New Enantioselective Approaches to the Synthesis of Amino Acid Derivatives and Peptides Using Chiral Proton Catalysis

By

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Chapter I

Background

1.1. Asymmetric Brønsted Acid Catalysis

The start of the 21st century has brought with it an explosion of growth in the area of purely organic catalysts, which have emerged as a third class of powerful asymmetric catalysts, in addition to enzymes and synthetic metal complexes.\(^1\) Organocatalysis has been defined as acceleration of chemical reactions by purely organic and metal-free small molecules in a substoichiometric quantity.\(^1, 2\) Small organic molecule catalysts are generally stable to oxygen and moisture and are often based on nontoxic compounds.

In this area, asymmetric Brønsted acid catalysis has become the subject of increasing interest among chemists and has gradually become a powerful tool for building complex molecular skeletons.\(^3\) The most studied chiral Brønsted acid catalysts have been ureas/thioureas, chiral diols, phosphoric acids and cinchona alkaloids.

1.1.1. Thiourea Derivatives

Curran and co-workers initially discovered that in the presence of an electron-poor diaryl urea \( \text{I} \), the stereoselectivity of the radical allylation of sulfoxides was altered.\(^4\)

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They also found that the same catalyst was able to accelerate a dipolar Claisen rearrangement.\(^5\)

![Figure 1. Thiourea](image)

Jacobsen and co-workers first brought the urea/thiourea derivatives to asymmetric synthesis in 1998. From a parallel synthetic library, \(2a\) was discovered to catalyze the enantioselective hydrocyanation of a broad variety of imine substrates with high enantioselectivity (Scheme 1, eq 1).\(^6\) Subsequently, Jacobsen’s thiourea catalysts came to be utilized in the asymmetric Mannich-type reaction of silylketene acetal with \(N\)-Boc-aldimines (Scheme 1, eq 2),\(^7\) the hydrophosphonylation of imines with bis(2-nitrobenzyl) phosphite (Scheme 1, eq 3),\(^8\) and the aza-Baylis-Hillman reaction of \(N\)-nosyl imines with methyl acrylate (Scheme 1, eq 4),\(^9\) all with high enantioselectivities.


The scope of thiourea catalysis was also extended to the enantioselective acyl-Pictet-Spengler reaction. With the modified thiourea catalyst 3, indole 4 was converted to tetrahydro-β-carboline 5 in good yields with high enantioselectivity (Scheme 2).\textsuperscript{10}

More recently, Jacobsen and co-workers used primary amine thiourea catalyst 6 in the direct conjugate addition of $\alpha,\alpha$-disubstituted aldehydes to nitroalkenes, achieving excellent enantioselectivities while forming a hindered quaternary center (Scheme 3, eq 5).\textsuperscript{11} The same catalyst was also applied in the enantioselective conjugate addition of ketones to nitroalkenes (Scheme 3, eq 6).\textsuperscript{12}

Takemoto and co-workers developed novel bifunctional thiourea catalyst 7, bearing a tertiary amine moiety, with which they obtained high enantioselectivity and good yields in both the Michael addition of malonates to nitroolefins (Scheme 4, eq 7).\textsuperscript{13}

and the Michael addition of malonitrile to α,β-unsaturated imides (Scheme 4, eq 8).\textsuperscript{14}

They proposed the catalyst had a bifunctional role, activating both the electrophile via hydrogen bonding with the thiourea, and the nucleophile via assisted deprotonation using the dimethyl amine (Figure 2). They also used the same catalyst in the aza-Henry reaction, which will be further discussed in the next section.

\textbf{Scheme 4}

\textbf{Figure 2.} The Transition-state Model of Michael Addition Using Thiourea Catalyst 7

Another bifunctional thiourea organocatalyst 8, based on the BINAM scaffold, was developed by Wang and co-workers to promote the enantioselective Morita-Baylis-Hillman reaction of cyclohexenone with aldehydes, producing allylic alcohol building blocks in high yields and high enantioselectivities (Scheme 5, eq 9).\textsuperscript{15} The same catalyst

\begin{itemize}
\end{itemize}
can efficiently catalyze the Michael addition of diketones to nitroalkenes, delivering high enantioselectivity with as low as 1 mol% catalyst loading (Scheme 5, eq 10).

Scheme 5

Since then, various thiourea catalysts have been developed by several groups to achieve a wide range of enantioselective reactions, including acylcyanation of imines, a three-component acyl-Strecker reaction, Petasis-type reaction of quinolines, transfer hydrogenation of nitroolefins, Pictet-Spengler-type cyclizations of hydroxylactams, formal imine-allene [3+2] cycloadditions, enolate addition to oxocarbenium ions, Claisen rearrangements, formal [3+2] cycloaddition of azomethine ylides with nitroalkenes and aldol additions of α-isothiocyanato imides to aldehydes.

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The natural product cinchona alkaloids (Figure 3) have recently been widely applied in organocatalysis. While they are commonly used as chiral Lewis base catalysts, some modified cinchona alkaloids incorporating a thiourea moiety have been developed, which act as bifunctional organocatalysts.

![Figure 3. Cinchona Alkaloids](image)

Soós and co-workers first reported a cinchona alkaloid-based thiourea catalyst (9a) which was used in the enantioselective Michael addition of nitromethane to chalcones (Scheme 6, eq 11). Connon and co-workers utilized the same catalyst in an enantioselective Michael addition of malonate to nitroalkenes (Scheme 6, eq 12). Since then, 9a, or the similar catalyst 9b, was utilized universally in the conjugate addition of a wide range of nucleophilic enol species to enones or nitroalkenes (Scheme 6, eq 13).

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The methodology was further applied in the stereoselective synthesis of functionalized nitrocyclopropanes (Scheme 6, eq 14).\textsuperscript{32}

**Scheme 6**

![Scheme 6 diagram]

The cinchona alkaloid-based thiourea catalyst (9b) has also been applied to the Mannich reaction of malonates with N-Boc imines (Scheme 7, eq 15),\textsuperscript{33} and as well as intramolecular oxa-Michael addition of a phenol to β-ketoester alkylidenes (Scheme 7, eq 16).\textsuperscript{34} A subsequent acid-catalyzed decarboxylation was then conducted in the same pot to provide flavanone derivatives. The strategy was further extended to a Knoevenagel

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condensation/Michael addition/decarboxylation sequence in the presence of 9b to achieve a one-pot synthesis of the natural product flindersiachromanone (10) in good yield and high ee (Scheme 7, eq 17).

Scheme 7

Rouden and co-workers reported using a similar cinchona alkaloid-based thiourea (11) in a stoichiometric amount to effect an enantioselective decarboxylative protonation of aminomalonates 12, affording α-aminoesters 13 in an enantioenriched form (Scheme 8, eq 18).\textsuperscript{35} The same catalyst was also used for asymmetric conjugate addition of nitroalkanes to vinyl sulfone 14 (Scheme 8, eq 19).\textsuperscript{36} The resulting adducts 15 could be further converted to α-alkylated chiral amines 16.


1.1.2. Chiral diols

Chiral diols and biphenols such as BINOL and TADDOL have long been used in metal complexes for asymmetric catalysis. It was not until 2003 that chiral diols found their application in general acid catalysis, when Rawal and co-workers reported that (R,R)-1-naphthyl TADDOL \( (17) \) catalyzed hetero-Diels-Alder reactions of aminodienes with a variety of aliphatic and aromatic aldehydes. The cycloadduct enol ethers \( (18) \) were further transformed to dihydropyrones \( (19) \) when treated with AcCl (Scheme 9, eq 20).\(^{37}\) Later, the same group extended this mode of catalysis to the all-carbon Diels-Alder reaction of Rawal’s diene with substituted acroleins to afford \( (20) \) (Scheme 9, eq 21).\(^{38}\) Later, they reported an enantioselective and diastereoselective Mukaiyama aldol reaction using the slightly modified catalyst \( (21) \) (Scheme 9, eq 22).\(^{39}\) Most recently, TADDOL \( (21) \) was used in the asymmetric Mukaiyama aldol reaction between \( N,O \)-ketene acetal and acetyl phosphonate.\(^{40}\)

Also by using catalyst 17, Yamamoto and co-workers achieved the N-nitroso aldol reaction of enamines in 77-91% ee (Scheme 10, eq 23). Interesting chemoselectivity was observed that the glycolic acid derivative 22 could also catalyze the reaction but instead afforded the O-nitroso aldol products with high enantioselectivity (Scheme 10, eq 24).\textsuperscript{41}

The enantioselective hetero-Diels-Alder reaction between Brassard’s diene and aldehydes was achieved when TADDOL \textit{ent-17} was used as the catalyst (Scheme 11, eq 25). The utility of the methodology was demonstrated by a one-step synthesis of the natural product (S)-(+-)-dihydrokawain (23), in 50% isolated yield and with 69% ee (Scheme 11, eq 26).\footnote{Du, H. F.; Zhao, D. B.; Ding, K. L. Chem. Eur. J. \textbf{2004}, \textit{10}, 5964.}

McDougal and Schaus utilized the axial chirality characteristic of BINOL derivatives and designed a novel catalyst \textit{24}, applying it to the Morita-Baylis-Hillman
reaction of cyclohexenone with aldehydes in good yields and high enantioselectivity (Scheme 12). The asymmetric aza-Morita-Baylis-Hillman reaction was achieved by Sasai and co-workers using a novel bifunctional BINOL derivative 25 (Scheme 13). The pyridyl moiety plays the role of a Lewis base and the diol moiety acts as the Brønsted acid. A similar bifunctional catalyst 26 was also developed by the same group to achieve the same goal.

Recently, Wu and Chong developed BINOL derivative 27a, which catalyzed the highly enantioselective conjugate alkenylation reaction of enones with borates (Scheme

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Schaus and co-workers demonstrated that similar BINOL derivatives 27b could deliver high levels of enantioselectivity for the allylboration of ketones (Scheme 14, eq 28), and 27c for the allylboration of acyl imines (Scheme 14, eq 29). They further extended the strategy to an asymmetric Petasis reaction using VAPOL catalyst 28 (Scheme 15).

Scheme 14

![Scheme 14 Diagram](image)

Scheme 15

![Scheme 15 Diagram](image)

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1.1.3. Phosphoric Acids

In 2004, the research groups of Akiyama and Terada independently developed a new class of chiral Brønsted acid catalysts based on phosphoric acid, which initiated the rapid development of this area. The phosphoric acid catalysts are proposed to be bifunctional, featuring the BINOL backbone with the phosphoric acid hydroxyl group as the Brønsted acid and the phosphoryl moiety as the Lewis base (Figure 4).

Using their chiral phosphoric acid catalysts, Akiyama and co-workers achieved the asymmetric Mannich-type reaction of ketene silyl acetal with aldimine (Scheme 16, eq 30), the hydrophosphonylation of aldimines with dialkyl phosphite (Scheme 16, eq 31), the aza-Diels-Alder reaction of aldimines with Brassard’s diene or Danishefsky’s diene (Scheme 16, eq 32), the inverse electron-demand aza-Diels-Alder reaction of

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Figure 4. Chiral Phosphoric Acid Catalysts

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azabutadiene with electron-rich alkenes (Scheme 16, eq 33),\textsuperscript{56} and the Friedel-Crafts alkylation of indoles with nitroalkenes (Scheme 16, eq 34).\textsuperscript{57}

**Scheme 16.** Chiral Phosphoric Acid-Catalyzed Asymmetric Reactions Reported by Akiyama

Using similar chiral phosphoric acid catalysts, Terada and co-workers reported the asymmetric Mannich reaction of 1,3-diketones to N-Boc aldimines (Scheme 17, eq 35),\textsuperscript{51} the direct alkylation of an α-diazoester to aldimines (Scheme 17, eq 36),\textsuperscript{58} the az-

Friedel-Crafts-type alkylation of an electron-rich furan (Scheme 17, eq 37), an aza-ene-type reaction (Scheme 17, eq 38), and the aldol-type reaction of azlactone with vinyl ethers (Scheme 17, eq 39).

Scheme 17. Chiral Phosphoric Acid-catalyzed Asymmetric Reactions Reported by Terada

Rueping and co-workers first demonstrated the use of chiral phosphoric acid 29b as a catalyst for the asymmetric hydrogenation of ketimines by Hantzsch ester 30 with good enantioselectivity (Scheme 18, eq 40). Subsequently, they also successfully

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applied the strategy to the asymmetric reduction of quinolines,\textsuperscript{63} benzoxazines, benzothiazines, benzoxazinones,\textsuperscript{64} and pyridines.\textsuperscript{65} You and co-workers employed chiral phosphoric acid \textit{29f} in the enantioselective hydrogenation of $\alpha$-iminoesters (Scheme 18, eq 41),\textsuperscript{66} which provided an organocatalytic approach to enantioenriched $\alpha$-amino acid derivatives.

\textbf{Scheme 18}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme18}
\end{figure}

Zhou and List described an elegant triple organocatalytic cascade reaction (aldol condensation/Michael addition/reduction) using chiral phosphoric acid catalyst \textit{29c} (Scheme 19), which afforded 3-substituted cyclohexylamines in a highly enantioselective mode.\textsuperscript{67}

\textsuperscript{64} Rueping, M.; Antonchick, A. P.; Theissmann, T. \textit{Angew. Chem. Int. Ed.} 2006, 45, 6751.
Nakashima and Yamamoto encountered difficulty when attempting to use chiral phosphoric acid catalysts for a Diels-Alder reaction, most likely due to their low acidity. Therefore, they developed chiral $N$-triflyl phosphoramide 31a as a stronger chiral Brønsted acid and demonstrated its high efficiency in the Diels-Alder reaction of $\alpha,\beta$-unsaturated ketones with silyloxydienes (Scheme 20, eq 42). The similar $N$-triflyl phosphoramide catalyst (31b) was developed by Rueping and co-workers, and applied in the first enantioselective Brønsted acid catalyzed Nazarov reaction (Scheme 20, eq 43), which provided the substituted cyclopentenones in good yields and with high enantioselectivity.

\[ \text{Scheme 19. Organocatalytic Asymmetric Reaction Cascade to Substituted Cyclohexylamines} \]

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Besides common BINOL-based phosphoric acids, Antilla and co-workers developed a chiral phosphoric acid bearing a VAPOL backbone (32), which also delivered high enantioselectivity in the hydrogenation of \( \alpha \)-iminoesters (Scheme 21, eq 44). The same catalyst also exhibited high efficiency in the enantioselective addition of amides or imides to imines (Scheme 21, eq 45), and desymmetrization of meso-aziridines with TMSN\(_3\) (Scheme 21, eq 46). Akiyama and co-workers described a TADDOL-based phosphoric acid catalyst 33 and applied it to an asymmetric Mannich-type reaction (Scheme 22).

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1.2. Aza-Henry Reaction

The aza-Henry reaction, also known as the nitro-Mannich reaction, is a powerful carbon-carbon bond forming reaction which involves the nucleophilic addition of nitroalkanes to imines (Scheme 23).\textsuperscript{74} A base or an acid is usually necessary to either generate the corresponding nitronate or activate the imine, respectively. The aza-Henry adduct β-nitroamine (34) can be transformed into synthetically valuable compounds such as vicinal diamines by reduction of the nitro group, α-amino carbonyl compounds by the

The discovery of the aza-Henry reaction can be traced back to 1950, when Hurd and Strong reported the condensation of nitromethane with \(N\)-benzylidene aniline (35) in refluxing ethanol, affording \(N\)-(2-nitro-1-phenylethyl)aniline (36) in 65% yield (Scheme 24).\(^{75}\) They also reported the nitroethane addition to 35, which resulted in the aza-Henry adduct in 35% yield, however, there was no comment on the diastereoselectivity of the reaction.

It was not until 1998 that chemists revisited the aza-Henry reaction and applied it to the synthesis of vicinal diamines. Anderson and co-workers reported that the deprotonated nitroalkanes (alkyl nitronate anions) reacted with PMB imines, producing the aza-Henry adducts (β-nitro amines, 37) in greater than 90% yield with up to 10:1 diastereoselection favoring the \textit{anti} diastereomer.\textsuperscript{76} The adducts (37) were reduced with samarium diiodide and the PMB group was removed with CAN, in good overall yields, to give 1,2-diamines (38) without erosion of diastereoselectivity (Scheme 25). In 2000, the same group reported that Sc(OTf)\textsubscript{3} could catalyze the aza-Henry reaction, improving both the yield and diastereoselectivity.\textsuperscript{77} In the following year, Qian and co-workers discovered Yb(O\textsubscript{i}Pr)\textsubscript{3} was an excellent catalyst for the aza-Henry reaction of nitromethane with sulfonylimines, affording β-nitro amines in 81–100% isolated yields.\textsuperscript{78}


1.2.1 Metal-Catalyzed Enantioselective Aza-Henry Reactions

The first catalytic enantioselective aza-Henry reaction was reported by Shibasaki and co-workers in 1999. The heterobimetallic complex (39) formed by Yb, K and BINOL in the ratio of 1:1:3 successfully catalyzed the nitromethane addition to \( N \)-phosphinoylimines 40, affording the aza-Henry adduct (41) with up to 91\% ee (Scheme 26).\(^7\)

Scheme 26. The First Enantioselective Aza-Henry Reaction and Proposed Structure of the Catalyst

However, one drawback of catalyst 39 is that it is not able to promote the reaction of imines with substituted nitroalkanes at low temperature. After changing the catalyst to \( \text{AlLi[}(R)-\text{binaphthoxide]}_2 \) (42), the Shibasaki group extended the scope of their aza-Henry reaction to a variety of aryl imines with substituted nitroalkanes, producing the aza-Henry adducts (43) with good diastereoselectivity (3:1 to 7:1 dr), but slightly lower enantioselectivity (60-83\% ee), favoring the \textit{anti} diastereomer (Scheme 27).\(^8\) This methodology was then applied in the syntheses of two biologically active compounds

ICI-199441 (44) and CP-99994 (45), which contain the chiral diamine moiety (Figure 5).\textsuperscript{81}

Another significant advancement in this area occurred in 2001 when Jørgensen and co-workers developed the catalytic asymmetric aza-Henry reaction of silyl nitronates 46 with α-imino esters 47 catalyzed by their copper(II)-bisoxazoline complex 48 (Scheme 28, eq 47).\textsuperscript{82} Excellent enantioselectivity and diastereoselectivity were obtained, as well as high yields. Immediately after this publication, the same group published a direct aza-Henry reaction in which an external base was used in addition to the slightly modified chiral copper(II)-bisoxazoline catalyst (49) (Scheme 28, eq 48).\textsuperscript{83} Avoiding preformation of the silyl nitronate nucleophile, direct nitroalkane addition to α-imino esters was


realized using Et₃N, providing valuable β-nitro-α-amino esters 50 in good to excellent enantioselectivity and diastereoselectivity.

Scheme 28

Following Jørgensen’s discovery, several other catalysts (Figure 6) have been reported for the asymmetric aza-Henry reactions of aldimines with nitromethane, including ’Bu-BOX-Cu(OTf)₂ complex 51 by Anderson,⁸⁴ a combination of (-)-N-methylephedrine (52) and Zn(OTf)₂ by Palomo,⁸⁵ dinuclear zinc catalyst 53 by Qian⁸⁶ and Trost⁸⁷ and an N,N’-dioxide(54)-Cu(OTf) complex by Feng (Figure 6).⁸⁸ Another similar catalyst 55-CuOTf was developed by Feng and co-workers for the first enantioselective aza-Henry reaction of nitromethane addition to ketimines (Scheme 29).⁸⁹ Although the yields were moderate, high enantioselectivity was obtained consistently with a range of aryl alkyl ketimines.

Most reported aza-Henry reactions with nitroalkanes as nucleophiles generated anti-diastereomers. However, Shibasaki and co-workers recently utilized a heterobimetallic Cu-Sm-Schiff base complex 56 to afford syn adducts as the only observed diastereomers with excellent enantioselectivity (Scheme 30). More recently, the same group developed a dinuclear Ni₂-Schiff complex 57 for the addition of substituted tert-butyl nitroacetate addition to N-Boc imines (Scheme 31). anti-α-Nitro-β-amino esters bearing α-quarternary center were obtained with high enantioselectivity and diastereoselectivity.

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1.2.2 Organocatalytic Enantioselective Aza-Henry Reactions

Rapid progress has also been made in the area of organocatalytic aza-Henry reactions since 2004. With their chiral thiourea catalyst (7), as described in section 1.1.1, Takemoto and co-workers demonstrated that nitromethane addition to phosphinoylimine 40 could deliver β-nitroamines 41 in up to 76% ee with up to 91% yield (Scheme 32, eq 49). The catalyst was proposed to be bifunctional, in the sense that the tertiary amine group deprotonated the nitroalkane, forming a nitronate, which then attacked the imine that was activated by the thiourea moiety in the catalyst via hydrogen bonding. In 2006, by using N-Boc aryl imines 61 as the substrates and the same catalyst 7, Takemoto and co-workers extended their aza-Henry reaction to include a broader scope of imines and

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nitroalkanes with high enantioselectivity and diastereoselectivity.\(^{93}\) The utility of the \(\beta\)-nitroamine product (58) was demonstrated by its reduction to \(\alpha\)-amino acid derivative 59 and transformation to vicinal diamine 60 by Nef reaction (Scheme 32).

**Scheme 32.** Aza-Henry Reaction with Takemoto’s Thiourea Catalyst and Demonstration of the Utility of the Aza-Henry Adduct

In 2005, Jacobsen and co-workers utilized their similar thiourea catalyst 62 for the aza-Henry reaction of \(N\)-Boc aryl imines 61 and nitroalkanes. *anti*-\(\beta\)-Nitroamines 63 were obtained with high enantioselectivity and diastereoselectivity in excellent yields (Scheme 33).\(^{94}\) With 2 equiv. of base, sterically hindered secondary nitroalkanes such as 2-nitropropane delivered the corresponding adduct with 92% ee in 87% yield.

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Since then, various chiral urea/thiourea catalysts (Figure 7) bearing different chiral backbones have been reported to catalyze the enantioselective and diastereoselective aza-Henry reaction, including 9a by Schaus,95 9b by Ricci,96 64 by Ellman,97 65 by Chang,98 66 by Zhou,99 67 by Chen,100 68 by Wang101 and 69 by Wulff.102

Scheme 33

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The asymmetric aza-Henry reaction catalyzed by chiral phosphoric acid 29g described in 1.1.3 was realized by Rueping and co-workers.\textsuperscript{103} Nitroalkane addition to $\alpha$-iminoester 70 provided $\beta$-nitro-$\alpha$-amino esters 71, a valuable precursor to $\alpha,\beta$-diamino esters, in good yields and excellent enantioselectivity (Scheme 34).

\textsuperscript{103} Rueping, M.; Antonchick, A. P. Org. Lett. 2008, 10, 1731.
Most reported asymmetric aza-Henry reactions utilized N-carbamoyl aryl imines as substrates, which are not sufficiently stable for long-time storage. That N-carbamoyl alkyl imines readily isomerize to the corresponding ene carbamates makes it an obstacle to isolate and use them in aza-Henry reactions. Herrera, Bernardi and co-workers reported the first asymmetric aza-Henry reaction using α-amido sulfones 72 as the substrates. \(^\text{104}\) Cinchona alkaloid-based phase-transfer catalyst 73 carried nitromethane addition to N-carbamoyl imines generated in situ under basic conditions (KOH), to afford β-nitroamines with high ee (Scheme 35). Palomo and co-workers also reported the same reaction, using the same catalyst, but with CsOH·H₂O as the additional base, and extended the scope to nitroethane addition. \(^\text{105}\)

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Around the same time that Takemoto published their thiourea-catalyzed aza-Henry reaction in 2004, the Johnston group developed a novel “chiral proton” catalyst, the protonated chiral bisamidine (H,Quin-BAM·HOTf, 74·HOTf), for the highly enantioselective aza-Henry reaction of N-Boc-aldimines 61 with nitromethane.106 When nitroethane was used as the nucleophile, anti-β-amino nitroalkanes 63 were obtained in high enantioselectivity and diastereoselectivity (Scheme 36). These developments established the foundation for the discoveries described in this dissertation.

Scheme 36.

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Chapter II.

Chiral Proton Catalysis: Asymmetric Synthesis of \( \alpha,\beta \)-Diamino Acid and \( \beta \)-Diamino Acid Derivatives

2.1. Aza-Henry Reaction/Reduction Sequence to Afford \( \alpha,\beta \)-Diamino Acid Derivatives

\( \alpha,\beta \)-Diamino acid derivatives have been found as important constituents in natural products demonstrating valuable biological properties. They have also been used as useful building blocks in replacing natural amino acids in synthetic peptides in the search for modifications of the biological activities and stabilities to peptidases.\(^{107}\) While classical resolution was traditionally used to approach enantiomerically pure \( \alpha,\beta \)-diamino acid derivatives, some novel catalytic asymmetric methods have emerged in recent years (Scheme 37), including glycine Schiff base addition to imines (approach a),\(^{108}\) dimerization of glycinates (approach b),\(^{109}\) nucleophilic synthetic equivalents of \( \text{CO}_2\text{R} \) addition to imines (approach c),\(^{110}\) olefin dimation of \( \alpha,\beta \)-unsaturated esters (approach


d)\textsuperscript{111} and electrophilic amination of enolates (approach e).\textsuperscript{112} Nucleophilic amination of serine (approach f),\textsuperscript{113} Curtius rearrangement of aspartic acid\textsuperscript{114} or Hofmann rearrangement of asparagine derivatives\textsuperscript{115} were also utilized occasionally to achieve $\beta$-unsubstituted $\alpha,\beta$-diamino acid derivatives.

