), 4.42 (br m, 1H), 4.36 (br m, 1H), 4.23 (br s, 1H), 2.08 (dqq, *J* = 7.2, 7.2, 7.2 Hz, 1H), 0.71 (d, *J* = 5.4 Hz, 3H), 0.64 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 171.3, 169.8, 160.4, 155.6, 143.8, 143.7, 141.2, 136.6, 135.1, 128.6 (2C), 128.5, 128.4, 128.0, 127.7, 127.5, 127.1, 125.1, 119.1, 106.0, 102.3, 70.0, 67.2, 58.9, 57.2, 47.0, 31.4, 18.8, 17.2; HRMS (ESI): Exact mass calcd for $C_{49}H_{47}N_2O_7$ $[M+H]^+$ 775.3378, found 775.3381.

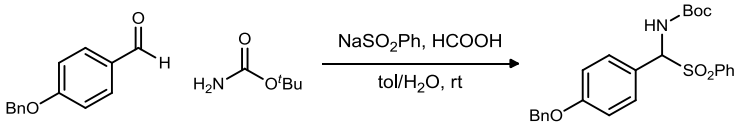


(*S*)-Benzyl 2-((*R*)-2-amino-2-(3,5-bis(benzyloxy)phenyl)acetamido)-3-methylbutanoate (321). Following the procedure used by Boger and coworkers,[167] upon treatment with TBAF (1 M in THF, 270 μL, 265 μmol) and ^{i}PrOH (25 μL, 330 μmol) in THF (0.03 M), the Fmoc-protected peptide (26 mg, 33 μmol) provided the free amine (single diastereomer) after flash column chromatography (30% acetone in hexanes) as a viscous yellow oil (22 mg, 87%). $[\alpha]_D^{20}$ -27.2 (*c* 0.72, $CHCl_3$); R_f = 0.31 (100% EtOAc/hexanes); IR (film) 3034, 2963, 1674, 1600, 1454, 1202, 1157 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.56 (br s, 1H), 7.29 (m, 15H), 6.85 (s, 2H), 6.58 (s, 1H), 5.12 (d, *J* = 12.0 Hz, 1H), 4.98 (d, *J* = 12.6 Hz, 1H), 4.95 (d, *J* = 11.4 Hz, 2H), 4.92 (d, *J* = 11.4 Hz, 2H), 4.52 (br m, 1H), 2.64 (br s, 2H), 2.04 (dqq, *J* = 6.0, 6.0, 6.0 Hz, 1H), 0.64 (d, *J* = 6.6 Hz, 3H), 0.60 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 172.0, 168.0, 160.5, 136.4, 134.9, 134.5, 128.5, 128.4, 127.9, 127.5, 106.6, 103.9, 70.0, 67.5, 57.7, 56.9, 31.0, 18.7, 17.1; HRMS (ESI): Exact mass calcd for $C_{34}H_{37}N_2O_5$ $[M+H]^+$ 553.2697, found 553.2687.

[167] Rew, Y.; Shin, D.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2004**, *126*, 1041.



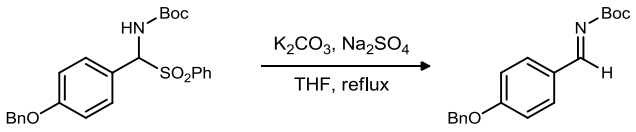
(5*R*,8*R*,11*S*)-Benzyl 5-(4-(benzyloxy) phenyl)-8-(3,5-bis (benzyloxy) phenyl) -11-isopropyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oate (322). Following General Procedure E, the α-bromo nitroalkane (74 mg, 150 μmol) and the free amine dipeptide (68 mg, 130 μmol) provided the tripeptide (single diastereomer) after flash column chromatography (40% ethyl acetate in hexanes) as a yellow foam (23 mg, 20%). $[\alpha]_D^{20}$ -70.7 (*c* 0.08, $CHCl_3$); R_f = 0.08 (30% EtOAc/hexanes); IR (film) 2922, 2361, 1716, 1581, 1510, 1229, 913 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.38 (m, 25H), 7.01 (s, 1H), 6.99 (s, 2H), 6.96 (s, 2H), 6.94 (s, 2H), 6.62 (br s, 1H), 6.57 (br s, 1H), 6.03 (br s, 1H), 6.00 (br s, 1H), 5.13 (m, 11H), 2.72 (br s, 1H), 2.07 (br m, 1H), 0.90 (d, *J* = 6.0 Hz, 3H), 0.87 (d, *J* = 6.0 Hz, 3H).[168]