\textbf{Scheme 37.} Synthetic Approaches toward $\alpha,\beta$-Diamino Acid Derivatives

\begin{footnotesize}


\end{footnotesize}
As discussed above, the Johnston group developed a novel chiral proton catalyst for the asymmetric aza-Henry reaction (Scheme 36). A 3-D $C_2$-symmetric protonated bis(amidine) complex was obtained by PCModel (Figure 8).

**Figure 8.** 3-D Views of BAM-Proton Complex Generated by PCModel

Chem 3D was used to place a representative $N$-Boc-aldimine into the binding pocket of the PCModel-minimized protonated BAM, ultimately arriving at the complex shown below (Figure 9).\(^{116}\) The front quinoline ring blocks the $Re$ face, leaving the $Si$ face more exposed for attack, which leads to the enantiomer observed in practice. From this model, it appeared that the substitution at the 6-position on the pyridine ring would be most beneficial in terms of distinguishing the two faces of attack by the nucleophile. Experimental data confirmed that the substitution at this position effectively shielded one face of the substrate from attack by the incoming nucleophile.\(^{116}\) The facial selectivity was greatest when using a quinoline ring as in H,Quin-BAM (74), so that both 5- and 6-positions of the pyridine ring are substituted, which translates to the highest enantioselectivity.

We sought the use of nitroacetic acid derivatives, since they could serve as masked amino acids. Nitroacetic acid derived nucleophiles have been utilized in a variety of transformations, but their use in enantioselective transformations was limited to only two recent cases that produce non-epimerizable nitroacetate derivatives at the time of our studies (Scheme 38). The challenge in using unsubstituted nitroacetates is the possibility of competitive product deprotonation.

Figure 9. Proposed Catalyst - Substrate Complex and Model for the Transition State


With the optimal conditions for nitroalkane pronucleophiles, we first examined commercially available ethyl α-nitroacetate as a nucleophile in the chiral proton catalyzed enantioselective aza-Henry reaction. Compared to the aza-Henry reaction with nitroalkanes which required the use of the nucleophile as a solvent, the reaction of imine \(61a\) with ethyl nitroacetate delivered adduct \(77\) using a single equivalent of the more acidic nucleophile when catalyzed by 10 mol\% H,Quin-BAM-HOTf (74·HOTf) in toluene at -20 °C, and in substantially shorter time (Scheme 39). The adduct was obtained in 75% yield with 80% ee, however, these results were contrasted by a leak of diastereoselectivity at the 1:1 level (Table 1, entry 1). Use of the larger tert-buty l α-nitroacetate nucleophile provided adduct \(78a\) in 80% yield with 84% ee and slightly higher dr (2:1) (Table 1, entry 2). Lowering the reaction temperature to -78 °C and decreasing the catalyst loading to 5 mol% maintained both the enantioselectivity and the reaction yield (Table 1, entry 4).
We discovered that if the crude reaction mixture was slowly warmed to room temperature and then filtered through a plug of silica gel, the diastereoselection would increase to 6:1 favoring the syn-diastereomer (Table 2, entry 1) by the selective epimerization at the α-carbon of the carbonyl group in the adduct. Catalyst loading of 4 mol% provided a similar level of enantioselectivity (85% ee) (Table 2, entry 2), while
lowering the catalyst loading to 3 mol% and 1 mol% dropped the ee value to 75% and 67%, respectively (Table 2, entries 3 and 4). The 6:1 diastereoselection was realized in all cases regardless of the difference in catalyst loading, which suggested that the catalyst has no effect on the diastereoselection after epimerization.

Table 2. Chiral Proton Catalyzed Aza-Henry reaction: Effect of Catalyst Loading

<table>
<thead>
<tr>
<th>entry</th>
<th>X</th>
<th>dr</th>
<th>%ee</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>syn</td>
<td>anti</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>6:1</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>6:1</td>
<td>85</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>6:1</td>
<td>75</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>6:1</td>
<td>67</td>
<td>68</td>
</tr>
</tbody>
</table>

*All reactions were 0.3 M in substrate and proceeded to conversion. *Diastereomer and enantiomer were measured using chiral stationary phase HPLC. *Isolated yield.

In order to obtain optically pure adduct syn-78a, we examined a series of solvents for recrystallization. The adduct (78a) dissolves readily in THF, CH2Cl2, CHCl3, DME, MeCN, MeNO2, benzene, xylene and ethylbenzene at room temperature, and therefore they were not the suitable solvents for recrystallization. The results obtained using other solvents are summarized in Table 3. The recrystallization performed in 20% EtOAc/Hex provided 99% ee but lower dr (Table 3, entry 1). A mixture of 10% iPrOAc/hex maintained, but did not improve the ee and dr after recrystallization (Table 3, entry 2). EtOH delivered high dr (54:1) but did not increase ee (Table 3, entry 3). In MeOH, iPrOH and nPrOH, retro-aza-Henry reaction occurred upon heating, which degraded the ee
considerably (Table 3, entries 4-6). All of the alkane solvents screened (heptane, octane, methyl cyclohexane and cyclohexane) provided high enrichment of one enantiomer, and among them, cyclohexane not only enhanced ee (>98%), but also increased the dr to >50:1. The masked diamino acid derivative (syn-78a) was obtained as a single enantiomer and diastereomer in 50% yield. The absolute configuration of optically pure syn-78a was secured by X-ray crystallography (Figure 10).

**Table 3. Stereoisomer Enrichment of the Aza-Henry Adduct by Recrystallization**

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>dr</th>
<th>%ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20% EtOAc/Hex</td>
<td>3:1</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>10% PrOAc/Hex</td>
<td>6:1</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>54:1</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>MeOH</td>
<td>6:1</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>PrOH</td>
<td>6:1</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>PrOH</td>
<td>3:1</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>heptane</td>
<td>6:1</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>octane</td>
<td>6:1</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>methylcyclohexane</td>
<td>7:1</td>
<td>98</td>
</tr>
<tr>
<td>10</td>
<td>cyclohexane</td>
<td>&gt;50:1</td>
<td>&gt;98</td>
</tr>
</tbody>
</table>

*Diastereomer and enantiomer ratios were measured using chiral stationary phase HPLC.

Examination of the solid state structure of syn-78a suggests that the thermodynamically-controlled epimerization favoring the syn-diastereomer reflects its ability to form an intramolecular H-bond from the carbamate N-H to the nitro oxygen (2.284 Å). The crystal structure features a gauche arrangement of the hydrogen bond donor and acceptor, as well as the nitro group and the aryl substituent. This arrangement also allows the ester group to orient *anti* to the aryl group (Figure 10). Indeed, the
importance of the intramolecular hydrogen bond to achieve 6:1 selectivity for the syn diastereomer was supported by the erosion of this ratio to 2:1 when the mixture was warmed to 50 °C in ethanol, a competitive hydrogen bond donor.

**Figure 10.** X-ray Structure and Newman Projection of Optically Pure syn-78a (most hydrogen atoms omitted for clarity)

However, the recrystallization of syn-78a to a single enantiomer and diastereomer was successfully performed only four times. In the trials afterwards, we were able to obtain syn-78a with >98% ee but with only 4:1-7:1 dr, reproducibly. Later, we discovered that the relatively high acidity of the hydrogen adjacent to the ester group led the syn diastereomer to epimerize on standing as a solid, returning to the thermodynamic ratio of 4:1 dr. Prootic solvents tend to accelerate the epimerization. For example, from its diastereomerically pure form, syn-78a reached a 4:1 mixture of diastereomers at room temperature in 2 hours in AcOH and 4 hours in ethanol (Table 4, entries 1 and 2). In nonpolar aprotic solvents, the epimerization also occurred, although more slowly. It took 24 hours for the diastereomerically pure syn-78a to reach a 4:1 dr mixture in CHCl₃, but took 8 days in cyclohexane (Table 4, entries 4 and 5). In all cases, the mixture eventually
converged to a 4:1 dr, therefore this is believed to reflect the thermodynamic equilibrium. Even as a crystalline solid, the epimerization occurred slowly (4 weeks to reach 7:1 dr). It should be noted that the configuration at the benzylic carbon did not change during the epimerization process, which indicated that no retro aza-Henry reaction was involved.

The nitro group can be viewed as a masked amine; thus, the amine functionalities are orthogonally protected, providing the opportunity for further chemoselective modifications. The utility of aza-Henry adduct 78 was demonstrated by the reduction of the nitro group to afford α,β-diamino acid derivatives. Various catalytic transfer hydrogenation methods were initially tested. Hydrogenation under a hydrogen atmosphere with Pt/C, PtO₂/C, Raney Ni, or Pd/C as the catalyst did not provide the desired amine (79a), but instead dechlorinated amine 80, in low yields (Table 5, entries 1-4). Using ammonium formate as the internal hydrogen source dramatically increased the yield to 80% (Table 5, entry 5), while using ammonium formate in conjunction with a hydrogen atmosphere afforded an even better yield of amine 80 (90%, Table 5, entry 6).

Table 4. Self-Epimerization of syn-78a in Various Solvents

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOH</td>
<td>2 h</td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>4 h</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>12 h</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>24 h</td>
</tr>
<tr>
<td>5</td>
<td>cyclohexane</td>
<td>8 d</td>
</tr>
</tbody>
</table>

*Diastereomer and enantiomer were measured using chiral stationary phase HPLC.

The nitro group can be viewed as a masked amine; thus, the amine functionalities are orthogonally protected, providing the opportunity for further chemoselective modifications. The utility of aza-Henry adduct 78 was demonstrated by the reduction of the nitro group to afford α,β-diamino acid derivatives. Various catalytic transfer hydrogenation methods were initially tested. Hydrogenation under a hydrogen atmosphere with Pt/C, PtO₂/C, Raney Ni, or Pd/C as the catalyst did not provide the desired amine (79a), but instead dechlorinated amine 80, in low yields (Table 5, entries 1-4). Using ammonium formate as the internal hydrogen source dramatically increased the yield to 80% (Table 5, entry 5), while using ammonium formate in conjunction with a hydrogen atmosphere afforded an even better yield of amine 80 (90%, Table 5, entry 6).
Dechlorination occurred concomitantly with reduction of the nitro group with all of the transfer hydrogenation methods that were surveyed.

The reduction of 78a by zinc in acetic acid prevented the unwanted dechlorination, producing the corresponding amine (79a) in 38% yield, but along with partially reduced hydroxyimine 81 in 40% yield (Scheme 40).

Table 5. Catalytic Transfer Hydrogenation of the Aza-Henry Adduct

<table>
<thead>
<tr>
<th>entry</th>
<th>condition</th>
<th>T (°C)</th>
<th>yield b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H2, 10% Pt/C, EtOH</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>H2, 10% PtO2/C, EtOH</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>H2, Raney Ni, EtOH</td>
<td>25</td>
<td>&lt;10</td>
</tr>
<tr>
<td>4</td>
<td>H2, 10% Pd/C, EtOH</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>10% Pd/C, HCOONH4, EtOH</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>H2, 10% Pd/C, HCOONH4, EtOH</td>
<td>40</td>
<td>90</td>
</tr>
</tbody>
</table>

* a All reactions were 0.1 M in substrate and proceeded to conversion. b Isolated yield.

Scheme 40

The combination of NaBH4 with transition metal salts such as cobalt(II),119,120 nickel(II),120, 121 copper(II),122 tin(II),123 and zirconium(IV)124 all exhibit enhanced

reducing ability as compared to NaBH$_4$ alone, and they have been utilized in the reduction of nitro groups, nitriles and oximes. When applied in the reduction of 78a, Cu(acac)$_2$/NaBH$_4$\textsuperscript{122} and ZrCl$_4$/NaBH$_4$\textsuperscript{124} did not deliver the desired amine (79a) in any appreciable amount (Table 6, entries 1 and 2). NiCl$_2$·6H$_2$O/NaBH$_4$\textsuperscript{121} provided amine 79a in 78% yield (Table 6, entry 3), along with a small amount of the dechlorination product (80). The best result was obtained using the combination of CoCl$_2$·6H$_2$O and NaBH$_4$,\textsuperscript{119} which selectively reduced the nitro group in 90% yield (Table 6, entry 4). Ni$_2$B and Co$_2$B were found to be the actual effective reagents generated when mixing NaBH$_4$ with NiCl$_2$·6H$_2$O and CoCl$_2$·6H$_2$O, respectively.\textsuperscript{120} Commercially available Ni$_2$B or Co$_2$B from Aldrich combined with NaBH$_4$, however, did not provide amine 79a (Table 6, entry 5 and 6). This is probably due to the particle size difference from that of the Ni$_2$B or Co$_2$B generated \textit{in situ}. We also tested CoCl$_2$/LiAlH$_4$ in THF, another powerful reducing system,\textsuperscript{125} but no reaction was observed.

\textbf{Table 6. Metal-salt Assisted Reduction of Nitro Group by NaBH$_4$}

\begin{center}
\begin{tabular}{c c c}
\hline
entry & metal salt & yield$^a$ \\
\hline
1 & Cu(acac)$_2$ & $<5$ \\
2 & ZrCl$_4$ & $<5$ \\
3 & NiCl$_2$·6H$_2$O & 78 \\
4 & CoCl$_2$·6H$_2$O & 50 \\
5 & Ni$_2$B & $<5$ \\
6 & Co$_2$B & $<5$ \\
\hline
\end{tabular}
\end{center}

$^a$ Isolated yield


The reduction of 78a by CoCl$_2$·6H$_2$O/NaBH$_4$ generated the highest yield, but normally with a slight drop in the diastereomeric purity. This is probably because of the heat generated in the reaction of NaBH$_4$ with the hydrate, thereby accelerating the epimerization of the $\alpha$-hydrogen of the ester. When CoCl$_2$·6H$_2$O and NaBH$_4$ were premixed in methanol, and then combined with the substrate 78a after the gas generation subsided, only a trace amount of the reduction product could be observed. Hydrogen gas was then bubbled through the reaction mixture overnight, but NMR of the crude mixture showed only 30% conversion. These results demonstrated that the internal hydrogen source was essential to the reduction. The combination of anhydrous CoCl$_2$ with NaBH$_4$ was eventually found to effectively carry out the reduction, without any erosion of dr or ee, providing 79a in 90% yield.

We then tested the recrystallization of amine 79a after the reduction. Only aliphatic alkanes were promising candidates since all other solvents readily dissolved the substrate. Hexanes provided the best result (syn-79a in stereochemically pure form in 45-53% overall yield). The opposite diastereomer anti-79a was isolated from the mother liquor by chromatography in >97% ee and 20:1 dr in 10% overall yield (Scheme 41). Stereochemically pure syn-79a can also be isolated by chromatography in 74% yield.
In the meantime, a variety of BAM ligands were synthesized to study the stereoselection of the aza-Henry reaction by chiral proton catalysis. The following \( C_2 \)-symmetrical BAM ligands \( 83-86 \), which provided a range of steric and electronic influences, were made from Pd(0)-catalyzed coupling of \((1R,2R)\)-cyclohexane-1,2-diamine \( 82 \) with corresponding chloropyridines or chlorobenzoquinoline (Scheme 42). As stated in Chapter 1, chiral ureas/thioureas have been utilized as Brønsted acid organocatalysts. Using this idea, we wanted to test if the structurally similar carbamate can also act as a hydrogen bond donor and effectively catalyze the aza-Henry reaction. Thus, \( 88 \) was synthesized via coupling of mono-\( H,\text{Quin-BAM} \) \( 87 \) with ethyl chloroformate (Scheme 43).

![Scheme 41](image-url)
With the new catalysts in hand, the nitroacetate addition to imine \(61a\) was revisited. Enantioenrichment values were measured after aza-Henry adducts \(78a\) were reduced to afford \(\alpha,\beta\)-diamino acid derivatives \(79a\). The results of the catalyst screen are summarized in Table 1. As mentioned previously, H,Quin-BAM·HOTf (\(74\cdot\text{HOTf}\), Table 7, entry 1) gave 85% ee of \(78a\). No enantioselectivity was obtained when \(83\cdot\text{HOTf}\) and \(84\cdot\text{HOTf}\) were used (Table 7, entries 2 and 3). Catalyst \(85\cdot\text{HOTf}\) (Table 7, entry 4) gave a slightly lower ee than H,Quin-BAM·HOTf. Catalyst \(86\cdot\text{HOTf}\) promoted the hydrolysis of the imine (\(61a\)) (Table 7, entry 5), as did catalyst \(88\cdot\text{HOTf}\) (Table 7, entry 6). When free base \(88\) was used instead of its protonated counterpart, diamino ester \(79a\) was obtained with only moderate enantioselection (56%, Table 7, entry 7). The dr of 2-3:1 was
observed consistently in the catalyst screen study, which supports the notion that the catalysts have no effect on the diastereoselection after epimerization.

We hypothesized that the nitroacetate addition to imine would observe the same trend in the transition state (Figure 9) as that in the nitroalkane addition, that the substitution on the 6-position of the pyridine ring of the BAM ligands would effectively shield one face of the substrate from attack by the incoming nucleophile. On this basis, we synthesized the following unsymmetrical BAM ligands 89-93 from Pd(0)-catalyzed coupling of mono-H,Quin-BAM (87) with the corresponding halopyridines (Scheme 44).

It appeared that the steric hindrance of the group on the 6-position of the pyridine ring did have a significant effect on the enantioselectivity (Table 8). A clear trend was observed from catalyst 90·HOTf to catalyst 93·HOTf, that the catalysts bearing bulkier substitution tended to provide higher ee, and the catalyst bearing the large anthracene group (93·HOTf) provided the best enantioselectivity (93% ee, Table 8, entry 5).

Table 7. Chiral Proton Catalyzed Additions of Nitroacetate to Imines: Effect of Ligand Structure

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>%ee&lt;sup&gt;b&lt;/sup&gt; of 79a</th>
</tr>
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<tr>
<td>1</td>
<td>74·HOTf</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>83·HOTf</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>84·HOTf</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>85·HOTf</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>86·HOTf</td>
<td>&lt;c</td>
</tr>
<tr>
<td>6</td>
<td>88·HOTf</td>
<td>&lt;c</td>
</tr>
<tr>
<td>7</td>
<td>88</td>
<td>56</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions were 0.30 M in substrate and proceeded to complete conversion. <sup>b</sup>Diastereomer and enantionmer ratios were measured using chiral stationary phase HPLC. <sup>c</sup>No aza-Henry adduct 78a was obtained.
Scheme 44. Synthesis of Unsymmetrical BAM Ligands

Table 8. Chiral Proton Catalyzed Additions of Nitroacetate to Imines: Effect of Ligand Structure

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>%ee of 79a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>89-HOTf</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>90-HOTf</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>91-HOTf</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>92-HOTf</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>93-HOTf</td>
<td>93</td>
</tr>
</tbody>
</table>

*All reactions were 0.30 M in substrate and proceeded to complete conversion. *Enantiomer and enantiomer ratios were measured using chiral stationary phase HPLC.
A comparison of H,Quin(6(9-Anth)2Pyr)-BAM·HOTf (93·HOTf) and H,Quin-BAM·HOTf (74·HOTf) was performed using several imine substrates. Better enantioselection (generally 10-20% ee higher) was obtained for all substrates using ligand 93 which contains the bulkier anthracene group at the 6-position of the pyridine ring (Table 9).

Table 9. Chiral Proton Catalyzed Additions of Nitroacetate to Imines: Ligand Comparison

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>74·HOTf</th>
<th>93·HOTf</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>83</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>p-F</td>
<td>67</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>p-Cl</td>
<td>86</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>p-Me</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>o-CF3</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>Ar=1-naphthyl</td>
<td>62</td>
<td>83</td>
</tr>
</tbody>
</table>

*All reactions were 0.30 M in substrate and proceeded to complete conversion. Enantiomeric and enantiomeric ratios of 78 were measured using chiral stationary phase HPLC.*

A more exciting discovery was that H,Quin(6(9-Anth)2Pyr)-BAM·HOTf (93·HOTf) not only provided higher ee but also higher dr for aza-Henry adduct 78 favoring the anti-diastereomer, as indicated by $^1$H NMR. Direct reduction of adduct 78 (without purification) in the same pot at 0 °C and remeasurement of the stereoisomer ratios provided values consistent with full conservation of dr and ee for amine 79 (Scheme 45). The use of the CoCl$_2$/NaBH$_4$ reducing system is rather important in this context, as it effects the fast reduction of the adducts without epimerization at the $\alpha$-position.
This aza-Henry addition-reduction sequence was then applied to a broader scope of imine substrates. The general protocol to form the desired N-Boc aldimines (61) is via the elimination of the sulfonic acid from the Boc-protected α-amido sulfones (94), which are derived from the corresponding aldehydes and tert-butyl carbamate (Scheme 46).126

Scheme 46. The General Protocol for the Synthesis of N-Boc Aldimines 61

For all the imines that were tested bearing diverse electronic properties and substitution positions, the corresponding anti-α,β-diamino acid derivatives anti-79 were consistently obtained in good yields (70-93%, two steps) along with high enantioselectivity (84-95% ee) (Table 10).127 Moderate to good diastereoselectivity (5:1 to 11:1) was observed for the adducts and conserved after the nitro reduction, as indicated by the measurement of dr of adduct 78 by 1H NMR and dr of amine 79 by HPLC or GC.

The aza-Henry addition using nitroalkanes and nitro acetates as the nucleophile both generated *anti*-diastereomers. This indicates that the chiral proton catalysts play an important role in determining diastereoselection (Figure 11). The nitro group of the nucleophile and the imine nitrogen could both have possible hydrogen bonding interaction with the chiral proton catalysts. The *syn*-diastereomer might be disfavored by possible repulsive interactions between the carbamate Boc group and the alkyl (or ester) group on the nucleophile.

### Table 10. Chiral Proton Catalyzed Asymmetric Synthesis of α,β-Diamino Acid Derivatives: Imine Scope

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar</th>
<th>dr&lt;sup&gt;b&lt;/sup&gt;</th>
<th>dr&lt;sup&gt;c&lt;/sup&gt;</th>
<th>%ee&lt;sup&gt;d&lt;/sup&gt;</th>
<th>yield&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pCl</td>
<td>5:1</td>
<td>5:1</td>
<td>95</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>pAcO</td>
<td>11:1</td>
<td>11:1</td>
<td>89</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>2-Np</td>
<td>12:1</td>
<td>11:1</td>
<td>91</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>pF</td>
<td>-</td>
<td>7:1</td>
<td>93</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>pMe</td>
<td>6:1</td>
<td>6:1</td>
<td>95</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>pCF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>7:1</td>
<td>7:1</td>
<td>88</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>mMe</td>
<td>5:1</td>
<td>5:1</td>
<td>84</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>mPhO</td>
<td>6:1</td>
<td>6:1</td>
<td>87</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>pCl</td>
<td>10.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>10.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>87</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>pMeOAc</td>
<td>8:1</td>
<td>8:1</td>
<td>95</td>
<td>84</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were 0.30 M in substrate and proceeded to complete conversion.

<sup>b</sup> Diastereomer ratios were measured by 1H NMR (a milliliter measurement was not possible for the addition product for entry 4). Enantiomer ratios were measured using chiral stationary phase HPLC. See Experimental Section for complete details.

<sup>c</sup> Isolated yield (two steps).

<sup>d</sup> Measured by GC.
While H,Quin-BAM-HOTf (74·HOTf) provided the nitroalkane addition adducts with high anti-diastereoselection, this preference was not observed in the nitroacetate addition. This might result from a competition between the ester and the nitro group in the nucleophile to establish a hydrogen bonding interaction with the catalyst (Figure 12). Thus the sterically more hindered catalyst H,Quin(6(9)Anth)2Pyr)-BAM-HOTf (93·HOTf) would discourage the hydrogen bonding interaction from the bulky t-butyl ester and therefore favor the anti-diastereomer.

![Figure 11. Newmann Projections for the Aza-Henry Addition using Nitroalkanes and Nitroacetates: Rationale for anti-Diastereoselectivity](image)

![Figure 12. Possible Competitive Hydrogen Bonding from the Ester and the Nitro Group](image)

It is evident that the anti-diastereoselection here represents the kinetic selectivity; however, if the adducts were not directly reduced at 0 °C, thermodynamically-controlled epimerization to the syn-diastereomers was observed, and silica gel was found to facilitate this process. For example, stirring addition product 78a (5:1 dr, anti:syn) with
silica gel at room temperature, followed by chromatography provided a viscous oil, which then slowly crystallized to a solid whose dr was measured after reduction to be 6:1 (syn:anti) (Scheme 47). Analysis of the syn-diastereomer established its enantiomeric ratio to be identical to its anti-precursor, thereby indicating that the benzylic amine carbon possesses the same configuration in both diastereomers and with the same level of enantioselection. The hypothesis is that during the concentration process, when the major diastereomer gradually crystallized out from the mother liquor, the minor diastereomer in the mother liquor slowly epimerized to the opposite diastereomer, which increased the dr of the crystals.

As summarized in Table 11, the post-addition epimerization occurred to all the substrates, furnishing a general protocol for asymmetric synthesis of syn-\(\alpha,\beta\)-diamino acid derivatives 79. For the substrates bearing different electronic properties and substitution at different positions on the aromatic ring, good yields (52-86% yield, two steps) were consistently obtained, and high enantioselection (88-95% ee) was conserved.
after epimerization and reduction. The thermodynamically-controlled diastereoselection ranged from 3.5:1 (Table 11, entry 7) to 12:1 (Table 11, entry 8).

**Table 11. Post-addition Epimerization Followed by Reduction: Synthesis of syn-α,β-Diamino Acid Derivatives**

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate (R=)</th>
<th>dr</th>
<th>%ee</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>6:1</td>
<td>91</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>6:1</td>
<td>93</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>4.5:1</td>
<td>90</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>5:1</td>
<td>89</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>OAc</td>
<td>8:1</td>
<td>92</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>CF₃</td>
<td>5:1</td>
<td>95</td>
<td>77</td>
</tr>
<tr>
<td>7</td>
<td>Br</td>
<td>3.4:1</td>
<td>95</td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td>Br</td>
<td>12:1</td>
<td>92</td>
<td>52</td>
</tr>
</tbody>
</table>

*All reactions were conducted in substrate and proceeded to completion. %ee and enantiomer ratios were measured using chiral stationary phase HPLC. Isolated yield after two steps.

In summary, the addition of nitroacetates as glycine equivalents to N-Boc aldimes catalyzed by H,Quin(6,9-Anth)₂Pyr)-BAM·HOTf (93-HOTf) followed by direct one-pot nitro reduction afforded *anti*-α,β-diamino acid derivatives with high enantioselectivity and diastereoselectivity. If the protocol of aza-Henry addition, slow crystallization/epimerization, then reduction was used, *syn*-α,β-diamino acid derivatives could also be obtained with the same high ee and good dr. Therefore the methodology is amenable towards forming either the *syn* or *anti* products selectively and provides a convenient preparation of *vic*-diamines and α,β-diamino acids. The products are also orthogonally protected for subsequent amide bond formation.
2.2. Aza-Henry Reaction/Denitration Sequence to Afford β-Amino Acid Derivatives

β-Amino acids are constituents of countless natural products, including several contemporary chemotherapeutics such as Taxol, and are also important building blocks for the synthesis of pharmaceutical targets. α-Unsubstituted β-amino acids, formally derived from an ‘acetate’ Mannich addition, are also expressed in natural products (Figure 13), including edeines A and B, streptothricin F, C-1027, viomycin and (+)-chaenorhine. These occurrences have stimulated the development of methods leading to the β-amino acid motif, especially in an enantioenriched form. Traditionally, preparations of β-amino acids predominantly relied on classical resolution of racemic β-amino acids. Recent preparations of α-unsubstituted β-amino acids include the homologation of natural α-amino acids via the Arndt-Eistert reaction, auxiliary-based methods such as the addition of chiral nonracemic amines to unsaturated

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esters, and enolate addition to chiral nonracemic imines. Enantioselective, catalytic approaches have also been developed, including hydrogenation of β-amino acrylates, two step procedures involving enol silane formation and catalyzed addition, and a three-step sequence involving Mannich addition of a malonate, hydrolysis and decarboxylation (Scheme 48). Beyond β-amino acid synthesis, the general study of Mannich additions for the synthesis of chiral amines holds historic and continuing importance in synthesis.

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Figure 13. Natural Products Containing β-Amino Acid Subunit

Scheme 48. Approaches towards Enantioenriched β-Amino Acids

As discussed in the first chapter, enantioselective Mannich reactions involving nitroalkanes have been subject to intensive study over the past decade. The Johnston group and others have also successfully employed α-nitro esters in these additions, but
the sole focus has resided in the value of the nitro group as an amine progenitor. We naturally wondered whether the nitro group, which is critical for activation and stereocontrol in the addition reaction, could be readily removed as part of a two step procedure leading ultimately to the α-unsubstituted β-amino acid substructure (Figure 14).

The strategy bears analogy to malonate Mannich addition/hydrolysis/decarboxylation, but differs by the potentially mild, pH-neutral conditions typical of stannane-mediated denitration.

Figure 14. General design of an acetate Mannich equivalent

The feasibility of the denitration step in this setting was first examined on β-amino-α-nitro esters 78 made from NEt₃ catalyzed aza-Henry reactions of α-nitro-tert-butyl acetate with N-Boc aldimines. That these substrates were racemates was of no consequence at this stage.

As shown in Table 12, the use of standard reagents and stannyl radical-generating conditions provided the desired β-amino ester products 95 in high isolated yield. Not unexpectedly, a variety of functionalized aryl groups furnished the denitrated products (95a-j) in good to excellent yield (Table 12, entries 1-10). Chlorinated (95a) and Fluorinated (95c) (Table 12, entries 1 & 3) substrates are tolerated, as well as the

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The experiments in Table 12 merely confirmed the expectation that the denitration is possible, but did not prognosticate the feasibility of the overall strategy with regard to enantioenriched product formation. In a chiral proton-catalyzed aza-Henry reaction (Scheme 49), α-nitro esters 78e are obtained as a thermodynamic ratio of 2:1 diastereomers at room temperature. The enantiomeric ratio for each diastereomer, however, is at the 94:6 level (88% ee each). We were gratified to find that reductive denitration of this mixture resulted in convergence to the desired amine with identical enantiomeric enrichment (88% ee). This finding indicated that stereocontrol to establish the configuration at the benzylic carbon proceeds with the same azomethine facial selectivity regardless of the diastereomer produced. Furthermore, the selectivity is at the

\[ \text{Table 12. Reductive Denitration of } \alpha\text{-Nitro Esters} \]

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( p\text{ClC}_2\text{H}_4 )</td>
<td>a 73</td>
</tr>
<tr>
<td>2</td>
<td>( p\text{MeOC}_2\text{H}_4 )</td>
<td>b 90</td>
</tr>
<tr>
<td>3</td>
<td>( p\text{FC}_2\text{H}_4 )</td>
<td>c 97</td>
</tr>
<tr>
<td>4</td>
<td>( m\text{MeC}_2\text{H}_4 )</td>
<td>d 90</td>
</tr>
<tr>
<td>5</td>
<td>( m\text{MeC}_2\text{H}_4 )</td>
<td>e 91</td>
</tr>
<tr>
<td>6</td>
<td>( 2\text{Np} )</td>
<td>f 83</td>
</tr>
<tr>
<td>7</td>
<td>( m\text{PhOC}_2\text{H}_4 )</td>
<td>g 83</td>
</tr>
<tr>
<td>8</td>
<td>( p\text{PhC}_2\text{H}_4 )</td>
<td>h 89</td>
</tr>
<tr>
<td>9</td>
<td>( p\text{AcOC}_2\text{H}_4 )</td>
<td>i 82</td>
</tr>
<tr>
<td>10</td>
<td>( 2\text{C}_2\text{H}_2\text{O} )</td>
<td>j 93</td>
</tr>
<tr>
<td>11</td>
<td>( 3\text{C}_2\text{H}_2\text{S} )</td>
<td>k 0</td>
</tr>
</tbody>
</table>

\( ^a\text{All reactions were }0.10\text{ M in substrate and proceeded to complete conversion.} \)
\( ^b\text{Isolated yields.} \)
same level in each case. Had the minor diastereomer formed with $R$ configurational selectivity and 88% ee, the product in Scheme 49 would have been isolated in 29% ee.

Scheme 49.

We investigated the scope of this overall approach as a two step protocol as outlined in Table 13. Optimized conditions for the aza-Henry step provided (S)-95e with slightly improved selectivity after reductive denitration (94% ee and 80% overall yield). The $\beta$-amino tyrosine derivative (S)-95b was produced in 85% ee and 88% yield overall using an identical protocol (Table 13, entry 2). Substitutions of the aromatic ring, varying both electronically and by position, provided the derived $\beta$-amino acids with good enantioselectivity and overall yield: (87-98% ee, 68-87% overall yield, Table 13, entries 3-9). Furthermore, an electron rich heterocycle such as furyl $\beta$-amino acid (S)-95j was obtained in 85% ee and 64% yield overall (Table 13, entry 10).
Among the products in Table 13, protected β-tyrosines are of particular note as they can be structural elements of natural products. We targeted one additional β-tyrosine derivative particularly for its relevance to natural product synthesis. (+)-Chaenorhine (97) is a macrocyclic spermine alkaloid isolated from *C. origanifolium* in which a β-amino acid is present as a key constituent of the macrocyclic core structure (Scheme 50).135 Wasserman has reported the only total synthesis of record, which provided access to the racemic chaenorhine.144

Our aza-Henry/denitration protocol was applied in the synthesis of the key β-amino acid (96) of (+)-chaenorhine (97). Addition of α-nitro tert-butyl acetate to imine 61l, followed by denitration, produced β-amino ester 95l in 88% ee and 75% yield overall, while using α-nitro methyl acetate resulted in slightly diminished enantiomeric excess (98, 72% ee) (Scheme 50). Thus, it was necessary to convert tert-butyl ester 95l to

---

Table 13. A Catalytic Asymmetric Acetate Mannich Reaction in Two Steps

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar</th>
<th>ee</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhClC₆H₄</td>
<td>a</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>p-MeOC₆H₄</td>
<td>b</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>p-FClC₆H₄</td>
<td>c</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>m-MeC₆H₄</td>
<td>d</td>
<td>87</td>
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<tr>
<td>5</td>
<td>p-MeC₆H₄</td>
<td>e</td>
<td>94</td>
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<td>6</td>
<td>t-Pr</td>
<td>f</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>p-FClC₆H₄</td>
<td>g</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>p-FClC₆H₄</td>
<td>h</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>p-NO₂C₆H₄</td>
<td>i</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>t-C₆H₅OH</td>
<td>j</td>
<td>86</td>
</tr>
</tbody>
</table>

*a* All reactions were 0.30 M (step 1) and 0.10 M (step 2) in substrate and proceeded to complete conversion.

---

Wasserman’s intermediate methyl ester 96. Direct transesterification under basic conditions (NaOMe in MeOH or DMSO) or neutral conditions (InCl$_3$ or Bu$_3$SnO in MeOH) was unsuccessful. Alternatively, methanolysis under acidic conditions and selective reprotection of the free amine then furnished the Wasserman β-amino ester intermediate 96 in 85% yield (two steps), but in an enantioenriched form as the $S$ enantiomer.

Scheme 50. Enantioselective Synthesis of Wasserman’s Chaenorhine Protected β-Amino Acid Intermediate

As a representative example, we examined the protocol developed by Fu$^{147}$ which employs a substoichiometric amount of stannane, in conjunction with a stoichiometric silane (Scheme 51). In our hands, this method worked well to provide 95a in 70%

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isolated yield (two steps), requiring only a longer reaction time when compared to the use of stannane alone. Again, no loss in enantiomeric enrichment was observed, as 95a was delivered in 97% ee (c.f. Table 13, entry 1).

Scheme 51.

In summary, the enantioselective synthesis of β-phenyl alanine derivatives using a two step procedure has been developed. The successful application of this strategy is in large part due to the ability of chiral proton catalyst 93•HOTf to provide each intermediate α-nitro ester diastereomer with high enantioselectivity and consistent configuration at the benzylic amine carbon. Convergence of these diastereomers to enantioenriched β-amino ester products is therefore possible by stannyl radical-mediated denitration. The Mannich addition/denitration protocol can be considered an equivalent to the analogous addition/decarboxylation sequence involving β-diesters. Whereas the latter requires ester to carboxylic acid conversion under either acidic or basic conditions, the free radical conditions used here for denitration are considered pH-neutral – in the present work, for example, the acetate in 95i/l was retained. The practitioner can now choose among this range of possibilities. Moreover, the lower molecular weight of the nitro group compared to an ester might render it more attractive when employed as a

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disposable functional group. The utility of the strategy was successfully demonstrated in the application to the synthesis of the β-amino acid component of (+)-chaenorhine, which should now be accessible in an enantioenriched form following the synthesis of Wasserman.
Chapter III

Umpolung Amide Synthesis

3.1. Background

Nature achieves great structural diversity in protein synthesis through the rather straightforward condensation of amino acids. Large and complex, yet functionally precise proteins are formed in this manner from a remarkably small number of naturally occurring amino acids. The formation of the amide bond is the strategic lynchpin, one that is often mirrored in the laboratory through condensative methods for the preparation of amides and peptides. Without the assistance from enzymes, chemists resort to well-designed coupling reagents (Figure 15), including chloroformates, carbodiimides such as DCC (99), uronium salts such as HATU (100) and phosphonium salts such as PyBOP (101), acid halogenating reagents such as TFFH (102) and many more. Activated esters or acid halides are generated as the reactive intermediate to lower the energy barrier of the condensative reaction. Additives such as DMAP (103) or HOBT (104) are often necessary in order to enhance the reaction rate and/or suppress racemization (Figure 16). Many of the coupling reagents are expensive, toxic or in some cases shock-sensitive and the use of them in superstoichiometric amounts also contributes considerably to the waste stream.

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The otherwise solid foundation of amide bond formation using coupling reagents often weakens as the size of the target increases, or when the steric, functional and stereochemical complexity places a greater demand on the condensative acyl carbon-nitrogen bond forming reaction. For example, the use of disubstituted amines, aryl glycines, or peptidic amine/carboxylic acid combinations are often met with low conversion and/or epimerization of the carboxylic acid.

In addition to solid phase peptide synthesis which often utilizes reagent excess to drive the condensation to completion,\textsuperscript{150} alternatives to conventional amide synthesis have emerged recently to address the practical challenges, including highly innovative approaches (Scheme 52)\textsuperscript{151} such as native chemical ligation,\textsuperscript{152} Staudinger ligation,\textsuperscript{153}


\textsuperscript{151} Bode, J. W. Curr. Opin. Drug Discovery Dev. 2006, 9, 765.

hydrative amide synthesis through alkyne-azide coupling,\textsuperscript{154} oxidative amidation of alcohols,\textsuperscript{155} aldehydes,\textsuperscript{156} or alkynes,\textsuperscript{157} and ketoacid-hydroxylamine ligation,\textsuperscript{158} among others.\textsuperscript{159}

\textbf{Scheme 52.} Selected Recent Innovative Amide Bond Formation Methods

With the rapid development of asymmetric Henry reactions,\textsuperscript{160} aza-Henry reactions\textsuperscript{161} and Michael additions to nitroalkenes\textsuperscript{162} in recent years, the population and

structural diversity of nitroalkanes are expanding at a rapid pace. We wondered whether a new amide synthesis could be discovered that utilizes the same amine feedstock as condensative amide synthesis, but explores new chemical space for the acyl donor through the implementation of nitroalkanes (Scheme 53).

Scheme 53.

3.2. Umpolung Amide Synthesis: Halonium-Promoted Bromonitroalkane

Amine Coupling

Our study of the basic bond forming reaction began with the hypothesis that an α-bromo nitroalkane (e.g. 107a) might provide the proper oxidation state for coupling to an amine. This basic design was guided by the knowledge that the nonbrominated parent of 107a, nitroalkane 106 is readily converted to the corresponding aldehyde using the Nef reaction in a two-step sequence involving nitronate formation (NaOMe, MeOH), followed by its treatment with aqueous acid (H₂SO₄, H₂O) (Scheme 54). An aza-Nef reaction was proposed by quenching nitronate 108 with more nucleophilic amines instead of water, which is of less nucleophilicity. The inclusion of water (3:1 THF:H₂O = 93

See Chapter 1 for a review and discussion.


equivalents) was based on the perceived need to hydrolyze the putative tetrahedral intermediate (109) to form the amide product (Scheme 54).

**Scheme 54. Nef Reaction and Proposed Aza-Nef Reaction**

By simply mixing α-bromo nitroalkane 107a with secondary amine 111, a trace amount of the desired amide (110) could be identified after 10 days at room temperature (Scheme 55 and Table 15, entry 1). Alongside this small amount of product, the formation of debrominated nitroalkane 106 was detected. This observation led to the hypothesis that an N-haloamine, formed through bromonium transfer from 107a to amine 111, might be a key intermediate in the desired transformation. Bromonitroalkane might then undergo electrophilic amination with the N-haloamine to form the putative tetrahedral intermediate.
N-Haloamines,\textsuperscript{165} formed by direct halogenation of amines, have been extensively utilized for Hoffman-Löffler-Freytag reaction,\textsuperscript{166} which contrasted their limited applications in electrophilic amination.\textsuperscript{167} Coleman and co-workers reported that monochloroammonia and monobromoammonia reacted with Grignard reagents to give primary amines in moderate to good yield (57-85\% yield for NH\textsubscript{2}Cl and 29-63\% yield for NH\textsubscript{2}Br, Scheme 56).\textsuperscript{168} The reaction occurs in an S\textsubscript{N}2 fashion and X\textsuperscript{-} acts as a leaving group. Since nitrogen exhibits an electronegativity comparable to the halogens, the N-haloamine functionality can have ambident character. A common competing reaction is a similar S\textsubscript{N}2 reaction occurring at the X site and NH\textsubscript{2}\textsuperscript{-} acts as the leaving group, which leads to the formation of alkyl halide and ammonia by-product (Scheme 57). The Coleman group later used N-chloro alkyl amines in the amination of Grignard reagents. The major products were primary amines from the corresponding N-chloro alkyl amines, and the electrophilic amination product secondary amines were isolated in low yields, which also reflected that Grignard reagents did not attack nitrogen selectively (Scheme


Recently, N-chloro alkyl amines 112 were utilized together with aryl Grignard reagents to prepare tertiary anilines 113 in moderate to good yields (Scheme 59).\textsuperscript{170}

\section*{Scheme 56.}
\[
\text{RMgX + NH}_2X' \xrightarrow{\text{Et}_2O} \text{RNH}_2 \quad \text{X=Cl, Br, I} \quad \text{X'=Cl, Br}
\]

\section*{Scheme 57.}
\[
\text{RMgX + NH}_2Cl \quad \xrightarrow{\text{HCl, H}_2\text{O}} \text{RNH}_2 + \text{MgCl} \quad \text{X=Cl, Br, I}
\]

\section*{Scheme 58.}
\[
\text{PhCH}_2\text{MgCl} + \text{CH}_2\text{NHCl} \xrightarrow{\text{Et}_2O, 5^\circ C} \text{PhCH}_2\text{NHCH}_3 + \text{CH}_3\text{NH}_2 \quad (14\%) \quad (70\%)
\]

\section*{Scheme 59.}
\[
\begin{array}{c}
\text{Ar}^1\text{N}^1\text{R}^1 \quad \text{Ar}^2\text{MgCl} \quad \text{Ar}^2\text{N}^2\text{R}^2 \\
\text{112} \quad \text{THF, -45}^\circ C \quad (33-73\%) \quad \text{113}
\end{array}
\]

Organoboranes, generated from the hydroboration of olefins, were reported to react with N-chloroamine to afford primary amines 114 in moderate yields (Scheme 60).\textsuperscript{171} Organolithium reagents\textsuperscript{172,173} and organozinc reagents\textsuperscript{172} have also been reported for the electrophilic amination of carbanions (Scheme 62, pathway b), although they were proved to be less useful than Grignard reagents,\textsuperscript{167} with the exception that in a recent report, Ni(0) catalyzed the reaction of diarylzinc reagents with N,N-dialkyl-N-

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\textsuperscript{170} Sinha, P.; Knochel, P. \textit{Synlett} \textbf{2006}, 3304.
chloroamines 115 to afford tertiary anilines 116 in high yields (Scheme 61). Electrophilic amination of enolates using N-haloamine was reported in a few cases as well, with the focus on the intermolecular version to afford nitrogen-containing heterocycles. All these protocols applied the reactants of reversed polarity to conventional nucleophilic amination (Scheme 62, pathway a), which represents an “umpolung” strategy in the C-N bond formation (Scheme 62, pathway b).

Scheme 60.

\[
\begin{align*}
\text{R}^1 \text{R}^2 & \xrightarrow{\text{B}_2\text{H}_6, \text{THF}} \text{aq. NaOH} \\
& \xrightarrow{\text{then NH}_2\text{Cl (8.5-58\%)} } \text{R}^1 \text{R}^2 \text{NH}_2
\end{align*}
\]

Scheme 61

\[
\begin{align*}
\text{Cl} & \xrightarrow{\text{Ph}_2\text{Zn, 5 molar\% Ni(COD)$_2$, 10 molar\% bipyridine}} \xrightarrow{\text{DMA/TFA, 0 °C (90\%)} } \text{Bu}^1 \text{Bu}
\end{align*}
\]

Scheme 62.

\[
\begin{align*}
\text{nucleophilic amination} & : \text{RNH}_2 + \text{RX} \\
\text{electrophilic amination} & : \text{RM} + \text{RNHX} \\
\text{M=Mg, Li, Zn, B} & \xrightarrow{\text{a}} \text{RRNH}
\end{align*}
\]

\[
\begin{align*}
\text{electrophilic component} & \quad \text{nucleophilic component}
\end{align*}
\]

Considering N-haloamines as a possible key intermediate in our amide bond formation (Table 14, entry 1), we therefore examined the action of various halonium sources as additives. N-chloro succinimide (NCS) and N-bromo succinimide (NBS) did improve the reaction conversion and isolated yield (Table 14, entries 2 and 3). Iodonium sources (N-iodo succinimide (NIS) and I₂) provided higher yields and NIS proved to be the best (61% yield, Table 14, entry 5 and Table 15, entry 2), most likely because iodide is a better leaving group than chloride or bromide in the electrophilic amination step involving the N-haloamine. Koser’s reagent (117) also delivered the amide product, although with modest yield (32%, Table 14, entry 7).

**Table 14. Bromonitroalkane Amine Coupling: Screen of Halonium Additives**

<table>
<thead>
<tr>
<th>entry</th>
<th>X⁺ additive</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>NCS</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>NBS</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>Br₂</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>NIS</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>I₂</td>
<td>48</td>
</tr>
<tr>
<td>⁷</td>
<td>OTs⁺</td>
<td>32</td>
</tr>
</tbody>
</table>

*Reactions employed 1 equivalent of bromonitroalkane 107a and 2 equivalents rac-111, with amine added as the final reagent at 25 °C.*

We initiated a spectroscopic study of the putative N-haloamine intermediate as illustrated in Figure 17. The addition of NIS (b, Figure 17) to α-methyl benzylamine (a, Figure 17) resulted in the complete conversion to two sets of new product peaks (c, Figure 17). The shift of NIS methylene protons from 3.03 ppm to 2.80 ppm indicated...
complete iodine transfer from NIS to form succinimide. Iodination of the amine produced two sets of peaks as indicated by a shift of the methyl doublet from 1.40 ppm to 1.45 and 1.50 ppm. The amine methine also shifted from a single quartet at 4.13 ppm to quartets at 4.10 and 3.78 ppm. Integration of these quartets, as well as the methyl doublets, indicated a 1:1 ratio. The production of two forms of the \( N \)-iodo \( \alpha \)-methyl benzylamine was unexpected, as i) the use of elemental iodine forms a single product by NMR (d, Figure 17) and ii) treatment of achiral benzyl amine with NIS results in a single iodoamine by NMR as well (not shown).
Figure 17. $^1$H NMR (400 MHz, CDCl$_3$, 25 °C) of a) $\alpha$-methyl benzyl amine, b) $N$-iodo succinimide (NIS) and reaction mixtures resulting from the combination of $\alpha$-methyl benzyl amine and c) NIS and d) iodine.
Figure 18. $^1$H NMR (400 MHz, CDCl$_3$, 25 °C) of a) reaction mixture resulting from the combination of $\alpha$-methyl benzyl amine and N-iodo succinimide (NIS), its b) dilution, and addition to this solution: c) 5% DMSO and d) 10% DMSO.
Figure 19. $^1$H NMR (400 MHz, CDCl$_3$, 25 °C) of a) $\alpha$-methyl benzyl amine, and reaction mixtures resulting from the combination of $\alpha$-methyl benzyl amine and b) N-chloro succinimide (NCS), c) N-bromo succinimide (NBS) and d) N-iodo succinimide (NIS).
Figure 20. $^1$H NMR (400 MHz, CDCl$_3$, 25 °C) of a) α-methyl benzyl amine, b) reaction mixtures resulting from the combination of α-methyl benzyl amine 111 and N-chloro succinimide (NCS), c) N-chloroamine 118 and d) N,N-dichloro amine 119.
The formation of two sets of peaks is further limited to the \textit{N}-iodo \textit{\alpha}-methyl benzylamine since the \textit{N}-bromo and \textit{N}-chloroamine derivatives exhibit similar shifts, but only a single set of peaks in the product (Figure 19). We hypothesize that the behavior of \textit{N}-iodo \textit{\alpha}-methyl benzylamine might be due to an equilibrium between distinct free (A) and bound (B) \textit{N}-iodoamine/succinimide (Scheme 63). Two singlets corresponding to succinimide protons are also observed, consistent with free and bound forms (2.83 & 2.80 ppm, Figure 18). The bound form should be favored at high concentration, and an experiment (Figure 18) in which the \textit{N}-iodoamine was formed at higher concentration (a, Figure 18) did show a single set of peaks (albeit broad), that reformed two sets of peaks upon dilution (b, Figure 18), and further changed in shape/size upon the addition of DMSO (c-d, Figure 18). The latter behavior is consistent with the use of DMSO as an additive to disrupt hydrogen bonding between the \textit{N}-iodoamine and succinimide. It is not clear which side of this equilibrium the \textit{N}-Br and \textit{N}-Cl cases might favor (free or bound), but one would expect a reasonably different effect of iodine on the i) polarizability of the nitrogen lone pair and ii) hydrogen bond donor ability of the \textit{N}-iodoamine. An alternative possibility is the existence of bound states in all three cases, but an inversion at nitrogen that is slow on the NMR time scale for the \textit{N}-iodo amine, resulting in observable diastereomeric \textit{N}-iodoamines (Scheme 63). Although this possibility is supported by the observation that achiral benzylamine forms a single set of product peaks upon treatment with NIS, the literature suggests that the inversion barrier should decrease along the order Cl, Br, I.\textsuperscript{178} Therefore, one would need to conclude that the succinimide binds to the \textit{N}-iodo \textit{\alpha}-methyl benzyl amine, and this complex exhibits an unusually high barrier to inversion. We have also noted that the addition of iodine (I\textsubscript{2}) to \textit{\alpha}-methyl benzyl amine

results in peak shifting relative to free amine, but the formation of a single product (d, Figure 17). Hence, we favor the hypothesis that succinimide is acting as a hydrogen bond donor/acceptor with each N-halo amine, but the formation of an equilibrium mixture of uncomplexed N-iodoamine and succinimide is significant.