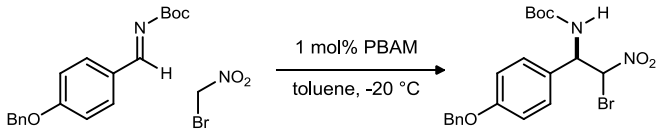
***tert*-Butyl (4-benzyloxy) (phenylsulfonyl) methylcarbamate (328).** Following the General Procedure B, *p*-bezyloxybenzaldehyde (5.0 g, 23.6 mmol) gave the sulfone (5.6 g, 52%), as a white powder. R_f = 0.46 (30% EtOAc/hexanes); mp = 98-100 °C; IR (film) 3340, 1694, 1601, 1507, 1225, 1198, 1161, 912 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.8 Hz, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.40 (m, 6H), 7.19 (t, *J* = 6.6 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 2H), 5.88 (d, *J* = 10.8 Hz, 1H), 5.67 (d, *J* = 10.2

[168] HRMS was attempted, but the desired mass was not able to be detected. This is most likely due to the instability of the compound.

Hz, 1H), 5.10 (s, 2H), 1.27 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 160.0, 153.2, 137.0, 133.8, 130.2, 129.4, 129.0, 128.6, 127.4, 125.3, 121.9, 115.1, 81.2, 73.4, 70.1, 28.0.[169]



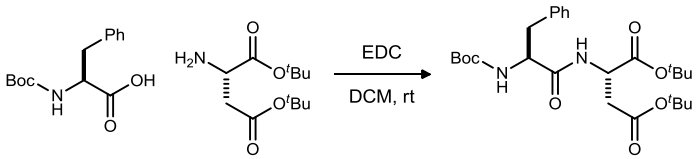
(*E*)-*tert*-Butyl-4-benzyloxybenzylidenecarbamate (329). Following General Procedure C, the sulfone (3.4 g, 7.5 mmol) provided the imine (2.1 g, 91%) as a white paste. IR (film) 2977, 1708, 1600, 1511, 1368, 1252, 1224, 1150, 1007 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.90 (d, *J* = 9.0 Hz, 2H), 7.42 (m, 4H), 7.36 (tt, *J* = 6.0, 1.2 Hz, 1H), 7.04 (d, *J* = 9.0 Hz, 2H), 5.13 (s, 2H), 1.60 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 169.7, 163.3, 162.8, 136.0, 132.5, 128.7, 128.2, 127.5, 127.1, 115.1, 81.8, 70.2, 27.9; HRMS (ESI): Exact mass calcd for $C_{19}H_{22}NO_3$ $[M+H]^+$ 312.1594, found 312.1591.



***tert*-Butyl (1*R*)-2-bromo-1-(4-benzyloxyphenyl)-2-nitroethylcarbamate (325).** Following General Procedure D, the *N*-Boc-imine (1.0 g, 3.2 mmol) and bromonitromethane (300 μL, 3.2 mmol) provided the α-bromo nitroalkane (1.2:1 mixture of diastereomers), after flash column chromatography (SiO_2, 10% ethyl acetate), as a white solid (1.3 g, 90%). The enantiomeric excess of the major and minor diastereomers was determined to be 92 and 90% ee, respectively, by chiral HPLC analysis (Chiralcel AD-H, 20% ^{i}PrOH/hexanes, 1 mL/min, (Chiralcel AD-H, 10% ^{i}PrOH/hexanes, 1.0 mL/min, $t_r(d_1e_1$, minor) = 15.6 min, $t_r(d_1e_2$, major) = 12.4 min, $t_r(d_2e_1$, minor) = 16.7 min,