A comparative analysis of the reaction of α-methyl benzylamine with NIS, NBS and NCS is provided in Figure 19. In contrast to iodination, bromination and chlorination with these reagents provides a single set of peaks which we have assigned to the bromo and chloramines. The upfield shift of the methylene peaks corresponding to succinimide is the basis for this assignment. The literature indicates that monohaloamines can exist in equilibrium with their dihalo counterparts, but that near neutral/slightly alkaline pH’s favor the monohaloamine.179

Scheme 63. Hypotheses for the Observation of Two Distinct Sets of Peaks in the Case of N-Iodoamine Formation

Exposure of amine 111 to NCS, NBS and NIS in CDCl₃ (25 °C) respectively all revealed rapid conversion to the corresponding N-haloamines. They all showed no

significant decomposition after several hours at room temperature in CDCl$_3$. Among them, N-chloroamine 118 could be isolated after flash column chromatography, albeit with much loss (Scheme 64). Isolated N-chloroamine 118 was fully characterized, although very unstable on its own. A small amount of N,N-dichloroamine 119 was also isolated and characterized. The downfield shift of all the peaks could be obviously observed from α-methyl benzyl amine (a, Figure 20) to N-chloroamine 118 (c, Figure 20), and N,N-dichloroamine 119 (d, Figure 20).

Scheme 64.

Using NIS as the halonium additive, a solvent screen of the amide bond formation demonstrated that ether solvents (THF, dioxane, methyl tert-butyl ether (MTBE)) were superior to toluene, acetonitrile and dichloromethane. And THF, which afforded slightly better yield than the other two ether solvents, was chosen as the optimal solvent for further studies of the amide bond formation.

Use of potassium carbonate when water was a co-solvent provided a biphasic reaction mixture wherein the equivalents of amine could be reduced from 2 to 1.2 relative to bromonitroalkane 107a (Table 15, c.f. entries 2-3). A by-product was always observed during the development, which was determined to be dinitroalkane 120. Dinitroalkane could result from direct nitration of bromonitroalkane 107a under the basic conditions, which indicated that NO$_2^-$ was generated as a co-product in the process of amide bond
formation. The similar reaction was first reported by ter Meer (Scheme 65, eq 50)\textsuperscript{180} and then applied by others for the synthesis of dinitroalkanes (Scheme 65, eq 51 and 52).\textsuperscript{181,182}

**Scheme 65.** Ter Meer Reaction for the Synthesis of Dinitroalkanes

When we treated bromonitroalkane 107a with KNO\textsubscript{2} under basic conditions, followed by acidic work up, we did isolate dinitroalkane 120, although in a low yield (Scheme 66, eq 53). When the dinitroalkane was mixed with amine 111, in the presence of NIS and K\textsubscript{2}CO\textsubscript{3}, only a trace amount of amide 110 could be observed (Scheme 66, eq 54). This indicated that the dinitroalkane is not the intermediate towards the amide product, but an undesired by-product.

In our development of halonium-promoted bromonitroalkane amine coupling, when the amount of water was reduced further to 5 equivalents, a heterogeneous mixture resulted, but the isolated yield of the amide was improved further to 70% (Table 15, entry 4). Although water could not be rigorously excluded from the reaction mixture with confidence, owing to the hydrophilic nature of the amine, we found that the desired amide could be isolated under nominally dry conditions at the expense of lower conversion and a more complex crude reaction mixture (Table 15, entry 5). We determined that 5 equivalents of (added) water would deliver the amide product in good yield. Furthermore, lowering the reaction temperature to 0 °C provided a cleaner reaction and modest improvement to overall yield without significantly lengthening the time to completion (75% yield, Table 15, entry 6). Limiting the amount of water to 5 equivalents and lowering the reaction temperature to 0 °C might reduce the amount of NO$_2^-$ dissolved in the reaction system, thus minimizing the formation of the undesired dinitroalkane by-product and leading to higher yield of the desired amide.
The reactivities of a series of α-halo nitroalkanes were then compared as shown in Table 16. Fluoronitroalkane 121a, being the least reactive, required room temperature for the reaction to occur, and provided the amide product with moderate yield (48%, Table 16, entry 1). Chloronitroalkane 121b and bromonitroalkane 121c afforded similarly good results (74% and 75%, Table 16, entry 2 and 3, respectively). Iodonitroalkane 121d, being the most reactive, generated the amide in 51% yield (Table 16, entry 4), as well as other by-products.

Table 15. Development of a Bromonitroalkane Amine Coupling

<table>
<thead>
<tr>
<th>entry</th>
<th>NIS (equiv)</th>
<th>H₂O (equiv)</th>
<th>K₂CO₃ (equiv)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>0</td>
<td>93</td>
<td>0</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2c</td>
<td>1.2</td>
<td>93</td>
<td>0</td>
<td>61</td>
</tr>
<tr>
<td>3d</td>
<td>1.0</td>
<td>93</td>
<td>2</td>
<td>58</td>
</tr>
<tr>
<td>4d</td>
<td>1.0</td>
<td>5</td>
<td>2</td>
<td>70</td>
</tr>
<tr>
<td>5d,e</td>
<td>1.0</td>
<td>0</td>
<td>2</td>
<td>55</td>
</tr>
<tr>
<td>6d,e</td>
<td>1.0</td>
<td>5</td>
<td>2</td>
<td>75</td>
</tr>
</tbody>
</table>

*a Reactions employed 1 equivalent of bromonitroalkane 107a (0.2 M in THF) and rac-111, with amine added as the final reagent at 25 °C. † Isolated yields.

*2 Equivalents of amine used. ††1.2 Equivalents of amine used. †* Reaction was conducted at 0 °C.
A standard experimental protocol was developed in order to ascertain an initial scope for the reaction, with a near equimolar amount of donor and acceptor established as an important characteristic. These conditions included NIS (1 equivalent), potassium carbonate (2 equivalents), water (5 equivalents), amine (1.2 equivalents) and bromonitroalkane (1 equivalent), operating at ice water temperature for two days as a standard reaction time. Although not necessarily optimized for any single example so as to provide a standard benchmark, these conditions provided a promising level of generality. The bromonitroalkane component was first examined using α-methyl benzyl amine as a representative acceptor (Table 17). Nitroalkane donors carrying aliphatic and aromatic chains are readily employed using this method (Table 17, entries 1-4), and amides bearing electrophilic halides (Table 17, entry 5) or an acid labile acetal/leaving group at the β-position (Table 17, entry 6) can be prepared without

---

Table 16. Development of Bromonitroalkane Amine Coupling: Scope of the α-Halo Nitroalkane Donor

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X = F</td>
<td>48%</td>
</tr>
<tr>
<td>2</td>
<td>X = Cl</td>
<td>74%</td>
</tr>
<tr>
<td>3</td>
<td>X = Br</td>
<td>75%</td>
</tr>
<tr>
<td>4</td>
<td>X = I</td>
<td>51%</td>
</tr>
</tbody>
</table>

\*NIS (1 equiv), K₂CO₃ (2 equiv), amine (1.2 equiv), H₂O (5 equiv), and nitroalkane (1 equiv, 0.2 M in THF) were stirred at 0 °C until complete consumption of the nitroalkane. \*Isolated yield. \*Reaction conducted at room temperature.

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Scope of the Halonium-Promoted Bromonitroalkane Amine Coupling

The α-bromo nitroalkane substrates are generated by deprotonation of the corresponding nitroalkane followed by bromination, in high yields, and often without the need of purification. Erickson, A. S.; Kornblum, N. J. Org. Chem. 1977, 42, 3764.
complication. At an extreme of donor steric congestion, α-bromo nitroalkane 107g was converted smoothly to amide 122g in 54% yield (Table 17, entry 7). Lactonization-prone carbinol 107h and its homolog 107i produced amides 122h and 122i in 48% and 70% isolated yield (Table 17, entries 8-9) using these standard conditions, and the terminal methyl ester 107j led to amide 122j in 70% yield (Table 17, entry 10).

The amine component was similarly examined (Table 18) using bromonitroalkane 107a as a constant. Simple monosubstituted amines bearing aliphatic and aromatic substituents performed well, delivering the desired amide in good isolated yields (most >70%). Particular attention was paid to common functional groups that might be desirable in more complex amide preparation, such as allyl and propargyl amines (Table
18, entries 2-3). Furthermore, an unprotected 1,4-amino alcohol formed the corresponding amide chemoselectively in 71% yield (Table 18, entry 4). Amide formation using glycine methyl ester provided a promising indication that applications in peptide synthesis might be possible (Table 18, entry 5). α-Amido nitriles are present in some pharmaceuticals (Figure 21), and this functionality is readily accessed using the key reaction as well (Table 18, entry 6). Amines with increasing steric hindrance provided comparable levels of efficiency (Table 18, entries 7-8), including tert-butyl amine (Table 18, entry 9). One limitation at present is the use of aromatic amines, such as aniline, as no coupling product could be retrieved using the standard reaction protocol (Table 18, entry 10). Beyond aromatic amines, however, there appear to be relatively few apparent limitations.

Table 18. Development of Bromonitroalkane Amine Coupling: Scope of the Amine Acceptor

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>yield (%)</th>
<th>entry</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhHNO2Bn</td>
<td>72</td>
<td>6</td>
<td>PhHNCN</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>PhHNO2H2N</td>
<td>73</td>
<td>7</td>
<td>PhHNMMe</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>PhHNO2Me</td>
<td>61</td>
<td>8</td>
<td>PhHNO2Ph</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>PhHNO2OH</td>
<td>71</td>
<td>9</td>
<td>PhHNBu</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>PhHNO2CO2Me</td>
<td>72</td>
<td>10</td>
<td>PhHNO2Ph</td>
<td>0</td>
</tr>
</tbody>
</table>

*entry*<sup>a</sup> NIS (1 equiv), K₂CO₃ (2 equiv), amine (1.2 equiv), H₂O (5 equiv), and nitroalkane (1 equiv, 0.2 M in THF) were stirred for a standard 2 day reaction time prior to workup. See the Supporting Information for complete details. *Isolated yield.

**Figure 21.** Pharmaceuticals Containing α-Amido Nitrile Moiety
Disubstituted amides import resistance to proteolysis and unusual conformational properties to peptides.\textsuperscript{185} However, their increased steric hindrance presents challenges to the synthetic community, such as slow coupling rates, low reaction conversion and partial racemization of the amino acids. Diethyl amine was evaluated as a representative disubstituted amine in our coupling reaction. The standard reaction protocol provided the desired disubstituted amide 124 in 50\% yield (Scheme 67).

\textbf{Scheme 67.}

![Scheme 67](image)

We also explored the potential of bromonitroalkane donors in peptide synthesis by coupling of dipeptide 125 with donor 107a and retrieved amide 126 in 72\% isolated yield (Scheme 68, eq 55). Furthermore, the successful demonstration of acylation of phenylalanine on 2-chlorotrityl resin (127) using our bromonitroalkane-amine coupling indicated the great potential of the application of our methodology in solid phase peptide synthesis (Scheme 68, eq 56).

Mechanistic Studies of the Halonium-Promoted Bromonitroalkane Amine Coupling

These exploratory experiments are consistent with the preliminary mechanistic hypothesis outlined in Scheme 69, which is not the originally targeted variation of the classic Nef reaction. NIS serves as a halogenating agent for the amine, converting it to the N-haloamine (129), an electrophilic partner for the nitronate (108). The latter is formed by proton transfer to amine, and ultimately to carbonate. The key carbon-nitrogen bond forming step involves \( S_N^2 \)-type nucleophilic attack by nitronate at nitrogen of the putative N-haloamine (129). The electrophilic amination delivers tetrahedral intermediate 130, which upon elimination of HBr generates nitroimine 131. Hydrolysis of this intermediate ultimately provides the amide product 123, leading to our current proposal that this reaction is formally a hydrative amide synthesis from bromonitroalkane and amine.
α-Bromo α-iodo nitroalkane 132 was observed by \(^1\)H NMR as an intermediate in the reaction mixture, which should derive from iodination of bromonitronate 108 (Scheme 70, pathway b). α-Bromo α-iodo nitroalkane 132 could then react with amine to form the combination of N-iodoamine 129 and bromonitronate 108 again, which would undergo electrophilic amination to form the tetrahedral intermediate (Scheme 70, pathway a). The competition between pathway a and b reflects the ambident character of N-halo amines. Alternatively, α-bromo α-iodo nitroalkane 132 could also be deiodinated to form N-bromoamine and iodonitronate (not shown in Scheme 70), and the observation of dibromonitroalkane by \(^1\)H NMR further confirmed the existence of the proposed equilibrium.
Although we were not able to isolate $\alpha$-bromo $\alpha$-iodo nitroalkane 132, we successfully synthesized dichloronitroalkane 133a and dibromonitroalkane 133b.\(^{186}\) Simply mixing the dihalonitroalkane with excess amine 111 in the presence of $\text{H}_2\text{O}$ afforded amide product 110 (Scheme 71). The condensation of a dibromonitroalkane with an amine to provide the corresponding amide was reported only once in literature without detailed reaction conditions and yield (Scheme 72).\(^{187}\)

Based on the proposed mechanism in Scheme 69, the amide may result from hydrolysis of the nitroimine intermediate (131). Therefore, using $\text{H}_2^{18}\text{O}$ in lieu of normal

---


H₂O should, in theory, give $^{18}\text{O}$ labeled amides. However, with all the reagents and the solvent effectively dried, subjecting the reaction to H₂$^{18}$O resulted in <1% $^{18}$O incorporation in the amide products (Scheme 73), which indicated that the amide was not formed via hydrolysis of the nitroimine intermediate (131). This is reminiscent of the fact that under nominally dry conditions, the amide product could still be generated (Table 15, entry 5). The only other source of oxygen in the reaction system is the nitro group.

Scheme 73.

It was reported that under heated conditions, bromonitromalonate 134 underwent rearrangement to the corresponding nitrite (135), followed by the elimination of nitrosyl bromide, to afford ketone 136 (Scheme 74, eq 57).\(^{188}\) Schollkopf and co-workers reported that under thermal conditions, substituted nitroacetate 137 partially rearranged to the corresponding nitrite (139), and the unreacted starting material was recovered with partial racemization (Scheme 74, eq 58).\(^{189}\) Based on these observations, the authors proposed that the nitro-nitrite rearrangement occurred via the radical pair intermediate (138) formed from homolytic cleavage of the C-N bond. Due to the ambident character of the nitro radical, recombination of the radical pair either formed the original C-N bond to


give the starting material, which explained the partial racemization, or formed the new C-O bond to give the rearranged product (nitrite 139). Sandall and co-workers provided further evidence for the reversible nitro-nitrite rearrangement (Scheme 74, eq 59). When nitroalkane 140 was dissolved in chloroform at 30 °C, a fast equilibrium was reached. The $^1$H NMR spectrum of the mixture showed three sets of peaks corresponding to starting material 140, nitrite 141 and alcohol 142, and the $^{13}$C NMR spectrum of the mixture showed two sets of peaks corresponding to starting material 140 and nitrite 141. The same equilibrium was also reached when alcohol 142 was treated with HNO$_2$.

Scheme 74.

When 1,2-dibromodinitroethylene (143) was treated with refluxing methanol, methyl bromonitroacetate (145) was isolated. The reaction was proposed to follow a path involving Michael addition of methanol to the nitroalkene, giving intermediate 144,

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followed by nitro-nitrite rearrangement and elimination to give the bromonitroacetate. Interestingly, only the \textit{gem}-bromo nitro moiety activated by methoxy group rearranged to the carbonyl group, but the other \textit{gem}-bromo nitro moiety on a secondary carbon was well-preserved in the product (Scheme 75).

Scheme 75.

The above reaction is analogous to other reported examples of the conversion of \textit{gem}-halo nitro moieties to carbonyl groups,\textsuperscript{192} in which the nitro-nitrite rearrangement is involved. These examples bear the common features that 1) only the tertiary \textit{gem}-halo nitro moiety can be converted to the corresponding carbonyl compound; and 2) at least one of the substitutions on the tertiary carbon has to be a radical stabilizing group, such as an ester or alkoxy group (Scheme 76). These features are consistent with Schollkopf’s mechanistic proposal that the rearrangement occurs via the radical pair intermediate.

Scheme 76.

In our halonium-promoted bromonitroalkane amine coupling, electrophilic amination of nitronate 108 generates tetrahedral intermediate 130 bearing the gem-bromo nitro moiety with the amine as the radical stabilizing group. This intermediate then undergoes nitro-nitrite rearrangement to provide intermediate 146. Elimination of NO₂⁻ and Br⁻, assisted by H₂O, finally delivers the amide product (Scheme 77).

Scheme 77. Revised Mechanistic Hypothesis for Bromonitroalkane Amine Coupling

Bromonitromethane did not provide the corresponding formamide (Scheme 78, eq 60), presumably because the putative tetrahedral intermediate is a secondary nitroalkane, which does not undergo nitro-nitrite rearrangement to give the amide product. As mentioned above, the halonium-promoted bromonitroalkane amine coupling reaction is presently not compatible with aromatic amines, such as aniline or indolino ester 147 (Scheme 78, eq 61 and 62), nor with tert-butyl carbamate (Scheme 78, eq 63), presumably because the less nucleophilic amines could not provide enough stabilization.
for the radical pair intermediate. All these results further proved the proposed reaction mechanism.

The possibility that bromonitroalkane 107a is simply a precursor to an electrophilic carbonyl intermediate, such as an aldehyde or acyl halide, was examined by a series of experiments summarized in Scheme 79. Phenyl acetaldehyde would be formed as an intermediate from 107a during a Nef-oxidative amidation sequence. When phenyl acetaldehyde was exposed to the reaction conditions, its consumption was eventually observed, but a complex mixture of products formed without evidence for formation of amide 110 (Scheme 79, eq 64). Separately, we monitored the behavior of nitroalkane 107a in the presence of NIS/K₂CO₃, but in the absence of amine, and again observed slow conversion to a mixture of products (Scheme 79, eq 65). We observed peaks (¹H NMR) consistent with production of α-bromo-α-iodo nitroalkane 132 in this experiment,
but this intermediate was also ultimately consumed during the formation of the complex mixture. In order to test whether this complex mixture contains an active ester of some type (e.g. acid halide), amine was added after \textbf{107a} was consumed, but again, amide \textbf{110} was not formed. Alternatively, we tested the potential formation of an electrophilic active ester by replacement of the amine with benzyl alcohol, but this variation failed to produce the ester product (Scheme 79, eq 66). The involvement of atmospheric oxygen was also considered, but little difference was observed between the 1) typical reaction setup and variants that were 2) degassed, or 3) run with an oxygen atmosphere.

\textbf{Scheme 79.} Experiments Designed to Probe Intermediacy of Possible Carbonyl Electrophiles

![Chemical Structures](image_url)

All of these mechanistic studies supported the proposed mechanism shown in Scheme 77, wherein the inherent polarity of the acyl donor and amine are reversed from conventional variants (‘umpolung’) in the key C-N bond forming step (Figure 22).
The relatively high price of NIS might be a limitation of our umpolung amide synthesis. Ca(ClO)$_2$, a less reactive, but much cheaper halonium source than NIS, was demonstrated as an effective substitute in the amide coupling. Bromonitroalkane 107a or iodonitroalkane 121d, together with only 0.6 equivalents of Ca(ClO)$_2$ (1.2 equivalents of Cl$^+$) generated amide 110 in 64%, or 70% yield, respectively (Scheme 80, eq 67 & 68).

Although bromonitroalkanes are readily accessible from the corresponding nitroalkanes, it would be more convenient to use nitroalkanes directly as the substrates for the amide coupling. Two equivalents of NIS would be necessary to iodinate both the

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**Figure 22.** Comparison of Component Polarization in Conventional Condensative Amide Synthesis and Bromonitroalkane Amine Coupling

Scheme 80.
nitroalkane and the amine, and in theory, iodonitroalkane 121d could be formed in situ to perform the coupling with N-iodoamine 129. Due to the lower acidity of nitroalkanes than bromonitroalkanes, K$_2$CO$_3$ was not basic enough to promote the reaction, and hence, no amide product 110 was observed (Table 19, entry 1). However, additional 10 mol% DBU facilitated the deprotonation, and generated the amide product in 50% yield (Table 19, entry 2). NaOH and KOtBu could deprotonate the nitroalkane 106, but the reaction went with moderate conversion and yield (39% and 25%, respectively, Table 19, entries 3 and 4). Until now, Cs$_2$CO$_3$ has provided the best result, affording amide product 110 in 57% yield (Table 19, entry 5).

**Table 19. Iodonium-Promoted Nitroalkane Amine Coupling: Effect of Base on Reaction Yield**

<table>
<thead>
<tr>
<th>entry$^a$</th>
<th>base</th>
<th>yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K$_2$CO$_3$</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>K$_2$CO$_3$, DBU$^c$</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>NaOH</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>KOtBu</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>Cs$_2$CO$_3$</td>
<td>57</td>
</tr>
</tbody>
</table>

$^a$NIS (2.1 equiv), base (2 equiv), amine (1.2 equiv), H$_2$O (5 equiv), and nitroalkane (1 equiv, 0.2 M in THF) were stirred for a standard 2 day reaction time prior to workup.

$^b$Isolated yield. $^{c}$10 mol% DBU as an additive.

### 3.3. Application of Umpolung Amide Synthesis

The studies described above establish a preliminary scope in the context of simple intermolecular α-bromonitroalkane couplings with amines, and provide a new framework
for amide synthesis under mild, near pH-neutral conditions with a heterogeneous base. We next focused on the generation of chiral nonracemic \(\alpha\)-bromonitroalkane donors that would deliver amides of protected \(\alpha\)-amino acids directly from this amide synthesis protocol.

Aryl glycine derivatives are important chiral building blocks in organic synthesis and subunits of many natural products,\(^{193}\) among which the vancomycin (148) class of antibiotics provides particularly prominent examples. A number of unique synthetic small molecule therapeutics, including cephalexin (149), cefadroxil (150) and amoxicillin (151), contain the aryl glycine substituent as well (Figure 23).

**Figure 23. Antibiotics Containing Aryl Glycine Subunit**

Optically pure aryl glycines have traditionally been obtained by resolution. Diastereoselective approaches towards aryl glycines involving chiral auxiliaries have been well-summarized by Williams.\(^{193}\) Common strategies include the Strecker reaction

of a chiral aryl imine, followed by hydrolysis, electrophilic amination of a chiral aryl acetic ester, or nucleophilic addition of aryl group to a chiral iminoester (Scheme 81).

Scheme 81. Diastereoselective Approaches towards Optically Active Aryl Glycines

Enantioselective methods have emerged in recent years. The most common strategy is the enantioselective Strecker reaction followed by hydrolysis of the nitrile under acidic conditions (Scheme 82). A variety of catalysts for the asymmetric Strecker reaction were reported, which have been well-documented in recent reviews.\(^\text{194}\)

Scheme 82.

Other novel methods of enantioselective aryl glycine synthesis have been reported. Park and Beak reported the benzylic lithiation of \(^\text{152}\) under the influence of a stoichiometric amount of (-)-sparteine followed by nucleophilic addition of the chiral

anion to CO$_2$ to generate protected aryl glycine 153 with high enantioselectivity (Scheme 83).\textsuperscript{195}

Scheme 83.

Reddy and Sharpless applied their asymmetric aminohydroxylation strategy on styrene to form aryl glycinal, which could be subsequently oxidized to carbamate-protected aryl glycine 154 (Scheme 84).\textsuperscript{196}

Scheme 84.

In 2006, a novel rhodium complex containing chiral phosphine ligand 155 was developed by Zhang and co-workers for the enantioselective hydrogenation of iminoester 156 (Scheme 85).\textsuperscript{197} Only 1 mol\% of the catalyst was needed to effectively deliver PMP-protected aryl glycine ester 157 with excellent enantioselectivity.

\textsuperscript{197} Shang, G.; Yang, Q.; Zhang, X. M. Angew. Chem. Int. Ed. 2006, 45, 6360.
In 2007, Lee and Fu developed a Cu/bpy*(158)-catalyzed asymmetric insertion of α-diazocarbonyl compounds into the N-H bond of carbamate 159 to generate car bamate-protected aryl glycine ester 160 with high enantioselectivity (Scheme 86).  

More recently, Lu and co-workers developed a palladium-catalyzed arylboronic acid addition to iminoester 162 to generate aryl glycine ester 163 with moderate to good

ee and yield (Scheme 87).\textsuperscript{199} Iminoester 162 could be prepared in situ by thermal [2+2] cycloaddition of \( p \)-toluenesulfonyl isocyanate and ethyl glyoxylate.

\textbf{Scheme 87.}

\textbf{Scheme 88. Epimerization of Aryl Glycine during Coupling}

\begin{flushleft}
\end{flushleft}
We envisioned that we could utilize the bromonitromethane aza-Henry adduct in our umpolung amide coupling to afford aryl glycine amides (Scheme 89). We first tested the asymmetric addition of bromonitromethane to aryl imine 61a using various chiral proton catalysts. While H,Quin-BAM·HOTf (74·HOTf) provided the adduct with 83% ee (Table 20, entry 1), H,Quin(6,9-Anth)2Pyr-BAM·HOTf (93·HOTf) afforded the adduct with excellent enantioselectivity and high yield (Table 20, entry 2). The addition product that resulted was retrieved as a 1:1 mixture of diastereomers, each with 98% ee and homochiral at the benzylic carbon. Moreover, both PBAM·HOTf (166·HOTf) and the free base PBAM (166) provided similarly good results as well (Table 20, entries 3-4).

\[200\text{ With Dawn Makley.}\]
Scheme 89.

Table 20. Catalyst Screen for Bromonitromethane Addition

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>%ee</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74•HOTf</td>
<td>83</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>93•HOTf</td>
<td>98</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>166•HOTf</td>
<td>94</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>166</td>
<td>99</td>
<td>94</td>
</tr>
</tbody>
</table>

*All reactions were 0.30 M in substrate and proceeded to complete conversion (2 d). Enantionomer ratios were measured using chiral stationary phase HPLC.
*Isolated yield.

Using PBAM (166) as the catalyst allowed us to form the N-Boc imine 61a in situ from α-amido sulfone 94a in the presence of a stoichiometric amount of exogenous base K₂CO₃. Following the elimination, the direct aza-Henry reaction afforded adduct 164 with similarly high ee and high yield (Scheme 90, eq 69). We further demonstrated that the α-amido sulfone formation, the sulfinic acid elimination and the aza-Henry addition could be conducted entirely in one-pot without deterioration of the enantioselectivity of the adduct (Scheme 90, eq 70). Bypassing the isolation of the imine intermediate, which is unstable to moisture and not suitable for long-time storage, these one-pot reactions...
provided a more convenient approach towards the enantioselective synthesis of aza-Henry adducts.

Scheme 90.

Aza-Henry adduct 164 was then coupled to both rac-amine 111 and (R)-111 (96% ee) using our standard reaction protocol, delivering 167 in 76% yield in each case (Scheme 91, eq 71). The use of racemic amine allowed a careful analysis of the diastereomeric ratio in the example derived from (R)-111 (96% ee) to determine that it is >98:2 as expected. This is significant as aryl glycines often undergo some degree of epimerization when active ester intermediates are used in couplings with amines. Moreover, the absence of epimerization here is consistent with the mechanism proposed in Scheme 77. This behavior could be further generalized as a component of peptide synthesis. Dipeptide 125 (Ala-Phe-OMe) delivered aryl glycine tripeptide 168 as a single diastereomer in 72% yield using bromonitroalkane 164 under our standard reaction conditions (Scheme 91, eq 72) and sterically hindered proline ester 169 afforded aryl glycine dipeptide 170 in 67% yield, again as a single diastereomer (Scheme 92, eq 73). As a comparison, conventional amide coupling of aryl glycine 171 with proline ester 169
mediated by EDC and HOBT generated the same dipeptide in higher yield (85%), however, 9% epimerization of the aryl glycine moiety was observed, leading to a mixture of inseparable diastereomers with a ratio of 10:1 (Scheme 92, eq 74).

Scheme 91.

We have also demonstrated the feasibility of this umpolung amide synthesis on solid phase, as shown in Scheme 93. Preliminary results showed that coupling products dipeptide 172 and tripeptide 175 could be isolated in modest yields after resin cleavage.
In addition to the practical advantages associated with the use of an enantioselective, organocatalytic addition reaction to prepare the acyl donor equivalent and the mild conditions employed in the amide synthesis, this method provides a conceptually new approach to enantioselective peptide construction (Scheme 94). Commercially available bromonitromethane constitutes the amide carbonyl carbon in the final product, and serves as the lynchpin of the synthesis while providing the synthetic equivalent of a carbonyl dianion. This umpolung reactivity offers an attractive alternative to traditional condensative amide synthesis.

Scheme 94. Enantioselective Peptide Synthesis: A Carbonyl Dianion Synthon Approach
Conclusion

In summary, we have discovered a nonconventional amide synthesis using iodonium-promoted nitroalkane-amine coupling. The conditions are only mildly basic and have been shown to accommodate a range of nitroalkanes and amines. The successful demonstration of the coupling on solid phase significantly broadens the application of the reaction. At the level of strategy, this amide synthesis appears to reverse the reactive polarity of acyl and amine subunits relative to traditional condensative approaches, providing a nucleophilic acyl donor and an electrophilic amine acceptor. This new approach led to the development of an asymmetric aryl glycine amide synthesis without epimerization or extensive protection/deprotection schemes. And the first use of commercially available bromonitromethane in stereoselective peptide synthesis establishes a practical alternative to the longstanding reliance on the carboxylic acid feedstock. This strategic shift may ultimately enable the efficient fully chemical synthesis of chiral, nonracemic peptides using a combination of entirely enantioselective methods and bromonitroalkane-amine coupling, and will be especially useful for the synthesis of non-proteinogenic amino amides and peptides.
Chapter IV

Experimental Section

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. Diethyl ether (Et₂O), tetrahydrofuran (THF), dichloromethane (CH₂Cl₂) and benzene (C₆H₆) were dried by passage through a column of activated alumina as described by Grubbs. Benzene was additionally passed through a column containing activated Q-5 reactant. Methanol was distilled from Mg under N₂ immediately before use. Triethylamine (NEt₃) was distilled from calcium hydride. The aldimines, Pd(dba)₂, and α-nitro tert-butyl acetate were prepared as reported in the literature. Palladium-mediated aryl amination was executed using a Buchwald protocol. AIBN was recrystallized from acetone with careful temperature control. All organic layers collected from extractions were dried over MgSO₄ unless otherwise indicated.

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

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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 Varian INOVA-400 (400 MHz), a Bruker VXR-400 (400 MHz), a Bruker DRX-500 (500 MHz), or a Bruker AV- II-600 (600 MHz) instrument. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to 7.26 and 77.1 (CDCl\(_3\)). Mass spectra were recorded on a Kratos MS-80 spectrometer by use of chemical ionization (CI) or electron impact ionization (EI) or a Synapt hybrid quadrupole/oa-TOF Mass Spectrometer equipped with a dual chemical ionization/electrospray (ESCI) source. 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. Atlantic Microlabs, GA, performed combustion analyses.

**tert-Butyl (3-phenoxyphenyl)(phenylsulfonyl)methylcarbamate (94g)**

*tert*-Butyl carbamate (2.68 g, 22.9 mmol) and benzenesulfinic acid sodium salt (7.52 g, 45.8 mmol) were dissolved in a solution of methanol in water (1:2, 69 mL). 3-Phenoxybenzaldehyde (5.45 g, 27.5 mmol) was then added to the solution, followed by formic acid (98%, 1.73 mL). The reaction was allowed to stir for 48 h at room temperature, during which time the white solid precipitated out from the clear solution. The solid was filtered in a Büchner funnel and washed with Et\(_2\)O. After drying *in vacuo,*
the product was obtained as a white solid (4.48 g, 45%). IR (neat) 3442, 1717, 1484, 1251, 1145 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.89 (d, J = 7.8 Hz, 2H), 7.64 (t, J = 7.2 Hz, 1H), 7.54 (t, J = 7.6 Hz, 2H), 7.38-7.34 (m, 3H), 7.18 (d, J = 7.6 Hz, 1H), 7.14 (t, J = 7.3 Hz, 1H), 7.08 (s, 1H), 7.05-7.00 (m, 3H), 5.87 (d, J = 10.7 Hz, 1H), 5.68 (d, J = 10.6 Hz, 1H), 1.26 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) ppm 157.6, 156.6, 153.5, 137.0, 134.1, 131.8, 130.2, 130.0, 129.5, 129.2, 123.8, 123.6, 120.0, 119.3, 81.4, 73.7, 28.1.

**tert-Butyl 3-phenoxybenzylidene carbamate (61g)**

The sulfone (3.90 g, 8.87 mmol) was added to a suspension of K₂CO₃ and Na₂SO₄ in anhydrous THF (44 ml), and the reaction was stirred at room temperature and monitored by removal of an aliquot and examination by NMR each day, until the sulfone was consumed (8 days). The solids were removed via filtration through a medium glass frit. The filtrate was concentrated and dried under vacuum to give the desired imine as a colorless oil (2.89 g, 98%). IR (neat) 2977, 1715, 1580, 1487, 1239, 1157 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.78 (s, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.55 (s, 1H), 7.43 (t, J = 7.9 Hz, 1H), 7.35 (dd, J = 7.7, 7.7 Hz, 2H), 7.22-7.20 (m, 1H), 7.14 (dd, J = 7.4, 7.4 Hz, 1H), 7.01 (d, J = 8.1 Hz, 2H), 1.57 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) ppm 168.8, 162.5, 158.1, 156.6, 136.0, 130.3, 130.0, 125.4, 124.0, 123.9, 119.3, 81.5, 73.7, 28.0; HRMS (CI) Exact mass calc'd for C₁₈H₂₀(NO₃)[M+H]⁺ 298.1438. Found 298.1437.
**H,4,6-Me$_2$-BAM (85)**

Pd(dba)$_2$ (44.5 mg, 77.4 μmol), BINAP (96.4 mg, 155 μmol) and NaO'Bu (1.12 g, 11.6 mmol) were loaded into a round bottom flask in a glove box. Toluene (25.8 mL, 0.15 M) was added to the mixture followed by 1,2-(R,R)-trans-diaminocyclohexane (442 mg, 3.87 mmol) and 2-bromo-4,6-dimethylpyridine (1.44 g, 7.74 mmol). The reaction was allowed to stir at reflux for 12 h, and then cooled to room temperature, filtered through Celite, concentrated, and purified by flash column chromatography on silica gel (20% EtOAc in hexanes) to afford the bis(amidine) as a yellow solid (603 mg, 48%).

[α]$_D^{20}$ +100.4 (c 1.0, CHCl$_3$); R$_f$ = 0.08 (20% EtOAc in hexanes); Mp 114-115 °C; IR (neat) 3241, 3058, 2921, 2855, 1611, 1573, 1452, 802 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 6.22 (s, 2H), 5.90 (s, 2H), 4.95 (br s, 2H), 3.64 (br s, 2H), 2.33 (s, 6H), 2.22 (br d, J = 13.4 Hz, 2H), 2.12 (s, 6H), 1.75-1.72 (m, 2H), 1.45-1.40 (m, 2H), 1.34-1.25 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 158.6, 156.4, 148.3, 113.2, 104.6, 55.3, 32.4, 24.5, 24.3, 21.6; HRMS (Cl) Exact mass calcd for C$_{20}$H$_{29}$N$_4$ [M+H]$^+$ 325.2387. Found 325.2392.
H6-OBn-BAM (86)

Pd(dba)$_2$ (58.0 mg, 0.101 mmol), BINAP (126 mg, 0.202 μmol) and NaO'Bu (1.21 g, 12.6 mmol) were loaded into a round bottom flask in a glove box. Toluene (50.5 mL, 0.1 M) was added to the mixture, followed by the amine (577 mg, 5.05 mmol) and 2-(benzyloxy)-6-bromopyridine (2.67 g, 10.1 mmol). The reaction was allowed to stir at 100 °C for 10 h, and then cooled to room temperature, filtered through Celite, concentrated, and purified by flash column chromatography on silica gel (5% EtOAc in hexanes) to afford the desired bis(amidine) as a yellow oil (2.19 g, 90%). R$_f$ = 0.29 (10% EtOAc in hexanes). IR (neat) 2933, 1602, 1579, 1446, 1222, 728 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.43 (d, $J$ = 7.4 Hz, 4H), 7.35 (t, $J$ = 7.4 Hz, 4H), 7.28 (t, $J$ = 7.3 Hz, 2H), 7.17 (t, $J$ = 7.8 Hz, 2H), 5.99 (d, $J$ = 7.9 Hz, 2H), 5.61 (d, $J$ = 7.9 Hz, 2H), 5.35 (d, $J$ = 12.7 Hz, 2H), 5.31 (d, $J$ = 12.7 Hz, 2H), 4.53 (br d, $J$ = 4.5 Hz, 2H), 3.65-3.57 (m, 2H), 2.14 (br d, $J$ = 13.0 Hz, 2H), 1.77 (br d, $J$ = 8.7 Hz, 2H), 1.40-1.31 (m, 2H), 1.25-1.21 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 162.7, 157.6, 139.7, 138.5, 128.5, 127.6, 127.5, 99.4, 97.2, 67.1, 56.1, 33.3, 25.2; HRMS (CI) Exact mass calcd for C$_{30}$H$_{33}$N$_4$O$_2$ [M+H]$^+$ 481.2598. Found 481.2602.
2-(Anthracen-9-yl)-6-bromopyridine (S-1)

Pd(PPh₃)₄ (92.8 mg, 80.3 μmol) and Ba(OH)₂·8H₂O (950 mg, 3.01 mmol) were added to a solution of 9-anthracenylboronic acid (446 mg, 2.01 mmol) in 15 mL DME/H₂O (2:1), followed by the addition of 2,6-dibromopyridine (571 mg, 2.41 mmol). The reaction was allowed to stir under reflux for 10 h. After cooling to room temperature, the reaction mixture was extracted with chloroform and the organic layer was dried, filtered, concentrated and purified by flash column chromatography on silica gel (3% EtOAc in hexanes) to give the bromopyridine as a yellow solid (503 mg, 75%). Rf = 0.30 (10% EtOAc in hexanes). Mp 88-91 °C; IR (neat) 3056, 2921, 1577, 1546, 1119, 908, 731 cm⁻¹; ^1H NMR (500 MHz, CDCl₃) δ 8.55 (s, 1H), 8.04 (d, J = 9.5 Hz, 2H), 7.78 (t, J = 7.7 Hz, 1H), 7.67 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 6.7 Hz, 2H), 7.49 (d, J = 8.1 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.42-7.38 (m, 2H); ^13C NMR (125 MHz, CDCl₃) δ 159.5, 142.3, 138.6, 133.3, 131.4, 130.0, 128.6, 128.2, 127.0, 126.3, 125.9, 125.7, 125.3; HRMS (CI) Exact mass calcd for C₁₉H₁₅NBr [M+H]^+ 334.0226. Found 334.0210.
H,Quin(69Anth)2Pyr)-BAM (93)

Pd(dba)$_2$ (27.5 mg, 47.9 µmol), rac-BINAP (29.8 mg, 47.9 µmol) and NaO'Bu (230 mg, 2.40 mmol) were loaded into a round bottom flask in a glove box. Toluene (14.1 mL, 0.1 M) was added to the mixture followed by the amine (289 mg, 1.20 mmol) and 2-(anthracen-9-yl)-6-bromopyridine (400 mg, 1.20 mmol). The reaction was allowed to stir at reflux temperature for 12 h, and then cooled to room temperature, filtered through Celite, concentrated, and purified by flash column chromatography on silica gel (20% EtOAc in hexanes), to afford the desired bis(amidine) as a yellow foam (363 mg, 61%). [α]$_D^{20}$ +405.1 (c 1.0, CHCl$_3$); R$_f$ = 0.10 (20% EtOAc in hexanes). IR (neat) 2928, 1618, 1599, 1518, 1452, 755 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.52 (s, 1H), 8.06 (t, J = 8.4 Hz, 2H), 7.82 (t, J = 9.6 Hz, 2H), 7.67 (d, J = 8.6 Hz, 1H), 7.53-7.35 (m, 8H), 7.16 (t, J = 7.1 Hz, 1H), 6.70 (d, J = 7.0 Hz, 1H), 6.40 (br d, J = 7.3 Hz, 1H), 6.15 (br d, J = 8.2 Hz, 1H), 5.56 (br d, J = 6.0 Hz, 1H), 5.37 (br d, J = 6.6 Hz, 1H), 4.04 (br d, J = 8.0 Hz, 1H), 3.86 (br d, J = 8.0 Hz, 1H), 2.25 (br t, J = 8.0 Hz, 2H), 1.71-1.61 (m, 2H), 1.45-1.32 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 158.8, 156.8, 155.8, 148.0, 137.0, 136.0, 136.5, 131.6, 131.5, 130.1, 129.9, 129.3, 128.5, 128.3, 127.4, 127.0, 126.9, 126.8, 126.0, 125.5, 125.4, 125.2, 125.1, 123.3, 121.6, 115.5, 113.1, 107.4, 55.6, 55.1, 32.7, 32.0, 24.6, 24.4; HRMS (CI) Exact mass calcd for C$_{34}$H$_{31}$N$_4$ [M+H]$^+$ 495.2543. Found 495.2529.
6,6’-(1R,2R)-cyclohexane-1,2-diylbis(azanediyl)dipyridin-2(1H)-one (S-2)

To a solution of H,6-OBn-BAM (804 mg, 1.67 mmol) in MeOH/EtOAc (2:1) was added 80.4 mg 10% Pd/C. The mixture was stirred for 2 h under hydrogen atmosphere and then filtered through Celite. After concentration, the residue was filtered through a short plug of silica gel and then washed with 5% MeOH in CHCl₃. The filtrate was concentrated to give the pyridinone as a light purple solid (460 mg, 91%). Rₓ = 0.68 (5% MeOH in CHCl₃). IR (neat) 3260, 3106, 1612, 1432, 1164, 1141 cm⁻¹; ¹H NMR (500 MHz, d₆-acetone) δ 7.27 (t, J = 8.1 Hz, 2H), 6.42 (br s, 2H), 5.86 (d, J = 8.0 Hz, 2H), 5.66 (d, J = 8.1 Hz, 2H), 3.87 (br s, 2H), 2.09 (br s, 2H), 2.04-1.99 (m, 2H), 1.74-1.66 (m, 4H), 1.57-1.54 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 166.1, 155.4, 142.8, 99.0, 95.0, 48.2, 26.1, 20.6; HRMS (CI): Exact mass calcd for C₁₆H₂₁N₄O₂ [M+H]⁺ 301.1659 Found 301.1657.

Ethyl (1R,2R)-2-(quinolin-2-ylamino)cyclohexylcarbamate (88)
The solution of the amine (61.0 mg, 0.253 mmol) and NEt₃ (39.0 µL, 0.278 mmol) in THF was cooled to 0 °C, and then ethyl chloroformate (24.1 µL, 0.253 mmol) was added dropwise. The mixture was warmed to room temperature, stirred overnight and then filtered, concentrated, diluted with Et₂O, and washed with water. The organic layers were dried, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (30% EtOAc in hexanes), to afford the desired carbamate as a yellow solid (70.0 mg, 88%). Mp 147-149 °C; R_f = 0.20 (40% EtOAc in hexanes); IR (neat) 3317, 2924, 1683, 1537, 1244, 1040, 818 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.72 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.51 (ddd, J = 7.0, 1.4, 1.4 Hz, 1H), 7.19 (ddd, J = 7.9, 1.1, 1.1 Hz, 1H), 6.52 (d, J = 8.8 Hz, 1H), 6.00 (br s, 1H), 4.89 (br d, J = 6.6 Hz, 1H), 4.04 (br d, J = 10.8 Hz, 1H), 3.96-3.88 (m, 2H), 3.45 (br d, J = 7.5 Hz, 1H), 2.20 (d, J = 8.0 Hz, 2H), 1.77 (m, 2H), 1.41-1.33 (m, 4H), 1.00 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 157.3, 156.9, 147.8, 137.1, 129.5, 127.4, 126.2, 123.4, 122.0, 112.7, 60.5, 56.9, 54.6, 33.1, 33.0, 25.0, 24.8, 14.5; HRMS (Cl) Exact mass calcd for C₁₈H₂₃N₃O₂ [M+H]⁺ 314.1863. Found 314.1858.

(2S,3R)-tert-Butyl

3-(tert-butoxycarbonylamino)-3-(4-chlorophenyl)-2-nitroproanoate (syn-78a).

A solution of the imine (5.08 g, 21.2 mmol) and H,Quin-BAM-HOTf (438 mg, 848 µmol) in toluene (42.4 ml, 0.5 M) was cooled to -78 °C. tert-Butyl nitroacetate
(3.418 g, 21.2 mmol) was added via syringe and the reaction was stirred at -78 °C and monitored by thin layer chromatography. The reaction was warmed to room temperature and the solvent was removed by rotary evaporation in a 40 °C water bath to afford the crude mixture as an off-white solid. After being filtered through a plug of silica gel (22 g) by CH₂Cl₂ (125 ml) and concentrated, the mixture was recrystallized from cyclohexane (60 ml) to afford the desired product as a white solid (4.270 g, 50%), which was determined to be >98% ee, >50:1 dr by HPLC analysis (Chiracel AD, 80:20 hexanes: iPrOH, 1 ml/min, \( t_\text{f}(\text{cis}, \text{major}) = 27.4 \text{ min} \), \( t_\text{f}(\text{cis}, \text{minor}) = 7.2 \text{ min} \), \( t_\text{f}(\text{trans}, \text{major}) = 15.6 \text{ min} \), \( t_\text{f}(\text{trans}, \text{minor}) = 10.8 \text{ min} \)). [\( \alpha \)]\( \text{D} \)^{25} +29.5 (c 1.0, CHCl₃) (syn-78a was obtained after recrystallization in a >98% ee, and >50:1 dr form in a few tests, while in most cases, 4:1 to 7:1 dr was obtained with 60-70% yield); Mp 149-150 °C; \( R_f = 0.41 \) (20% EtOAc/hexanes); IR (neat) 3455, 2980, 2931, 1743, 1709, 1566, 1485, 1151 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta 7.33 \) (d, \( J = 8.6 \text{ Hz} \), 2H), 7.23 (d, \( J = 8.6 \text{ Hz} \), 2H), 6.15 (br d, \( J = 8.6 \text{ Hz} \), 1H), 5.65 (br d, \( J = 5.7 \text{ Hz} \), 1H), 5.58 (br s, 1H), 1.51 (s, 9H), 1.44 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl₃) ppm 161.6, 154.8, 135.1, 134.5, 129.3, 127.5, 91.8, 86.2, 80.8, 53.5, 28.4, 27.8; HRMS (Cl) Exact mass calcd for C\(_{18}\)H\(_{26}\)ClN\(_2\)O\(_6\) [M+H]^+ 401.1474. Found 401.1465. Anal. Calcd for C\(_{18}\)H\(_{25}\)ClN\(_2\)O\(_6\): C, 53.93; H, 6.29; N, 6.99. Found C, 54.00; H, 6.29; N, 6.86.
**tert-Butyl 2-Amino-3-(tert-butoxycarbonylamino)-3-(4-chlorophenyl)propanoate (79a)**

The nitroacetate (1.07 g, 7:1 dr, 97% ee/97% ee) and anhydrous cobaltous chloride (347 mg) were dissolved in methanol (0.1 M solution) and cooled to 0 °C. Sodium borohydride (506 mg) was added in three portions. Evolution of hydrogen gas was observed and a black suspension appeared during the addition of sodium borohydride. The reaction was warmed to room temperature and stirred for one hour, and then quenched with 1 M HCl until the black suspension completely disappeared and a clear pink solution was observed. The pH was adjusted to 9 by concentrated NH₄OH, and the mixture turned brown with some precipitation. MeOH was removed under vacuum, and the mixture was extracted with EtOAc and concentrated to a dark brown oil. The oil was washed through a plug of silica gel with 50% EtOAc in hexanes, and then concentrated to a brown solid under vacuum. The solid was recrystallized from hexanes (4.6 mL) to give the desired product as off-white crystals (524 mg, 53%), which was determined to be >98% ee, 60:1 dr by HPLC analysis (Chiracel AD, 10% 1PrOH/hexanes, 1 mL/min, tᵣ(syn, major) = 19.7 min, tᵣ(syn, minor) = 11.8 min, tᵣ(anti, major) = 14.8 min, tᵣ(anti, minor) = 9.7 min). *syn-79a:* Mp 125-127 °C; Rₛ = 0.10 (20% EtOAc/hexanes); IR (neat) 3381, 2981, 1711, 1507, 1156 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.26 (m, 4H), 5.72 (br
(2S,3R)-tert-Butyl 2-amino-3-(4-bromophenyl)-3-(tert-butoxycarbonylamino)propanoate (syn-79k)

A solution of the imine (1.12 g, 3.94 mmol) and H,Quin-BAM-HOTf (102 mg, 197 µmol) in toluene (8.0 ml, 0.5 M) was cooled to -78 °C. tert-Butyl nitroacetate (762 mg, 4.72 mmol) was added via syringe and the reaction was stirred at -78 °C for 40 h. The reaction was warmed to room temperature and the solvent was removed by rotary evaporation in a 40 °C water bath to afford the crude mixture as an off-white solid. The
solid was filtered through a plug of silica gel using CH$_2$Cl$_2$ and the solvent was removed to afford 1.60 g of the crude. A portion (871 mg) of this mixture was recrystallized from cyclohexane (4.5 mL) to afford the aza-Henry adduct as a white solid (249 mg, 29%), which was determined to be 99% ee, 4:1 dr by HPLC analysis (Chiracel AD, 20% iPrOH/hexanes, 1 mL/min, $t_r$(cis, major) = 30.0 min, $t_r$(cis, minor) = 7.1 min, $t_r$(trans, major) = 19.0 min, $t_r$(trans, minor) = 15.0 min).