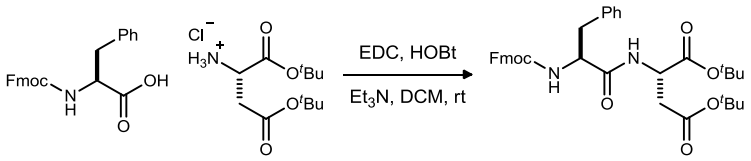
[169] HRMS was attempted, but the desired mass was not able to be detected. This is most likely due to the instability of the compound.

t_r(d_2e_2, major) = 20.7 min). R_f = 0.38 (20% EtOAc/hexanes); mp = 144-146 °C; IR (film) 3361, 2979, 1691, 1564, 1510, 1354, 1249, 1163, 735 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, 1.2:1 mixture of diastereomers) δ 7.42 (m, 8H), 7.35 (t, *J* = 6.0 Hz, 2H), 7.25 (d, *J* = 7.2 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 6.6 Hz, 2H), 6.32 (br s, 1H), 6.28 (br s, 1H), 5.65 (br s, 1H), 5.58 (br d, *J* = 4.2 Hz, 1H), 5.43 (br s, 1H), 5.32 (br s, 1H), 5.08 (s, 2H), 5.07 (s, 2H), 1.47 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 159.3 (2C), 154.6 (2C), 136.5 (4C), 128.6 (2C), 128.2 (2C), 128.1 (2C), 127.4 (2C), 115.3 (2C), 85.1, 82.0, 80.9 (2C), 70.1 (2C), 57.2 (2C), 28.2, 28.1; HRMS (ESI): Exact mass calcd for $C_{20}H_{23}BrN_2NaO_5$ $[M+Na]^+$ 473.0688, found: 473.0681.

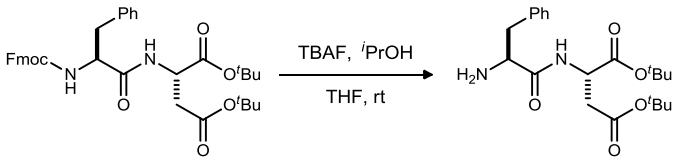


(*S*)-Di-*tert*-butyl 2-((*S*)-2- ((*tert*-butoxycarbonyl) amino) -3-phenylpropanamido) succinate (S-17). Upon treatment with EDC (590 mg, 3.1 mmol) in dichloromethane (0.1 M), *N*-Boc L-phenylalanine (540 mg, 2.0 mmol) and L-aspartic acid di-^{t}butyl ester (500 mg, 2.0 mmol) provided the dipeptide (single diastereomer) after an aqueous work up as a yellow foam (730 mg, 73%). $[\alpha]_D^{20}$ +17.8 (*c* 1.94, $CHCl_3$); R_f = 0.34 (30% EtOAc/hexanes); IR (film) 3313, 2979, 1739 (broad), 1518, 1369, 1250, 1162 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 10.2, 2.4 Hz, 2H), 7.20 (m, 3H), 6.91 (d, *J* = 7.8 Hz, 1H), 5.01 (br d, *J* = 6.0 Hz, 1H), 4.62 (ddd, *J* = 9.0, 4.8, 4.8 Hz, 1H), 4.41 (br s, 1H), 3.13 (dd, *J* = 14.4, 6.0 Hz, 1H), 3.02 (br dd, *J* = 12.6, 6.0 Hz, 1H), 2.84 (dd, *J* = 16.8, 4.2 Hz, 1H), 2.67 (dd, *J* = 17.4, 4.8 Hz, 1H), 1.43 (s, 9H), 1.40 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 170.8, 169.9, 169.2, 155.1, 136.3, 129.3, 128.4, 126.7,

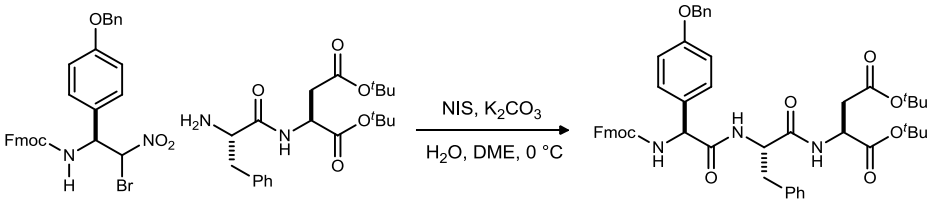
82.2, 81.4, 79.8, 55.3, 49.0, 38.3, 37.3, 28.1, 27.9, 27.7; HRMS (EI): Exact mass calcd for $C_{26}H_{40}N_2O_7$ $[M]^+$ 492.2836, found 492.2812.