The aza-Henry adduct (249 mg, 4:1 dr, 99% ee/99% ee) and anhydrous cobaltous chloride (72.6 mg) were dissolved in methanol (5.6 mL, 0.1 M solution) and cooled to 0 °C. Sodium borohydride (105 mg) was added in three portions. Evolution of hydrogen gas was observed and a black suspension appeared during the addition of sodium borohydride. The reaction was warmed to room temperature, stirred for one hour, and then quenched with 1 M HCl until the black suspension disappeared completely and a clear pink solution was observed. The pH was adjusted to 9 by concentrated NH$_4$OH, resulting in a brown mixture and the formation of a precipitate. MeOH was removed under vacuum, and the resulting aqueous layer was extracted with EtOAc and concentrated to a dark brown oil. The oil was washed through a plug of silica gel with 50% EtOAc in hexanes, and then concentrated to a brown solid under vacuum. The solid was recrystallized from hexanes (1.0 mL) to give the desired product as white crystals (67 mg, 29%), which was determined to be 98% ee/98% ee, 68:1 dr by chiral HPLC analysis (Chiracel AD, 10% iPrOH/hexanes, 1 mL/min, $t_r$(cis, major) = 19.7 min, $t_r$(cis, minor) = 11.8 min, $t_r$(trans, major) = 14.8 min, $t_r$(trans, minor) = 9.7 min). Mp 119-120 °C; IR (neat) 3375, 2977, 1711, 1489, 1367, 1247, 1157 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.46 (d, $J = 8.5$ Hz, 2H), 7.21 (d, $J = 8.5$ Hz, 2H), 5.72 (br s, 1H), 5.11 (br s, 1H), 3.74
(br s, 1H), 1.47 (s, 9H), 1.40 (s, 9H), 1.34 (s, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) ppm 171.4, 155.1, 139.7, 131.7, 128.4, 121.3, 82.4, 79.6, 58.7, 56.0, 28.4, 28.0; HRMS (Cl) Exact mass calcd for C$_{18}$H$_{28}$BrN$_2$O$_4$ [M+H]$^+$ 415.1227. Found 415.1212. Anal. Calcd for C$_{18}$H$_{27}$BrN$_2$O$_4$: C, 52.05; H, 6.55; N, 6.74. Found C, 52.21; H, 6.58; N, 6.71.

**General procedure for the synthesis of nitroacetate adducts 78**

A solution of imine (1.0 equiv) and H,Quin$^6$($^9$Anth)$^2$Pyr-BAM•HOTf (93•HOTf) (0.05 equiv) in toluene (0.3 M) was cooled to -78 °C and treated with tert-butyl nitroacetate (1.1 equiv). The reaction was stirred at -78 °C until complete as determined. The solution was concentrated at 0 °C and the product was immediately subjected to reduction. Diastereomeric ratio of the adducts was determined by $^1$H NMR.

**General procedure for the reduction of aza-Henry adducts anti-79**

A solution of the nitroacetate adduct (1.0 equiv) and cobalt (II) chloride (1.0 equiv) in MeOH (0.1 M) was cooled to 0 °C followed by the addition of sodium borohydride (5.0 equiv). The resulting black suspension was stirred at 0 °C for 15 minutes and then at room temperature until complete (monitored by TLC). The reaction was quenched by the dropwise addition of 3 M aq. HCl until pH 2 was reached. Then 1M aq. NH$_4$OH was added dropwise until the solution attained pH 9. Methanol was removed, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, water, and then dried over magnesium sulfate. Filtration and concentration afforded the crude product which was subjected to purification by column chromatography.
(2R,3R)-tert-Butyl 2-amino-3-(tert-butoxycarbonylamo)-3-(4-chlorophenyl)propanoate (anti-79a)

According to the general procedure on Page 127, tert-butyl 4-chlorobenzylidene carbamate (46.9 mg, 0.20 mmol) provided anti-79a after flash column chromatography (40% ethyl acetate in hexanes) as a yellow oil (63.8 mg, 88%), which was determined to be 95% ee, 5:1 dr by chiral HPLC analysis (Chiralcel AD, 10% iPrOH/hexanes, 1 mL/min, $t_d$(anti, major) = 14.8 min, $t_d$(anti, minor) = 9.7 min, $t_d$(syn, major) = 19.7 min, $t_d$(syn, minor) = 11.8 min). See Page 125 for complete characterization data.

(2R,3R)-tert-Butyl 2-amino-3-(tert-butoxycarbonylamo)-3-(4-florophenyl)propanoate (anti-79d)

According to the general procedure on Page 127, tert-butyl 4-florobenzylidene carbamate (44.6 mg, 0.20 mmol) provided anti-79d after flash column chromatography (40% ethyl acetate in hexanes) as a yellow oil (57.3 mg, 81%), which was determined to be 93% ee, 6:1 dr by HPLC analysis (Chiralcel AD, 10% iPrOH/hexanes, 1 mL/min, $t_d$(anti, major) = 11.8 min, $t_d$(anti, minor) = 8.1 min, $t_d$(syn,
major) = 15.1 min, \( t_{f}(\text{syn, minor}) = 10.2 \text{ min} \). \( R_f = 0.10 \) (20% EtOAc/hexanes); IR (neat)
3411, 2976, 2924, 1712, 1508, 1157 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.30-7.24 (m, 2H), 6.98 (t, \( J = 8.7 \text{ Hz} \), 2H), 5.89 (br s, 1H), 5.03 (br s, 1H), 3.66 (br s, 1H), 1.46 (s, 2H), 1.41 (s, 9H), 1.37 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) ppm 172.2, 162.4 (d, \(^J_{CF} = 244.4 \text{ Hz}\)), 155.1, 134.4, 128.9 (d, \(^J_{CF} = 7.9 \text{ Hz}\)), 115.2 (d, \(^J_{CF} = 21.7 \text{ Hz}\)), 82.2, 79.7, 58.7, 55.4, 28.5, 28.1; \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) ppm -113.2. HRMS (CI): Exact mass calculated for C\(_{18}\)H\(_{26}\)FN\(_2\)O\(_4\) [M+H]\(^+\) 355.2028. Found 355.2035.

(2R,3R)-\textit{tert}-Butyl 2-amino-3-(\textit{tert}-butoxycarbonylamino)-3-\textit{p}-tolylpropanoate (\textit{anti}-79e)

According to the general procedure on Page 127, \textit{tert}-butyl 4-florobenzylidene carbamate (40.9 mg, 0.19 mmol) provided \textit{anti}-79e after flash column chromatography (40% ethyl acetate in hexanes) as a yellow oil (52.9 mg, 81%), which was determined to be 95% ee, 6:1 dr by chiral HPLC analysis (Chiralcel AD, 10% \(^1\)PrOH/hexanes, 1 mL/min, \( t_{f}(\text{anti, major}) = 10.7 \text{ min}, t_{f}(\text{anti, minor}) = 8.2 \text{ min}, t_{f}(\text{syn, major}) = 20.4 \text{ min}, t_{f}(\text{syn, minor}) = 12.8 \text{ min} \). \( R_f = 0.25 \) (40% EtOAc/hexanes); IR (neat)
3410, 2977, 2922, 1713, 1492, 1157, 732 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.20-7.13 (m, 2H), 7.10-7.07 (m, 2H), 5.85 (br d, \( J = 7.8 \text{ Hz} \), 1H), 5.02 (br s, 1H), 3.66 (br s, 1H), 2.30 (s, 3H), 1.47 (s, 2H), 1.41 (s, 9H), 1.39 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) ppm

129
172.5, 155.1, 137.4, 135.4, 129.1, 127.1, 82.0, 79.5, 59.0, 55.9, 28.5, 28.1, 21.2. HRMS (CI): Exact mass calculated for C_{19}H_{31}N_{2}O_{4} [M+H]^+ 351.2278. Found 351.2277.

**General Procedure for the Synthesis of syn-α,β-Diamino Ester 79**

Following the General procedure for the synthesis of nitroacetate adducts on Page 127, the resulting reaction crude mixture was concentrated and subjected to purification by flash column chromatography with silica gel. The adduct α-nitro-β-amino ester (78) was collected as a colorless oil after concentration, which was allowed to stand in the round bottom flask to slowly crystallize. The slow crystallization process often lasted one month. When the oil completely crystallized, it was subjected to the reduction conditions described on Page 127.

![Chemical structure](image)

(2S,3R)-**tert-Butyl 2-amino-3-(**tert-**butoxycarbonylamino)**-3-**p-tolylpropanoate (syn-79e)**

Following the General procedure on Page 130, the imine (38.5 mg, 176 mol) provided **syn-79e** after flash column chromatography (40% ethyl acetate in hexanes) as a yellow oil (46.5 mg, 76%), which was determined to be 90% ee, 4.5:1 dr by HPLC analysis (Chiralcel AD, 10% iPrOH/hexanes, 1 mL/min, t_r(anti, major) = 10.7 min, t_r(anti, minor) = 8.2 min, t_r(syn, major) = 20.4 min, t_r(syn, minor) = 12.8 min). R_f = 0.25 (40% EtOAc/hexanes); IR (neat) 3410, 2977, 2922, 1713, 1492, 1157, 732 cm^{-1}; ^1H NMR (400
MHz, CDCl$_3$) δ 7.21-7.10 (m, 4H), 5.70 (br s, 1H), 5.14 (br s, 1H), 3.77 (br s, 1H), 2.32 (s, 3H), 1.54 (s, 2H), 1.47 (s, 9H), 1.40 (s, 9H); $^{13}$C NMR (150 MHz, CDCl$_3$) ppm 171.7, 155.2, 137.4, 137.0, 129.3, 126.5, 82.2, 79.3, 59.0, 56.1, 28.4, 28.0, 21.1.

![Chemical reaction diagram]

(2S,3R)-tert-Butyl 2-amino-3-(tert-butoxycarbonylamino)-3-$m$-tolylpropanoate (79g)

Following the General procedure on Page 130, the imine (23.5 mg, 107 mol) provided syn-79g after flash column chromatography (40% ethyl acetate in hexanes) as a yellow oil (27.1 mg, 72%), which was determined to be 89% ee, 5:1 dr by HPLC analysis (Chiralcel AD, 10% $^t$PrOH/hexanes, 1 mL/min, $t_r$(anti, major) = 10.2 min, $t_r$(anti, minor) = 7.4 min, $t_r$(syn, major) = 17.7 min, $t_r$(syn, minor) = 12.2 min). $R_f$ = 0.16 (40% EtOAc/hexanes); IR (neat) 3381, 2978, 2929, 1716, 1493, 1368, 1159 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.24-7.16 (m, 1H), 7.11-7.04 (m, 3H), 5.74 (br d, $J = 6.8$ Hz, 1H), 5.14 (br d, $J = 4.4$ Hz, 1H), 3.78 (br s, 1H), 2.34 (s, 3H), 1.54 (br s, 2H), 1.47 (s, 9H), 1.40 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) ppm 171.5, 155.1, 140.1, 138.0, 128.3, 128.0, 127.2, 123.4, 82.0, 79.2, 58.8, 56.2, 28.3, 27.8, 21.4.
(2S,3R)-tert-Butyl 2-amino-3-(4-bromophenyl)-3-(tert-butoxycarbonylamino)propanoate (79k)

Following the General procedure on Page 130, the imine (27.0 mg, 95.0 mol) provided syn-79k after flash column chromatography (25-40% ethyl acetate in hexanes) as a white solid (27.9 mg, 71%), which was determined to be 95% ee, 3.4:1 dr by HPLC analysis. See Page 126 for complete characterization data.

General Procedure for the Synthesis of β-Amino Ester 95

Following the General procedure for the synthesis of nitroacetate adducts on Page 127, the resulting reaction crude mixture was concentrated and subjected to purification by flash column chromatography with silica gel. The adduct α-nitro-β-amino ester (78) was collected as a colorless oil after concentration. 3Bu3SnH (2.0 equiv) was added to a solution of the α-nitro-β-amino ester (78) (1.0 equiv) in benzene (0.10 M) followed by AIBN (0.2 equiv). The reaction mixture was stirred at 80 °C for 2 h, and then concentrated and purified by flash column chromatography on silica gel.
(2S,3R)-tert-Butyl 3-(tert-butoxycarbonylamino)-2-nitro-3-p-tolylpropanoate (78e)

Following the general procedure on Page 127, the imine (35.0 mg, 160 µmol) provided the nitro ester after flash column chromatography (10-15% ethyl acetate in hexanes) as a white solid (55.5 mg, 91%), which was determined to be 88% ee (each diastereomer) and 2:1 (syn:anti) dr by chiral HPLC analysis (Chiralcel AD-H, 10% iPrOH/hexanes, 1 mL/min, \( t_r(syn, \text{major}) = 17.1 \text{ min}, t_r(syn, \text{minor}) = 7.4 \text{ min}, t_r(anti, \text{major}) = 12.8 \text{ min}, t_r(anti, \text{minor}) = 8.8 \text{ min} \)). \( R_f = 0.45 \) (20% EtOAc/hexanes); IR (neat) 3453, 2981, 2933, 1746, 1722, 1565, 1158 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\), 2:1 mixture of diastereomers) major: \( \delta 7.23-7.13 \text{ (m, 4H)}, 6.14 \text{ (br d, } J = 8.1 \text{ Hz, 1H)}, 5.65 \text{ (br d, } J = 8.6 \text{ Hz, 1H)}, 5.59 \text{ (br s, 1H)}, 2.31 \text{ (s, 3H)}, 1.50 \text{ (s, 9H)}, 1.43 \text{ (s, 9H)} \); minor: \( \delta 7.23-7.13 \text{ (m, 4H)}, 5.95 \text{ (br s, 1H)}, 5.71 \text{ (br s, 1H)}, 5.29 \text{ (br d, } J = 5.4 \text{ Hz, 1H)}, 2.33 \text{ (s, 3H)}, 1.41 \text{ (s, 9H)}, 1.39 \text{ (s, 9H)} \); \(^1^3\)C NMR (100 MHz, CDCl\(_3\), 2:1 mixture of diastereomers) major: ppm 161.5, 154.9, 138.2, 133.5, 129.7, 125.9, 92.2, 85.8, 80.5, 53.8, 28.4, 27.8, 21.1; minor: ppm 161.8, 154.9, 138.4, 133.4, 129.7, 126.7, 89.6, 85.2, 80.4, 54.5, 28.3, 27.6, 21.1; HRMS (ESI): Exact mass calculated for C\(_{19}\)H\(_{28}\)N\(_2\)O\(_6\) [M+Na]\(^+\) 403.1845; found 403.1855.

\[
\begin{align*}
\text{H}_2\text{N}^\text{Boc} & \quad \text{Me} \\
\text{H}_2\text{N}^\text{Boc} & \quad \text{Me} \\
\text{CO}_2\text{Bu} & \quad \text{CO}_2\text{Bu}
\end{align*}
\]

(S)-tert-Butyl 3-(tert-butoxycarbonylamino)-3-p-tolylpropanoate (95e)

Following the general procedure on Page 132, the nitro acetate (28.6 mg, 75.2 µmol, 88% ee) provided the β-amino ester after flash column chromatography (10-15%
ethyl acetate in hexanes) as a white solid (22.6 mg, 90%), which was determined to be 88% ee by chiral HPLC analysis (Chiralcel AD-H, 10% \textsuperscript{1}PrOH/hexanes, 1 mL/min, \( t_r \) (major) = 9.0 min, \( t_r \) (minor) = 9.6 min). \([\alpha]^{20}_{D} -24.5 \ (c \ 1.30, \text{CHCl}_3); \ R_f = 0.48 \ (20\% \text{EtOAc/hexanes}); \) mp 98-100 °C; IR (neat) 3381, 2978, 2924, 1708, 1506, 1160 cm\(^{-1}; \) \textsuperscript{1}H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.18 (d, \( J = 8.0 \) Hz, 2H), 7.12 (d, \( J = 8.0 \) Hz, 2H), 5.39 (br s, 1H), 5.02 (br s, 1H), 2.73-2.65 (br m, 2H), 2.31 (s, 3H), 1.41 (s, 9H), 1.38 (s, 9H); \textsuperscript{13}C NMR (100 MHz, CDCl\(_3\)) 170.3, 155.1, 138.5, 137.0, 129.3, 126.2, 81.1, 79.5, 51.3, 42.3, 28.5, 28.0, 21.1; HRMS (ESI): Exact mass calculated for C\(_{19}\)H\(_{29}\)NNaO\(_4\) [M+Na]+ 358.1994; found 358.1995.

\(\text{(S)-\textit{tert}-\text{Butyl 3-(\textit{tert}-\text{butoxycarbonylamino)-3-(4-chlorophenyl)propanoate (95a)}}\)}\)

Following the General Procedures on Page 132, the imine (33.5 mg, 140 \( \mu \)mol) provided the \( \beta \)-amino ester after flash column chromatography (20% ethyl acetate in hexanes) as a white solid (36.5 mg, 73%), which was determined to be 98% ee by chiral HPLC analysis (Chiralcel AD-H, 10% \textsuperscript{1}PrOH/hexanes, 1 mL/min, \( t_r \) (major) = 10.3 min, \( t_r \) (minor) = 11.1 min). \([\alpha]^{20}_{D} +4.8 \ (c \ 1.00, \text{CHCl}_3); \ R_f = 0.44 \ (20\% \text{EtOAc/hexanes}); \) mp 102-104 °C; IR (neat) 3360, 2979, 2932, 1713, 1493, 1367, 1159 cm\(^{-1}; \) \textsuperscript{1}H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.29 (d, \( J = 8.5 \) Hz, 2H), 7.23 (d, \( J = 8.5 \) Hz, 2H), 5.44 (br s, 1H), 5.01 (br s, 1H), 2.71-2.69 (br m, 2H), 1.41 (s, 9H), 1.36 (s, 9H); \textsuperscript{13}C NMR (100 MHz, CDCl\(_3\))
ppm 170.1, 155.1, 140.2, 133.2, 128.7, 127.7, 81.5, 79.9, 51.0, 42.0, 28.4, 28.0; HRMS (CI): Exact mass calculated for C_{18}H_{27}ClNO_{4} [M+H]^+ 356.1623; found 356.1628.

The denitration was also performed using the silane method:^{206} tBu_{3}SnH (5.6 µL, 21 mmol) and PhSiH_{3} (25.8 µL, 210 mmol) were added to a solution of the α-nitro-β-amino ester (42.0 mg, 105 mmol) in benzene (1.1 mL, 0.10 M) followed by AIBN (3.4 mg, 21 mmol). The reaction mixture was stirred at 80 °C for 36 h, and then concentrated and purified by flash column chromatography on silica gel to provide the β-amino ester as a white solid (26.2 mg, 70%), which was determined to be 97% ee by chiral HPLC analysis.

(S)-tert-Butyl 3-(tert-butoxycarbonylamino)-3-(4-methoxyphenyl)propanoate (95b)

Following the General Procedures on Page 132, the imine (40.3 mg, 171 µmol) provided the β-amino ester after flash column chromatography (10-20% ethyl acetate in hexanes) as a white solid (52.9 mg, 88%), which was determined to be 85% ee by chiral HPLC analysis (Chiralcel AD-H, 10% iPrOH/hexanes, 1 mL/min, t_{f}(major) = 11.0 min,

$t_c$(minor) = 11.9 min. $[\alpha]^{20}_D$ -28.7 (c 1.00, CHCl$_3$); $R_f$ = 0.29 (20% EtOAc/hexanes); mp 80-82 $^\circ$C; IR (neat) 3307, 2972, 1703, 1516, 1252, 1158 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.21 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 5.38 (br s, 1H), 5.00 (br s, 1H), 3.78 (s, 3H), 2.74-2.64 (br m, 2H), 1.41 (s, 9H), 1.34 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) ppm 170.3, 158.9, 155.1, 133.7, 127.5, 113.9, 81.1, 79.5, 55.3, 51.0, 42.3, 28.4, 28.0; HRMS (ESI): Exact mass calculated for C$_{19}$H$_{29}$NNaO$_5$ [M+Na]$^+$ 374.1943; found 374.1946.

(S)-tert-Butyl 3-(tert-butoxycarbonylamino)-3-(4-fluorophenyl)propanoate (95c)

Following the General Procedures on Page 132, the imine (30.5 mg, 136 $\mu$mol) provided the $\beta$-amino ester after flash column chromatography (10-15% ethyl acetate in hexanes) as a colorless oil (39.6 mg, 85%), which was determined to be 93% ee by chiral HPLC analysis (Chiralcel AD-H, 10% EtOH/hexanes, 1 mL/min, $t_c$(major) = 7.5 min, $t_c$(minor) = 6.9 min). $[\alpha]^{20}_D$ -18.0 (c 1.16, CHCl$_3$); $R_f$ = 0.41 (20% EtOAc/hexanes); IR (neat) 3355, 2979, 2933, 1710, 1510, 1367, 1226, 1157 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.28-7.24 (m, 2H), 7.00 (dd, $J = 8.6$, 8.6 Hz, 2H), 5.51 (br s, 1H), 5.02 (br s, 1H), 2.73-2.65 (br m, 2H), 1.41 (s, 9H), 1.33 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 170.2, 162.1(d, $^1J_{CF}$ = 244.4 Hz), 155.0, 137.3, 127.9 (d, $^3J_{CF}$ = 7.9 Hz), 115.4 (d, $^2J_{CF}$ = 21.7 Hz), 81.4, 79.8, 50.9, 42.2, 28.4, 28.0; $^{19}$F NMR (282 MHz, CDCl$_3$) ppm -113.6; HRMS (ESI): Exact mass calculated for C$_{18}$H$_{26}$FNNaO$_4$ [M+Na]$^+$ 362.1744; found 362.1735.
(S)-tert-Butyl 3-(tert-butoxycarbonylamino)-3-m-tolylpropanoate (95d)

Following the General Procedures on Page 132, the imine (35.6 mg, 136 µmol) provided the β-amino ester after flash column chromatography (10-15% ethyl acetate in hexanes) as a colorless oil (47.2 mg, 87%), which was determined to be 87% ee by chiral HPLC analysis (Chiralcel AD-H, 10% iPrOH/hexanes, 0.7 mL/min, $t_r$(major) = 6.3 min, $t_r$(minor) = 6.0 min). [α]$_D^{20}$ -21.0 (c 0.82, CHCl$_3$); R$_f$ = 0.43 (20% EtOAc/hexanes); IR (neat) 3349, 2978, 2930, 1713, 1498, 1367, 1167 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.20 (dd, $J$ = 7.5, 7.5 Hz, 1H), 7.10-7.04 (m, 3H), 5.44 (br s, 1H), 5.02 (br s, 1H), 2.73-2.66 (br m, 2H), 2.33 (s, 3H), 1.42 (s, 9H), 1.34 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) ppm 170.3, 155.1, 141.4, 138.1, 128.5, 128.2, 127.1, 123.3, 81.1, 79.6, 51.6, 42.4, 28.4, 28.0, 21.5; HRMS (ESI): Exact mass calculated for C$_{19}$H$_{29}$NNaO$_4$ [M+Na]$^+$ 358.1994; found 358.1985.

(S)-tert-Butyl 3-(tert-butoxycarbonylamino)-3-(naphthalen-2-yl) propanoate (95f)

Following the General Procedures on Page 132, the imine (31.8 mg, 125 µmol) provided the β-amino ester after flash column chromatography (10-15% ethyl acetate in
hexanes) as a white solid (35.5 mg, 77%), which was determined to be 95% ee by chiral HPLC analysis (Chiralcel AD-H, 10% iPrOH/hexanes, 1 mL/min, \( t_r \) (major) = 11.8 min, \( t_r \) (minor) = 12.6 min). [\( \alpha \r{20} \)]\(_D\) -28.4 (c 1.09, CHCl\(_3\)); \( R_f \) = 0.41 (20% EtOAc/hexanes); mp 86-88 °C; IR (neat) 3360, 2976, 2924, 1709, 1509, 1306, 1250, 1160 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.84-7.82 (m, 3H), 7.76 (s, 1H), 7.49-7.43 (m, 3H), 5.62 (br s, 1H), 5.25 (br s, 1H), 2.85-2.83 (br m, 2H), 1.45 (s, 9H), 1.35 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) ppm 170.3, 155.2, 139.0, 133.4, 132.8, 128.5, 128.0, 127.7, 126.2, 125.9, 124.9, 124.6, 81.3, 79.7, 51.7, 42.2, 28.5, 28.0; HRMS (ESI): Exact mass calculated for C\(_{22}\)H\(_{20}\)NNaO\(_4\) [M+Na\(^+\)] 394.1994; found 394.2000.

(S)-tert-Butyl 3-(tert-butoxycarbonylamino)-3-(3-phenoxyphenyl)propanoate (95g)

Following the General Procedures on Page 132, the imine (46.2 mg, 155 μmol) provided the β-amino ester after flash column chromatography (10-15% ethyl acetate in hexanes) as a colorless oil (43.5 mg, 67%), which was determined to be 89% ee by chiral HPLC analysis (Chiralcel AD-H, 10% iPrOH/hexanes, 1 mL/min, \( t_r \) (major) = 10.9 min, \( t_r \) (minor) = 8.3 min). [\( \alpha \r{20} \)]\(_D\) -14.8 (c 1.15, CHCl\(_3\)); \( R_f \) = 0.40 (20% EtOAc/hexanes); IR (neat) 3360, 2977, 2928, 1715, 1585, 1488, 1367, 1247, 1163 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.34-7.26 (m, 3H), 7.11-7.08 (m, 1H), 7.03 (d, \( J = 8.6 \) Hz, 1H), 6.99-6.97 (m, 3H), 6.88 (d, \( J = 7.9 \) Hz, 1H), 5.50 (br s, 1H), 5.03 (br s, 1H), 2.70 (br s, 2H), 1.41 (s, 9H), 1.35 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) ppm 170.2, 157.4, 157.2, 155.1, 143.7, 129.9,
129.8, 123.3, 121.2, 118.9, 117.8, 116.8, 81.4, 79.7, 51.2, 42.2, 28.4, 28.0; HRMS (ESI): Exact mass calculated for C$_{24}$H$_{31}$NNaO$_5$ [M+Na]$^+$ 436.2100; found 436.2114.

(S)-**tert**-butyl 3-(biphenyl-4-yl)-3-(**tert**-butoxycarbonylamino)propanoate (95h)

Following the General Procedures on Page 132, the imine (30.5 mg, 108 µmol) provided the β-amino ester after flash column chromatography (10-15% ethyl acetate in hexanes) as a white solid (35.0 mg, 81%), which was determined to be 92% ee by chiral HPLC analysis (Chiralcel AD-H, 10% iPrOH/hexanes, 1 mL/min, $t_r$(major) = 12.8 min, $t_r$(minor) = 14.1 min). $[\alpha]_{D}^{20}$ -32.0 (c 1.00, CHCl$_3$); $R_f$ = 0.35 (20% EtOAc/hexanes); mp 98-100 °C; IR (neat) 3355, 2977, 2932, 1713, 1490, 1367, 1162 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.59-7.54 (m, 4H), 7.45-7.41 (m, 2H), 7.38-7.31 (m, 3H), 5.53 (br s, 1H), 5.11 (br s, 1H), 2.79-2.73 (br m, 2H), 1.44 (s, 9H), 1.36 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 170.3, 155.1, 140.8, 140.6, 140.4, 128.8, 127.4, 127.3, 127.1, 126.7, 81.3, 79.7, 51.3, 42.2, 28.5, 28.0; HRMS (ESI): Exact mass calculated for C$_{24}$H$_{31}$NNaO$_4$ [M+Na]$^+$ 420.2151; found 420.2152.

(S)-**tert**-Butyl 3-(4-acetoxyphenyl)-3-(**tert**-butoxycarbonylamino)propanoate (95i)

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Following the General Procedures on Page 132, the imine (30.2 mg, 115 μmol) provided the β-amino ester after flash column chromatography (20% ethyl acetate in hexanes) as a white solid (29.6 mg, 68%), which was determined to be 91% ee by chiral HPLC analysis (Chiralcel AD-H, 10% iPrOH/hexanes, 1 mL/min, \(t_\text{r(major)}\) = 12.8 min, \(t_\text{r(minor)}\) = 14.1 min). \([\alpha]_D^{20} -25.2 (c 1.00, \text{CHCl}_3); R_f = 0.23 (20\% \text{ EtOAc/hexanes}); \text{mp} 76-77 \degree C; \text{IR (neat)} 3375, 2979, 2925, 1764, 1726, 1681, 1514, 1197, 1164 \text{ cm}^{-1}; ^1H \text{ NMR (400 MHz, CDCl}_3\) δ 7.30 (d, \(J = 8.5 \text{ Hz}, 2\text{H}), 7.04 (d, \(J = 8.5 \text{ Hz}, 2\text{H}), 5.47\) (br s, 1H), 5.06 (br s, 1H), 2.72-2.69 (br m, 2H), 2.28 (s, 3H), 1.41 (s, 9H), 1.34 (s, 9H); ^13C \text{ NMR (100 MHz, CDCl}_3\) ppm 170.2, 169.5, 155.0, 149.9, 139.1, 127.4, 121.7, 81.4, 79.8, 51.0, 42.2, 28.4, 28.0, 21.2; HRMS (ESI): Exact mass calculated for C_{20}H_{25}NNaO_6 [M+Na]^+ 402.1893; found 402.1900.

(S)-tert-Butyl 3-(tert-butoxycarbonylamino)-3-(furan-2-yl)propanoate (95j)

Following the General Procedures on Page 132, the imine (36.0 mg, 184 μmol) provided the β-amino ester after flash column chromatography (20% ethyl acetate in hexanes) as a colorless oil (36.0 mg, 64%), which was determined to be 85% ee by chiral HPLC analysis (Chiralcel IA, 10% iPrOH/hexanes, 0.7 mL/min, \(t_\text{r(major)}\) = 8.3 min, \(t_\text{r(minor)}\) = 8.6 min); \([\alpha]_D^{20} -21.8 (c 1.66, \text{CHCl}_3); R_f = 0.51 (20\% \text{ EtOAc/hexanes}); \text{IR (neat)} 3351, 2979, 2933, 1720, 1500, 1368, 1162 \text{ cm}^{-1}; ^1H \text{ NMR (400 MHz, CDCl}_3\) δ 7.32 (s, 1H), 6.28 (s, 1H), 6.17 (s, 1H), 5.38 (br s, 1H), 5.13 (br s, 1H), 2.79 (dd, \(J = 140\)
15.2, 5.6 Hz, 1H), 2.71 (dd, J = 15.2, 6.1 Hz, 1H), 1.44 (s, 9H), 1.39 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 170.0, 155.0, 154.0, 141.8, 110.3, 106.0, 81.2, 79.8, 45.9, 39.8, 28.4, 28.0; HRMS (ESI): Exact mass calculated for C$_{16}$H$_{25}$NNaO$_5$ [M+Na]$^+$ 334.1630; found 334.1643.

(S)-tert-Butyl 3-(3-acetoxy-4-methoxyphenyl)-3-(tert-butoxycarbonylamino) propanoate (95l)

Following the General Procedures on Page 132, the imine (35.3 mg, 120 µmol) provided the β-amino ester after flash column chromatography (20-30% ethyl acetate in hexanes) as a yellow oil (37.2 mg, 75%), which was determined to be 88% ee by chiral HPLC analysis (Chiralcel IA, 10% EtOH/hexanes, 1 mL/min, $t_r$(major) = 7.7 min, $t_r$(minor) = 6.2 min). $R_f$ = 0.14 (20% EtOAc/hexanes); IR (neat) 3361, 2978, 2934, 1769, 1713, 1513, 1368, 1268, 1204, 1166 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.12 (dd, J = 8.4, 1.8 Hz, 1H), 6.97 (d, J = 2.0 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 5.40 (br s, 1H), 4.99 (br s, 1H), 3.79 (s, 3H), 2.72-2.63 (br m, 2H), 2.28 (s, 3H), 1.40 (s, 9H), 1.34 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 170.2, 168.8, 155.0, 150.4, 139.7, 134.2, 124.7, 120.9, 112.3, 81.3, 79.6, 56.0, 50.7, 42.1, 28.4, 28.0, 20.7; HRMS (CI): Exact mass calculated for C$_{21}$H$_{32}$NO$_7$ [M+H]$^+$ 410.2173; found 410.2188.
5-((tert-Butoxycarbonylimino)methyl)-2-methoxyphenyl acetate (61I)

Following the Greene protocol, the imine was obtained as a yellow oil. IR (neat) 2976, 1770, 1711, 1607, 1512, 1247, 1152, 1124, 732 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 8.73\) (s, 1H), 7.66-7.61 (m, 2H), 6.93 (d, \(J = 8.5\) Hz, 1H), 3.78 (s, 3H), 2.21 (s, 3H) 1.49 (s, 9H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) ppm 168.5, 168.3, 162.3, 155.6, 140.0, 130.6, 127.0, 123.6, 111.9, 81.7, 55.9, 27.7, 20.3; HRMS (CI): Exact mass calculated for C\(_{13}\)H\(_{19}\)NO\(_5\) [M]+ 293.1258; found 293.1263.

(S)-Methyl 3-((tert-butoxycarbonylamino)-3-(3-hydroxy-4-methoxyphenyl)propanoate (96)

SOCl\(_2\) (26.5 µL, 363 µmol) was added to a solution of the tert-butyl ester (37.2 mg, 90.8 µmol, 88% ee) in MeOH (1.8 mL, 0.05 M). The reaction was heated at reflux for 5 h. The resulting mixture was concentrated to a yellow oil under vaccum. This oil was diluted with dioxane and H\(_2\)O (1:1, 0.91 mL, 0.10 M), and treated with (Boc)\(_2\)O (39.6 mg, 182 µmol), followed by NEt\(_3\) (15.2 µL, 109 µmol). The reaction was stirred at room temperature overnight and then its pH was adjusted to 4 using 1 M HCl. The mixture was extracted with EtOAc, and the organic layers were dried, filtered and
concentrated. The residue was purified by flash column chromatography on silica gel (25-40% ethyl acetate in hexanes) to give the methyl ester as a colorless oil (25.0 mg, 85%), which was determined to be 88% ee by chiral HPLC analysis (Chiralcel OD-H, 10% iPrOH/hexanes, 1 mL/min, \( t_r^{\text{major}} = 18.1 \text{ min}, t_r^{\text{minor}} = 19.5 \text{ min} \). [\( \alpha \])_{D}^{20} -29.7 (c 1.45, CHCl\text{)}; R\text{}_{f} = 0.28 (40% EtOAc/hexanes). The \( ^1\text{H} \) NMR of the material obtained was identical to the racemic material reported earlier.\textsuperscript{207}

(S)-Methyl 3-(3-acetoxy-4-methoxyphenyl)-3-(\textit{tert}-butoxycarbonylamino) propanoate (98)

Following the General Procedures on Page 132, but with \( \alpha \)-nitro methyl acetate, the imine (46.9 mg, 160 \( \mu \)mol) provided the \( \beta \)-amino ester after flash column chromatography (20-30% ethyl acetate in hexanes) as a yellow oil (40.5 mg, 69%), which was determined to be 72% ee by chiral HPLC analysis (Chiralcel AD-H, 10% iPrOH/hexanes, 1 mL/min, \( t_r^{\text{major}} = 17.6 \text{ min}, t_r^{\text{minor}} = 19.3 \text{ min} \). [\( \alpha \])_{D}^{20} -16.9 (c 0.89, CHCl\text{)}; R\text{}_{f} = 0.29 (40% EtOAc/hexanes); mp 98-100 °C; IR (neat) 3381, 2987, 1762, 1730, 1686, 1514, 1270, 1205, 1165 cm\(^{-1}\); \( ^1\text{H} \) NMR (400 MHz, CDCl\text{)}\text{)} \( \delta \) 7.13 (dd, \( J = 8.5, 2.0 \text{ Hz, 1H} \)), 6.97 (d, \( J = 2.1 \text{ Hz, 1H} \)), 6.91 (d, \( J = 8.5 \text{ Hz, 1H} \)), 5.39 (br s, 1H), 5.03 (br s, 1H), 3.80 (s, 3H), 3.61 (s, 3H), 2.83-2.74 (br m, 2H), 2.29 (s, 3H), 1.41 (s, 9H); \( ^{13}\text{C} \) NMR (100 MHz, CDCl\text{)}\text{)} ppm 171.4, 168.9, 155.0, 150.5, 139.8, 133.9, 124.7, 120.9,

112.5, 79.8, 56.0, 51.9, 50.7, 40.7, 28.4, 20.7; HRMS (ESI): Exact mass calculated for C$_{18}$H$_{25}$NNaO$_7$ [M+Na]$^+$ 390.1529; found 390.1536.

![Chlorination of Amine](image)

**Chlorination of Amine**

NCS (159 mg, 1.19 mmol) was added to the solution of the amine (144 mg, 1.19 mmol) in CH$_2$Cl$_2$. The reaction mixture was stirred at room temperature for 10 min. The resulting mixture was concentrated and subjected to purification by flash column chromatography on silica gel (pure hexanes to 10% EtOAc in hexanes), to afford the desired N-chloroamine as a colorless oil (30.0 mg, 16%) and N,N-dichloroamine as a colorless oil (10.0 mg, 4%). The reaction occurred with complete conversion to the N-chloroamine, and decomposition and conversion to N,N-dichloroamine occurred during chromatography. The N-chloroamine and N,N-dichloroamine were not stable when concentrated, which decomposed at room temperature in hours.

**N-Chloro-1-phenylethanamine (118)**

R$_f$ = 0.54 (20% EtOAc/hexanes); IR (neat) 3267, 3062, 3031, 2978, 2930, 2875, 1681, 1453 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39-7.31 (m, 5H), 4.35 (br d, $J$ = 3.4, Hz, 1H), 4.19-4.13 (m, 1H), 1.50 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 142.0, 128.7, 128.2, 127.0, 64.7, 21.3.

**N,N-Dichloro-1-phenylethanamine (119)**
R_f = 0.74 (20% EtOAc/hexanes); IR (neat) 3064, 3033, 2991, 2937, 2902, 1454 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.42-7.35 (m, 5H), 4.57 (q, \(J = 6.6\) Hz, 1H), 1.75 (d, \(J = 6.6\) Hz, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) ppm 139.5, 129.0, 128.5, 128.3, 79.6, 18.8.

![Reaction Scheme](image)

**2-Bromo-2-nitroethyl**benzene (107a and 121c)

Following the Kornblum protocol,\(^{208}\) the nitroalkane\(^{209}\) (976 mg, 6.46 mmol) provided the \(\alpha\)-bromo nitroalkane without chromatography as a colorless oil (1.26 g, 85%). IR (neat) 3066, 3032, 2908, 1565, 1356 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.38-7.30 (m, 3H), 7.22-7.19 (m, 2H), 6.05 (dd, \(J = 8.2, 6.1\) Hz, 1H), 3.76 (dd, \(J = 14.6, 8.2\) Hz, 1H), 3.51 (dd, \(J = 14.6, 6.1\) Hz, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) ppm 133.3, 129.3, 129.2, 128.4, 79.2, 43.6; HRMS (CI): Exact mass calcd. for C\(_8\)H\(_8\)Br [M-NO\(_2\)]\(^+\) 182.9804, found 182.9791.

![Reaction Scheme](image)

**2-Chloro-2-nitroethyl**benzene (121b)

Following the Kornblum protocol,\(^{208}\) the nitroalkane (290 mg, 1.92 mmol) and NCS (256 mg, 1.92 mmol) provided the \(\alpha\)-chloro nitroalkane after flash column chromatography on silica gel (2-5% EtOAc in hexanes) as a colorless oil (338 mg, 95%).

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Rʃ = 0.63 (20% EtOAc/hexanes); IR (neat) 3067, 3034, 1566, 1358 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.34 (m, 3H), 7.24-7.21 (m, 2H), 5.97 (t, J = 6.8 Hz, 1H), 3.65 (dd, J = 14.3, 6.9 Hz, 1H), 3.45 (dd, J = 14.3, 6.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) ppm 132.6, 129.6, 129.1, 128.4, 91.7, 43.2; HRMS (CI): Exact mass calculated for C₈H₆Cl [M-NO₂]⁺ 139.0310, found 139.0312.

(2-Iodo-2-nitroethyl)benzene (121d)

Following the Kornblum protocol,²⁰⁸ the nitroalkane (520 mg, 3.44 mmol) and iodine (873 mg, 3.44 mmol) provided the α-iodo nitroalkane after flash column chromatography on silica gel (2% EtOAc in hexanes) as a yellow oil (880 mg, 92%). Rʃ = 0.52 (20% EtOAc/hexanes); IR (neat) 3031, 1557, 1351 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.31 (m, 3H), 7.20-7.17 (m, 2H), 6.32 (dd, J = 9.2, 5.8 Hz, 1H), 3.80 (dd, J = 14.7, 9.2 Hz, 1H), 3.53 (dd, J = 14.7, 5.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) ppm 135.1, 129.2, 129.0, 128.3, 52.8, 45.5; HRMS (CI): Exact mass calculated for C₈H₈I [M-NO₂]⁺ 230.9665, found 230.9673.

(2,2-Dinitroethyl)benzene (120)
KNO$_2$ (155 mg, 1.83 mmol) was added to the solution of the bromonitroalkane (140 mg, 608 µmol) in THF and H$_2$O (3:1). The reaction mixture was stirred at room temperature for 6 h. The resulting mixture was quenched with 1 M HCl until pH 3 was reached. THF was removed under vacuum, and the mixture was extracted with CH$_2$Cl$_2$. The organic solution was concentrated and subjected to purification by flash column chromatography on silica gel (2-10% EtOAc in hexanes), to afford the desired dinitroalkane as a colorless oil (24.0 mg, 20%). R$_f$ = 0.42 (20% EtOAc/hexanes); IR (neat) 3033, 2927, 1668, 1574, 1333 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.39-7.34 (m, 3H), 7.25-7.22 (m, 2H), 6.33 (t, $J = 2.6$ Hz, 1H), 3.81 (d, $J = 2.6$ Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 130.0, 129.4, 129.0, 128.8, 112.3, 37.1; HRMS (EI): Exact mass calculated for C$_8$H$_8$N$_2$O$_4$ [M]$^+$ 196.0479, found 196.0472. Phenyl acetic acid was also isolated in 31% yield (26.0 mg) after flash column chromatography with 5% MeOH in dichloromethane.

(Bromonitromethyl)cyclohexane (107d)

Following the Kornblum protocol,$^{208}$ the nitroalkane$^{210}$ (430 mg, 3.00 mmol) provided the α-bromo nitroalkane without chromatography as a colorless oil (560 mg, 84%). IR (neat) 2934, 2857, 1563 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.73 (d, $J = 8.0$ Hz, 1H), 2.16 (dddd, $J = 11.3$, 11.3, 8.0, 3.3, 3.3 Hz, 1H), 1.97-1.92 (m, 1H), 1.85-1.76 (m, 2H), 1.72-1.66 (m, 2H), 1.36-1.31 (m, 2H), 1.30-1.25 (m, 3H); $^{13}$C NMR (100 MHz,

CDCl₃) ppm 86.6, 43.5, 29.3, 28.8, 25.6, 25.3, 25.2; HRMS (CI): Exact mass calcd. for C₇H₁₂Br [M-NO₂]⁺ 175.0117, found 175.0116.

1-Bromo-4-chloro-1-nitrobutane (107c)

Following the Kornblum protocol,²⁰⁸ the nitroalkane²¹¹ (218 mg, 1.58 mmol) provided the α-bromo nitroalkane after flash column chromatography (5% ethyl acetate in hexanes) as a colorless oil (115 mg, 34%) (Reaction conditions were not optimized). R₇ = 0.49 (20% EtOAc/hexanes); IR (neat) 2964, 1565, 1353 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.98 (t, J = 6.8 Hz, 1H), 3.61-3.57 (m, 2H), 2.65-2.55 (m, 1H), 2.52-2.43 (m, 1H), 2.01-1.89 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) ppm 79.0, 43.1, 34.7, 28.7; HRMS (CI): Exact mass calcd. for C₄H₇BrCl [M-NO₂]⁺ 168.9414, found 168.9414.

2-(2-Nitroethyl)-1,3-dioxane (S-3)

NaNO₂ (1.24 g, 18.0 mmol) and phloroglucinol (1.39 g, 11.0 mmol) were added to a solution of the bromide (1.95 g, 10.0 mmol) in DMSO (33.3 mL). The reaction mixture was stirred at room temperature for 3 d. The resulting crude was added ice-water and then extracted with Et₂O. The organic layer was dried, filtered and concentrated. The

residue was purified by flash column chromatography on silica gel (15% ethyl acetate in hexanes) to give the nitroalkane as a colorless oil (1.12 g, 70%). \( R_f = 0.21 \) (20% EtOAc/hexanes); IR (neat) 2965, 2860, 1556, 1383, 1141 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.70 (t, \( J = 4.5 \) Hz, 1H), 4.51 (t, \( J = 7.0 \) Hz, 2H), 4.10-4.06 (m, 2H), 3.75 (ddd, \( J = 12.4, 12.4, 2.4 \) Hz, 2H), 2.29 (ddd, \( J = 6.9, 6.9, 4.6 \) Hz, 2H), 2.11-1.98 (m, 1H), 1.36-1.32 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) ppm 98.5, 70.5, 66.9, 32.3, 25.6; HRMS (CI): Exact mass calcd. for C\(_6\)H\(_{12}\)NO\(_4\) [M+H]\(^+\) 162.0761, found 162.0758.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{NO}_2 & \quad \text{NO}_2 \\
\text{1. KOH, MeOH/H}_2\text{O} & \quad 2. \text{Br}_2, \text{CH}_2\text{Cl}_2, -78^\circ\text{C} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

2-(2-Bromo-2-nitroethyl)-1,3-dioxane (107f)

Following the Kornblum protocol\(^{208}\) the nitroalkane (600 mg, 3.72 mmol) provided the \( \alpha \)-bromo nitroalkane without chromatography as a colorless oil (850 mg, 95%). \( R_f = 0.32 \) (20% EtOAc/hexanes); IR (neat) 2974, 2862, 1568, 1134, 1015 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 6.10 (dd, \( J = 8.1, 5.6 \) Hz, 1H), 4.66 (dd, \( J = 4.7, 4.7 \) Hz, 1H), 4.12-4.05 (m, 2H), 3.75 (ddd, \( J = 11.9, 11.9, 2.4 \) Hz, 1H), 3.72 (ddd, \( J = 11.9, 11.9, 2.4 \) Hz, 1H), 2.87 (ddd, \( J = 14.6, 8.1, 5.0 \) Hz, 1H), 2.48 (ddd, \( J = 11.9, 5.2, 4.8 \) Hz, 1H), 2.05 (dddd, \( J = 12.8, 12.8, 12.8, 5.0 \) Hz, 1H), 1.37-1.32 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) ppm 98.1, 74.2, 67.0, 66.9, 42.3, 25.5; HRMS (CI): Exact mass calcd. for C\(_6\)H\(_{11}\)BrNO\(_4\) [M+H]\(^+\) 239.9871, found 239.9868.
4-Bromo-3,3-dimethyl-4-nitrobutanenitrile (107g)

Following the Kornblum protocol, the nitroalkane (296 mg, 2.08 mmol) provided the α-bromo nitroalkane after flash column chromatography (6% ethyl acetate in hexanes) as a colorless viscous oil (380 mg, 83%). R$_f$ = 0.30 (20% EtOAc/hexanes); IR (neat) 2982, 2941, 2248, 1564, 1469, 1352 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.95 (s, 1H), 2.67 (d, J = 6.9 Hz, 1H), 2.62 (d, J = 6.9 Hz, 1H), 1.30 (s, 3H), 1.29 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 116.3, 88.1, 38.5, 27.2, 23.7, 23.0; HRMS (CI): Exact mass calcd. for C$_6$H$_{10}$BrN$_2$O$_2$ [M+H]$^+$ 220.9920, found 220.9928.

4-Bromo-4-nitrobutan-1-ol (107h)

Following the Kornblum protocol, the nitroalkane (170 mg, 1.43 mmol) provided the α-bromo nitroalkane after flash column chromatography (25-30% ethyl acetate in hexanes) as a colorless oil (230 mg, 81%). R$_f$ = 0.36 (40% EtOAc/hexanes); IR (neat) 3368, 2940, 2888, 1565, 1355, 1059 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.05 (t, J = 6.9 Hz, 1H), 3.71 (td, J = 5.9, 2.6 Hz, 2H), 2.60-2.50 (m, 1H), 2.45-2.35 (m, 1H), 1.86 (br s, 1H), 1.75-1.63 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 79.7, 61.3, 34.5, 28.7; HRMS (CI): Exact mass calcd. for C$_4$H$_9$BrNO$_3$ [M+H]$^+$ 197.9758, found 197.9760.