(*S*)-Di-*tert*-butyl 2- ((*S*)-2- ((((9H-fluoren-9-yl) methoxy) carbonyl) amino) -3-phenyl propanamido) succinate (S-18). Upon treatment with EDC (1.1 g, 5.7 mmol), HOBt (0.8 g, 5.7 mmol), and Et_3N (1.6 mL, 11.4 mmol) in dichloromethane (0.25 M), *N*-Fmoc L-phenylalanine (2.2 g, 5.7 mmol) and L-aspartic acid di-^{t}butyl ester (1.6 g, 5.7 mmol) provided the dipeptide (single diastereomer) after aqueous work up as a white solid (3.3 mg, 94%). $[\alpha]_D^{20}$ +11.6 (*c* 0.61, $CHCl_3$); R_f = 0.28 (30% EtOAc/hexanes); mp 65-67 °C; IR (film) 3311, 2978, 1729, 1664, 1530, 1368, 1251, 1154, 739 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 2H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.42 (dd, *J* = 7.8, 7.8 Hz, 2H), 7.27 (m, 7H), 6.86 (br d, *J* = 6.6 Hz, 1H), 5.34 (br d, *J* = 6.6 Hz, 1H), 4.66 (br m, 1H), 4.52 (br d, *J* = 5.4 Hz, 1H), 4.42 (dd, *J* = 10.8, 7.8 Hz, 1H), 4.30 (br dd, *J* = 7.2, 7.2 Hz, 1H), 4.20 (dd, *J* = 7.2, 7.2 Hz, 1H), 3.18 (br dd, *J* = 14.4, 6.6 Hz, 1H), 3.11 (br dd, *J* = 13.8, 6.6 Hz, 1H), 2.89 (dd, *J* = 16.8, 3.6 Hz, 1H), 2.71 (dd, *J* = 17.4, 4.8 Hz, 1H), 1.47 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 170.4, 170.1, 169.2, 155.7, 143.7, 141.2, 136.0, 129.4, 128.6, 127.7, 127.0, 125.0, 199.9, 82.5, 81.6, 67.1, 55.7, 49.2, 47.1, 38.5, 37.3, 28.0, 27.8; HRMS (ESI): Exact mass calcd for $C_{36}H_{42}N_2NaO_7$ $[M+Na]^+$ 637.2890, found 637.2874.

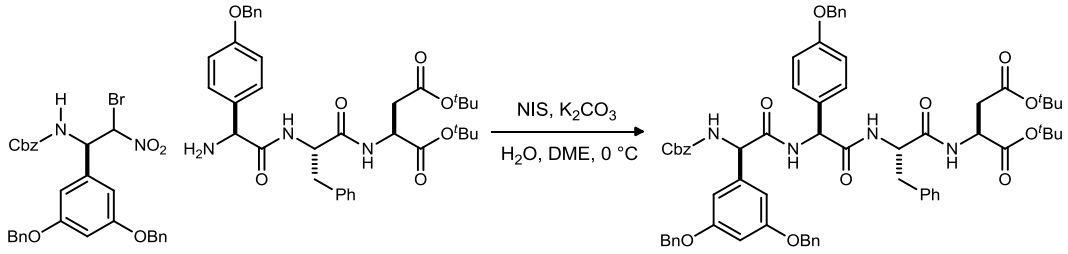


(*S*)-Benzyl 2-((*R*)-2-amino-2-(3,5-bis(benzyloxy) phenyl)acetamido) -3-methylbutanoate (334). Following the procedure used by Boger and coworkers,[167] upon treatment with TBAF (6.5 mL, 6.5 mmol) and ^{i}PrOH (6.2 mL, 8.1 mmol) in THF (0.03 M), the Fmoc-protected peptide (500 mg, 810 μmol) provided the free amine (single diastereomer) after flash column chromatography (30% acetone in hexanes) as a yellow oil (206 mg, 87%). $[\alpha]_D^{20}$ -7.3 (*c* 0.93, $CHCl_3$); R_f = 0.10 (30% EtOAc/hexanes); IR (film) 3377, 2978, 1732, 1676, 1509, 1455, 1369, 1252, 1156 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.4 Hz, 1H), 7.28 (m, 5H), 4.70 (ddd, *J* = 8.8, 4.5, 4.5 Hz, 1H), 6.37 (dd, *J* = 9.5, 3.8 Hz, 1H), 3.27 (dd, *J* = 13.8, 3.8 Hz, 1H), 2.90 (dd, *J* = 16.8, 4.5 Hz, 1H), 2.70 (m, 2H), 1.48 (s, 9H), 1.46 (s, 9H) [N*H*$_2$ not observed]; ^{13}C NMR (150 MHz, $CDCl_3$) ppm 174.0, 169.8, 155.4, 137.7, 129.2, 128.6, 126.8, 82.1, 81.4, 56.3, 48.7, 41.0, 37.8, 28.0, 27.9; HRMS (EI): Exact mass calcd for $C_{21}H_{32}N_2O_5$ $[M]^+$ 392.2311, found 392.2315.



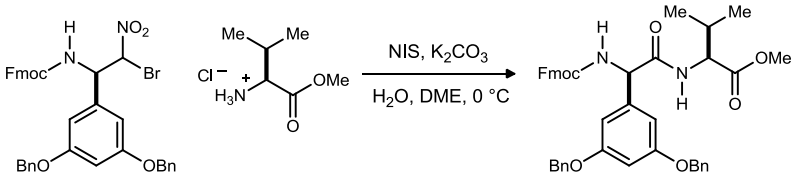
(6*R*,9*R*,12*S*)-Benzyl 6-(4- (benzyloxy) phenyl) -9-(3,5-bis (benzyloxy) phenyl) -12-isopropyl-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (335). Following General Procedure E, the α-bromo nitroalkane (40 mg, 70 μmol) and the free amine dipeptide (36 mg, 84 μmol) provided the tripeptide (single diastereomer) after

flash column chromatography (30% ethyl acetate in hexanes) as a yellow foam (33 mg, 56%). $[\alpha]_D^{20}$ +6.1 (*c* 0.18, $CHCl_3$); R_f = 0.11 (30% EtOAc/hexanes); IR (film) 3296, 1726, 1511, 1332, 1232, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (br m, 2H), 7.60 (br m, 2H), 7.35 (m, 14H), 6.99 (d, *J* = 7.2 Hz, 2H). 6.93 (d, *J* = 8.4 Hz, 2H), 6.74 (br s, 1H), 6.68 (br s, 1H), 6.32 (d, *J* = 6.8 Hz, 1H), 6.07 (br s, 1H), 5.98 (br s, 2H), 5.06 (d, *J* = 8.0 Hz, 2H), 4.40 (br m, 2H), 4.23 (br m, 1H), 3.21 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.05 (dd, *J* = 14.0, 6.8 Hz, 1H), 2.81 (dd, *J* = 17.2, 4.4 Hz, 1H), 2.61 (br m, 1H), 1.47 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 181.2, 170.1, 169.6, 156.5, 148.1, 143.8, 141.3, 141.2, 129.3, 128.6, 128.0, 127.7, 127.4, 127.0, 125.0, 120.0, 115.4, 82.4, 81.8, 70.0, 67.1, 66.9, 54.2, 53.4, 49.1, 47.1, 28.0, 27.8; HRMS (ESI): Exact mass calcd for $C_{51}H_{55}N_3NaO_9$ $[M+Na]^+$ 876.3836, found: 876.3833.



(6*R*,9*R*,12*S*)-Benzyl 6-(4- (benzyloxy) phenyl) -9-(3,5-bis (benzyloxy) phenyl) -12-isopropyl-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (336). Following General Procedure E, the α-bromo nitroalkane (44 mg, 74 μmol) and the free amine dipeptide (39 mg, 62 μmol) provided the tripeptide (single diastereomer) after flash column chromatography (15% ethyl acetate in hexanes) as a yellow viscous oil (37 mg, 54%). $[\alpha]_D^{20}$ -41.7 (*c* 0.24, $CHCl_3$); R_f = 031 (30% EtOAc/hexanes); IR (film) 3340, 2926, 1725, 1599, 1501, 1336, 1156, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.3 Hz, 1H), 8.02 (s, 2H), 7.40 (m, 28H), 7.12 (d, *J* = 2.0 Hz, 2H), 7.02 (d, *J* = 2.4 Hz,

2H), 6.80 (d, *J* = 10.2 Hz, 2H), 6.60 (br m, 2H), 5.30 (d, *J* = 14.8 Hz, 1H), 5.26 (d, *J* = 15.2 Hz, 1H), 5.12 (d, *J* = 21.0 Hz, 3H), 5.06 (d, *J* = 20.0 Hz, 3H), 4.77 (br m, 2H), 3.41 (br m, 1H), 3.25 (br m, 1H), 3.17 (br m, 1H), 2.90 (br m, 1H), 1.47 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 172.1, 169.1, 166.8, 164.2, 160.2, 156.6, 155.6, 150.4, 136.14 (2C), 136.07 (2C), 135.7, 135.0, 129.6, 129.52, 129.45, 129.4, 129.1, 129.0, 128.7, 128.64, 128.61, 128.56, 128.5, 128.11, 128.07, 127.7, 127.6, 127.5, 127.0, 106.5 (2C), 83.0, 81.2, 70.4, 68.0, 67.0, 58.3, 54.9, 49.7, 49.1, 38.4, 37.3, 27.9, 27.8.[170]



(*S*)-Methyl 2-((*R*)-2- ((((9H-fluoren-9-yl) methoxy) carbonyl) amino)-2- (3,5-bis (benzyloxy) phenyl)acetamido)-3-methylbutanoate (337). Following General Procedure F, the α-bromo nitroalkane (500 mg, 740 μmol) and the ammonium salt of L-valine (250 mg, 1.50 mmol) provided the dipeptide (single diastereomer) after flash column chromatography (20% ethyl acetate in hexanes) as a white solid (255 mg, 49%). $[\alpha]_D^{20}$ -26.3 (*c* 0.64, $CHCl_3$); R_f = 0.17 (30% EtOAc/hexanes); mp 174-176 °C; IR (film) 3305, 2961, 1741, 1659, 1600, 1533, 1450, 1250, 1209, 1158, 1053, 737 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.2 Hz, 2H), 7.60 (s, 2H), 7.36 (m, 14H), 6.70 (s, 2H), 6.59 (s, 1H), 6.21 (br s, 1H), 6.18 (br d, *J* = 7.2 Hz, 1H), 5.21 (br d, *J* = 3.0 Hz, 1H), 5.02 (d, *J* = 12.0 Hz, 2H), 5.00 (d, *J* = 11.4 Hz, 2H), 4.55 (dd, *J* = 8.4, 4.8 Hz, 1H), 4.41 (dd, *J* = 10.2, 10.2, 1H), 4.36 (dd, *J* = 7.2, 7.2 Hz, 1H), 4.36 (dd, *J* = 7.2, 7.2 Hz, 1H), 4.22 (br s, 1H), 3.75 (s, 3H), 0.75 (d, *J* = 5.4 Hz, 3H), 0.68 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150

[170] HRMS was attempted, but the desired mass was not able to be detected. This is most likely due to the instability of the compound.

MHz, $CDCl_3$) ppm 171.8, 169.1, 160.5, 155.5, 143.8, 143.7, 141.2, 136.5, 128.6, 128.0, 127.6, 127.5, 127.0, 125.1, 119.9, 106.1, 102.3, 70.1, 67.2, 59.0, 57.2, 52.3, 47.1, 31.4, 18.7, 17.3; HRMS (ESI): Exact mass calcd for $C_{43}H_{42}N_2NaO_7$ $[M+H]^+$ 699.3065, found: 699.3083.