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3-Bromo-3-nitropropan-1-ol (107i)

Following the Kornblum protocol, the nitroalkane (157 mg, 1.49 mmol) provided the α-bromo nitroalkane after flash column chromatography (20% ethyl acetate in hexanes) as a colorless oil (249 mg, 90%). Rf = 0.11 (20% EtOAc/hexanes); IR (neat) 3369, 2895, 1566, 1362, 1049 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.19 (t, J = 6.9 Hz, 1H), 3.86-3.81 (m, 2H), 2.70 (dddd, J = 14.7, 12.2, 6.5, 6.5 Hz, 1H), 2.47 (dddd, J = 14.7, 7.2, 5.2, 5.2 Hz, 1H), 1.52 (dd, J = 7.8, 4.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) ppm 77.4, 58.5, 39.7; HRMS (Cl): Exact mass calcd. for C₃H₇BrO[Br-NO₂]⁺ 136.9597, found 136.9590.

Methyl 4-bromo-4-nitrobutanoate (107j)

Following the Kornblum protocol, the nitroalkane (696 mg, 4.73 mmol) provided the α-bromo nitroalkane after flash column chromatography (10% ethyl acetate in hexanes) as a colorless oil (430 mg, 40%, reaction conditions not optimized). Rf = 0.45 (20% EtOAc/hexanes); IR (neat) 3014, 2955, 1735, 1565, 1438, 1203 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.15-6.12 (m, 1H), 3.72 (s, 3H), 2.76-2.65 (m, 1H), 2.63-2.49 (m,

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3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) ppm 171.6, 78.6, 52.3, 32.4, 30.0; HRMS (CI): Exact mass calcd. for C\(_5\)H\(_8\)BrO\(_2\) [M-NO\(_2\)]\(^+\) 178.9702, found 178.9706.

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

The amine (1.2 equiv) was added dropwise to a solution of \(\alpha\)-bromo nitroalkane (1.0 equiv, 0.2 M) and NIS (10 equiv) in THF and H\(_2\)O (5.0 equiv) at 0 °C, followed by K\(_2\)CO\(_3\) (2.0 equiv). The reaction mixture was stirred at 0 °C for 2 d. The resulting mixture was diluted with dichloromethane, dried with MgSO\(_4\) and then filtered through Celite. The filtrate was concentrated and subjected to purification by flash column chromatography on silica gel.

**General Procedure B: Amide Synthesis Using an Ammonium Salt**

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

\[
\text{Et} - \text{NO}_2 \quad \text{H}_2\text{N} - \text{Ph} \quad \text{NIS, K}_2\text{CO}_3 \quad \text{H}_2\text{O} \quad \text{THF, 0 °C} \quad \text{Et} - \text{N} - \text{Ph}
\]

\(N-(1\text{-Phenylethyl})\text{propionamide (122b)}\)

Following General Procedure A on Page 152, the \(\alpha\)-bromo nitroalkane (29.8 mg, 177 µmol) and amine (25.8 mg, 213 µmol) provided the amide after flash column
chromatography (30% ethyl acetate in hexanes) as a white solid (22.2 mg, 71%). $R_f = 0.11$ (20% EtOAc/hexanes); mp 58-60 °C; spectroscopic data ($^1$H NMR) was in complete accord with that previously reported.\textsuperscript{215}

\begin{center}
\includegraphics[width=0.5\textwidth]{reaction_diagram}
\end{center}

\textbf{N-(1-Phenylethyl)benzamide (122c)}

Following General Procedure A on Page 152, the α-bromo nitroalkane (29.5 mg, 137 µmol) and amine (19.7 mg, 164 µmol) provided the amide after flash column chromatography (15-25% ethyl acetate in hexanes) as an off-white solid (23.5 mg, 76%). $R_f = 0.22$ (20% EtOAc/hexanes); mp 118-119 °C; spectroscopic data ($^1$H NMR) was in complete accord with that previously reported.\textsuperscript{216}

\begin{center}
\includegraphics[width=0.5\textwidth]{reaction_diagram}
\end{center}

\textbf{2-Phenyl-N-(1-phenylethyl)acetamide (122a)}

Following General Procedure A on Page 152, the α-bromo nitroalkane (25.6 mg, 111 µmol) and amine (16.2 mg, 134 µmol) provided the amide after flash column chromatography (25-40% ethyl acetate in hexanes) as a white solid (20.0 mg, 75%). $R_f = 0.35$ (40% EtOAc/hexanes); mp 115-117 °C; spectroscopic data (IR, $^1$H NMR and $^{13}$C


\textsuperscript{216} Wang, Z.; Zhang, Y.; Fu, H.; Jiang, Y.; Zhao, Y. Org. Lett. 2008, 10, 1863.
NMR) was in complete accord with that previously reported.\textsuperscript{217} HRMS (ESI): Exact mass calcd. for C\textsubscript{16}H\textsubscript{18}NO [M+H]\textsuperscript{+} 240.1388, found 240.1389.

\[
\text{\begin{tikzpicture}

\node[align=center] (equation) at (0,0) {\text{\textsuperscript{1}H NMR) was in complete accord with that previously reported.\textsuperscript{217} HRMS (ESI): Exact mass calcd. for C\textsubscript{16}H\textsubscript{18}NO [M+H]\textsuperscript{+} 240.1388, found 240.1389.}};

\end{tikzpicture}}
\]

\textit{N-(1-Phenylethyl)cyclohexanecarboxamide (122d)}

Following General Procedure A on Page 152, the $\alpha$-bromo nitroalkane (25.5 mg, 115 $\mu$mol) and amine (16.7 mg, 138 $\mu$mol) provided the amide after flash column chromatography (20\% ethyl acetate in hexanes) as an off-white solid (18.6 mg, 70\%). $R_f = 0.25$ (20\% EtOAc/hexanes); mp 130-132 °C; spectroscopic data ($\textsuperscript{1}H NMR$) was in complete accord with that previously reported.\textsuperscript{218}

\[
\text{\begin{tikzpicture}

\node[align=center] (equation) at (0,0) {\text{\textit{N-(1-Phenylethyl)cyclohexanecarboxamide (122d)}}

Following General Procedure A on Page 152, the $\alpha$-bromo nitroalkane (25.5 mg, 115 $\mu$mol) and amine (16.7 mg, 138 $\mu$mol) provided the amide after flash column chromatography (20\% ethyl acetate in hexanes) as an off-white solid (18.6 mg, 70\%). $R_f = 0.25$ (20\% EtOAc/hexanes); mp 130-132 °C; spectroscopic data ($\textsuperscript{1}H NMR$) was in complete accord with that previously reported.\textsuperscript{218}};

\end{tikzpicture}}
\]

\textit{4-Chloro-N-(1-phenylethyl)butanamide (122e)}

Following General Procedure A on Page 152, the $\alpha$-bromo nitroalkane (29.0 mg, 134 $\mu$mol) and amine (19.5 mg, 161 $\mu$mol) provided the amide after flash column chromatography (25-30\% ethyl acetate in hexanes) as a yellow oil (24.5 mg, 81\%). $R_f = 0.28$ (40\% EtOAc/hexanes); spectroscopic data ($\textsuperscript{1}H NMR$) was in complete accord with that previously reported.\textsuperscript{219}

\[
\text{\begin{tikzpicture}

\node[align=center] (equation) at (0,0) {\text{\textit{4-Chloro-N-(1-phenylethyl)butanamide (122e)}}

Following General Procedure A on Page 152, the $\alpha$-bromo nitroalkane (29.0 mg, 134 $\mu$mol) and amine (19.5 mg, 161 $\mu$mol) provided the amide after flash column chromatography (25-30\% ethyl acetate in hexanes) as a yellow oil (24.5 mg, 81\%). $R_f = 0.28$ (40\% EtOAc/hexanes); spectroscopic data ($\textsuperscript{1}H NMR$) was in complete accord with that previously reported.\textsuperscript{219}};

\end{tikzpicture}}
\]

\begin{thebibliography}{99}
\end{thebibliography}
2-(1,3-Dioxan-2-yl)-N-(1-phenylethyl)acetamide (122f)

Following General Procedure A on Page 152, with an additional base wash (saturated aqueous K₂CO₃) before chromatography, the α-bromo nitroalkane (31.9 mg, 133 μmol) and amine (19.4 mg, 160 μmol) provided the amide after flash column chromatography (40% ethyl acetate in hexanes) as a white solid (24.0 mg, 72%). Rᵣ = 0.13 (40% EtOAc/hexanes); mp 113-114 °C; IR (neat) 3283, 2970, 2927, 2860, 1644, 150, 1142 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.30 (m, 4H), 7.27-7.23 (m, 1H), 6.46 (br d, J = 6.0 Hz, 1H), 5.14 (dq, J = 7.1, 7.1 Hz, 1H), 4.88 (dd, J = 4.7, 4.7 Hz, 1H), 4.14-4.09 (m, 2H), 3.82 (ddd, J = 12.1, 5.5, 2.5 Hz, 1H), 3.79 (ddd, J = 12.1, 5.5, 2.5 Hz, 1H), 2.57 (dd, J = 15.9, 4.8 Hz, 1H), 2.53 (dd, J = 15.9, 4.8 Hz, 1H), 2.05 (dddd, J = 13.4, 12.6, 12.6, 5.0, 5.0 Hz, 1H), 1.48 (d, J = 6.9 Hz, 3H), 1.39-1.34 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) ppm 167.8, 143.5, 128.6, 127.2, 126.1, 99.1, 67.1, 67.0, 48.6, 43.0, 25.6, 22.2; HRMS (CI): Exact mass calcd. for C₁₄H₂₀NO₃ [M+H]⁺ 250.1443, found 250.1446.

3-Cyano-2,2-dimethyl-N-(1-phenylethyl)propanamide (122g)
Following General Procedure A on Page 152, the α-bromo nitroalkane (31.4 mg, 142 μmol) and amine (20.7 mg, 171 μmol) provided the amide after flash column chromatography (20% ethyl acetate in hexanes) as an off-white solid (17.7 mg, 54%). Rf = 0.14 (20% EtOAc/hexanes); mp 69-71 °C; IR (neat) 3344, 2973, 2933, 2248, 1643, 1527 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.33 (m, 2H), 7.30-7.26 (m, 3H), 5.91 (br d, J = 6.0 Hz, 1H), 5.10 (dq, J = 7.1, 7.1 Hz, 1H), 2.66 (d, J = 6.7 Hz, 1H), 2.59 (d, J = 6.7 Hz, 1H), 1.51 (d, J = 6.9 Hz, 3H), 1.38 (s, 3H), 1.34 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) ppm 173.6, 142.8, 128.9, 127.6, 126.1, 118.0, 49.2, 40.9, 28.5, 25.1, 25.0, 21.6; HRMS (ESI): Exact mass calcd. for C₁₄H₁₉N₂O [M+H]⁺ 231.1497, found 231.1505.

4-Hydroxy-N-(1-phenylethyl)butanamide (122h)

Following General Procedure A on Page 152, the α-bromo nitroalkane (28.0 mg, 141 μmol) and amine (20.6 mg, 170 μmol) provided the amide after flash column chromatography (5% methanol in dichloromethane) as a yellow oil (14.0 mg, 48%). Rf = 0.12 (5% MeOH/CH₂Cl₂); IR (neat) 3286, 2970, 2930, 1645, 1548 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.26 (m, 5H), 5.88 (br s, 1H), 5.12 (dq, J = 7.1, 7.1 Hz, 1H), 3.68 (t, J = 5.7 Hz, 2H), 3.20-2.40 (br OH, 1H), 2.37-2.33 (m, 2H), 1.88 (tt, J = 6.4, 6.4 Hz, 2H), 1.49 (d, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) ppm 172.6, 143.1, 128.8, 127.6, 126.2, 62.5, 49.0, 34.2, 28.1, 21.8; HRMS (CI): Exact mass calcd. for C₁₂H₁₇NO₂ [M]⁺ 207.1259, found 207.1264.
3-Hydroxy-N-(1-phenylethyl)propanamide (122i)

Following General Procedure A on Page 152, the α-bromo nitroalkane (26.5 mg, 144 µmol) and amine (20.9 mg, 173 µmol) provided the amide after flash column chromatography (5% methanol in dichloromethane) as a yellow oil (19.6 mg, 70%). Rf = 0.15 (5% MeOH/CH2Cl2); IR (neat) 3290, 2973, 2928, 1645, 1551 cm⁻¹; ¹H NMR (400 MHz, CDCl3) δ 7.37-7.26 (m, 5H), 5.94 (br s, 1H), 5.14 (dq, J = 7.1, 7.1 Hz, 1H), 3.89 (t, J = 5.1 Hz, 2H), 2.92 (br s, 1H), 2.44 (dd, J = 6.1, 4.7 Hz, 2H), 1.51 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl3) ppm 171.7, 143.2, 128.8, 127.4, 126.1, 58.9, 48.8, 38.1, 22.0; HRMS (ESI): Exact mass calcd. for C₁₁H₁₅NO₂ [M+H]⁺ 194.1181, found 194.1174.

Methyl 4-oxo-4-(1-phenylethlamino)butanoate (122j)

Following General Procedure A on Page 152, the α-bromo nitroalkane (27.8 mg, 123 µmol) and amine (17.9 mg, 148 µmol) provided the amide after flash column chromatography (30% ethyl acetate in hexanes) as a yellow oil (20.2 mg, 70%). Rf = 0.16 (40% EtOAc/hexanes); spectroscopic data (¹H NMR) was in complete accord with that previously reported.²²⁰

**N-Benzyl-2-phenylacetamide (123a)**

Following General Procedure A on Page 152, the α-bromo nitroalkane (30.4 mg, 132 µmol) and amine (17.0 mg, 159 µmol) provided the amide after flash column chromatography (20-30% ethyl acetate in hexanes) as a white solid (21.5 mg, 72%). R<sub>f</sub> = 0.12 (20% EtOAc/hexanes); mp 118-119 °C. Spectroscopic data (¹H NMR) was in complete accord with that previously reported.<sup>221</sup>

**N- Allyl-2-phenylacetamide (123b)**

Following General Procedure A on Page 152, with an additional base wash (saturated aqueous K₂CO₃) before chromatography, the α-bromo nitroalkane (30.6 mg, 133 µmol) and amine (9.1 mg, 160 µmol) provided the amide after flash column chromatography (30-40% ethyl acetate in hexanes) as a white solid (17.0 mg, 73%). R<sub>f</sub> = 0.18 (40% EtOAc/hexanes); mp 55-57 °C; spectroscopic data (¹H NMR) was in complete accord with that previously reported.<sup>222</sup>

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2-Phenyl-N-(prop-2-ynyl)acetamide (123c)

Following General Procedure A on Page 152, the α-bromo nitroalkane (32.7 mg, 142 µmol) and amine (9.4 mg, 171 µmol) provided the amide after flash column chromatography (25-30% ethyl acetate in hexanes) as a yellow solid (15.0 mg, 61%). Rf = 0.27 (40% EtOAc/hexanes); spectroscopic data (¹H NMR) was in complete accord with that previously reported.²²³

N-(4-Hydroxybutyl)-2-phenylacetamide (123d)

Following General Procedure A on Page 152, the α-bromo nitroalkane (31.5 mg, 137 µmol) and amine (14.6 mg, 164 µmol) provided the amide after flash column chromatography (2-4% methanol in dichloromethane) as a white solid (21.6 mg, 71%). Rf = 0.19 (5% MeOH/CH₂Cl₂); mp 71-73 °C; IR (neat) 3270, 3085, 2939, 2865, 1656, 1630, 1565 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.33 (m, 2H), 7.31-7.29 (m, 1H), 7.26-7.24 (m, 2H), 5.62 (br s, 1H), 3.60 (t, J = 4.3 Hz, 2H), 3.57 (s, 2H), 3.24 (dt, J = 6.4, 6.1 Hz, 2H), 1.68 (br s, 1H), 1.54-1.49 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) ppm 171.3, 135.1, 129.6, 129.1, 127.4, 62.4, 44.0, 39.5, 29.7, 26.2; HRMS (ESI): Exact mass calcd. for C₁₂H₁₇NNaO₂ [M+Na]⁺ 230.1157, found 230.1164.

Methyl 2-(2-phenylacetamido)acetate (123e)

Following General Procedure B on Page 152, with an additional base wash (saturated aqueous K$_2$CO$_3$) before chromatography, the α-bromo nitroalkane (27.8 mg, 121 µmol) and ammonium salt (18.2 mg, 145 µmol) provided the amide after flash column chromatography (30-40% ethyl acetate in hexanes) as an off-white solid (18.1 mg, 72%). $R_f = 0.17$ (40% EtOAc/hexanes); mp 78-79 °C; IR (neat) 3249, 3077, 1753, 1643, 1558, 1212 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.39-7.35 (m, 2H), 7.32-7.28 (m, 3H), 5.88 (br s, 1H), 4.01 (d, $J = 5.2$ Hz, 2H), 3.73 (s, 3H), 3.63 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 171.2, 170.3, 134.5, 129.6, 129.2, 127.6, 52.4, 43.6, 41.4; HRMS (Cl): Exact mass calcd. for C$_{11}$H$_{14}$NO$_3$ [M+H]$^+$ 208.0974, found 208.0973.

$N$-(Cyanomethyl)-2-phenylacetamide (123f)

Following General Procedure B on Page 152, but with 4.5 equiv K$_2$CO$_3$ and an additional base wash (saturated aqueous K$_2$CO$_3$) before chromatography, the α-bromo nitroalkane (32.0 mg, 139 µmol) and ammonium salt (25.7 mg, 167 µmol) provided the amide after flash column chromatography (30-40% ethyl acetate in hexanes) as an off-
white solid (15.0 mg, 62%). $R_f = 0.11$ (40% EtOAc/hexanes); mp 87-88 °C; spectroscopic data ($^1$H NMR) was in complete accord with that previously reported.\(^{224}\)

\[\text{Ph} \; \text{NO}_2 \xrightleftharpoons{\text{NIS, K}_2\text{CO}_3, \text{H}_2\text{O}} \xrightarrow{\text{THF, } 0 \degree \text{C}} \text{Ph} \; \text{CONH}_2\]

**N-Cyclohexyl-2-phenylacetamide (123g)**

Following General Procedure A on Page 152, the α-bromo nitroalkane (27.9 mg, 121 μmol) and amine (14.4 mg, 146 μmol) provided the amide after flash column chromatography (25% ethyl acetate in hexanes) as a white solid (18.9 mg, 72%). $R_f = 0.11$ (20% EtOAc/hexanes); mp 128-130 °C; spectroscopic data ($^1$H NMR) was in complete accord with that previously reported.\(^{225}\)

\[\text{Ph} \; \text{NO}_2 \xrightarrow{\text{NIS, K}_2\text{CO}_3, \text{H}_2\text{O}} \xrightarrow{\text{THF, } 0 \degree \text{C}} \text{Ph} \; \text{CONH}_2\]

**N-tert-Butyl-2-phenylacetamide (123i)**

Following General Procedure A on Page 152, but with 1.8 equiv of tert-butylamine (16.4 mg, 225 μmol), the α-bromo nitroalkane (28.7 mg, 125 μmol) provided the amide after flash column chromatography (20% ethyl acetate in hexanes) as a white solid (14.3 mg, 60%). $R_f = 0.16$ (20% EtOAc/hexanes); mp 111-113 °C; spectroscopic data ($^1$H NMR) was in complete accord with that previously reported.\(^{226}\)


N,N-Diethyl-2-phenylacetamide (124)

Following General Procedure A on Page 152, the α-bromo nitroalkane (30.5 mg, 133 µmol) and amine (11.6 mg, 159 µmol) provided the amide after flash column chromatography (30% ethyl acetate in hexanes) as a yellow oil (12.7 mg, 50%). Rf = 0.28 (40% EtOAc/hexanes); spectroscopic data (1H NMR) was in complete accord with that previously reported.227

PhAc-Pro-OMe (S-4)

Following General Procedure B, with an additional base wash (saturated aqueous K2CO3) before chromatography, the α-bromo nitroalkane (26.7 mg, 116 µmol) and ammonium salt (23.1 mg, 139 µmol) provided the amide after flash column chromatography (35-50% ethyl acetate in hexanes) as a yellow oil (a mixture of two rotomers in approximately a 5:1 ratio, 14.7 mg, 51%). Rf = 0.12 (20% EtOAc/hexanes); IR (neat) 2954, 1745, 1647, 1421, 1197 cm⁻¹; 1H NMR (400 MHz, CDCl₃) major rotomer: δ 7.34-7.22 (m, 5H), 4.51 (dd, J = 7.4, 3.9 Hz, 1H), 3.72 (s, 3H), 3.72 (s, 2H), 3.62-3.58 (m, 1H), 3.54-3.46 (m, 1H),

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2.21-2.11 (m, 1H), 2.07-1.90 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) major rotomer: ppm 172.7, 169.7, 134.3, 128.9, 128.5, 126.7, 58.8, 52.1, 47.2, 41.8, 29.1, 24.8; HRMS (ESI): Exact mass calcd. for C$_{14}$H$_{17}$NNaO$_3$ [M+Na]$^+$ 270.1106, found 270.1105. Spectroscopic data (IR and $^1$H NMR) was in complete accord with that previously reported.\(^{228}\)

\[\text{(%)-Methyl 3-phenyl-2-((S)-2-(2-phenylacetamido)propanamido)propanoate (PhAc-Ala-Phe-OMe) (126)}\]

Following General Procedure B on Page 152, with an additional base wash (saturated aqueous K$_2$CO$_3$) before chromatography, the $\alpha$-bromo nitroalkane (24.4 mg, 106 µmol) and ammonium salt (36.5 mg, 127 µmol) provided the amide after flash column chromatography (50-80% ethyl acetate in hexanes) as a white solid (28.0 mg, 72%). $[\alpha]_D^{20} +19.9$ (c 1.00, CHCl$_3$); R$_{f}$ = 0.17 (50% EtOAc/hexanes); mp 141-142 °C; IR (neat) 3288, 3064, 3030, 2931, 1746, 1643, 1540, 1214 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36-7.20 (m, 8H), 7.09-7.07 (m, 2H), 6.57 (br d, $J = 7.7$ Hz, 1H), 5.98 (br d, $J = 7.2$ Hz, 1H), 4.78 (ddd, $J = 8.0$, 6.6, 6.6 Hz, 1H), 4.46 (dq, $J = 7.0$, 7.0 Hz, 1H), 3.71 (s, 3H), 3.55 (d, $J = 5.8$ Hz, 1H), 3.50 (d, $J = 5.8$ Hz, 1H), 3.11 (dd, $J = 14.0$, 5.6 Hz, 1H), 3.01 (dd, $J = 13.9$, 6.7 Hz, 1H), 1.25 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 171.7 (2C), 170.9, 136.8, 134.5, 129.4, 129.3, 129.1, 128.7, 127.5, 127.2, 53.3, 52.4, 48.8, 43.6,

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37.8, 18.0; HRMS (CI): Exact mass calcd. for C_{21}H_{23}N_{2}O_{4} [M-H]^− 367.1658, found 367.1652.

(R)-tert-Butyl 2-bromo-1-(4-chlorophenyl)-2-nitroethylcarbamate (164)\textsuperscript{229}

A solution of the imine (81.0 mg, 338 \( \mu \)mol) and H,Quin(\( ^6\)(Anth)\( ^2\)Pyr)-BAM\( ^-\)HOTf (10.9 mg, 16.9 \( \mu \)mol) in toluene (1.1 mL, 0.3 M) was cooled to -20 °C and treated with bromonitromethane (90%, 63.0 mg, 406 \( \mu \)mol). 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 \( \alpha\)-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% \(^1\)PrOH/hexanes, 1 mL/min, \( t_\text{r} (d_{1e1}, \text{major}) = 19.3 \) min, \( t_\text{r} (d_{2e1}, \text{major}) = 25.5 \) min, \( t_\text{r} (d_{1e2}, \text{minor}) = 14.5 \) min, \( t_\text{r} (d_{2e2}, \text{minor}) = 15.7 \) min). \( R_f = 0.49 \) (20% EtOAc/hexanes); IR (neat) 3358, 1682, 1519, 1161 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\), 1:1 mixture of diastereomers) see SI-II for the spectrum; \(^{13}\)C NMR (100 MHz, CDCl\(_3\), 1:1 mixture of diastereomers) ppm 154.7, 154.4, 135.4, 135.3, 133.9, 133.3, 129.5, 129.4, 128.5, 128.3, 84.9, 81.4, 57.7,

\textsuperscript{229} Racemic 164 was synthesized by addition of bromonitromethane to the imine catalyzed by 5 mol% NEt\(_3\) in CH\(_2\)Cl\(_2\) (rt, 30 min).
28.3, 28.2. The absolute configuration at the benzylic carbon was determined by chemical correlation as shown below.

K₂CO₃ (82.8 mg, 599 µmol) and PBAM (166, 2.2 mg, 4.3 µmol) were added to the solution of the sulfone (32.7 mg, 85.6 µmol) in toluene (0.43 ml, 0.2 M). The mixture was then cooled to -20 °C, and bromonitromethane (90%, 16.0 mg, 103 µmol) was added. The reaction mixture was stirred at -20 °C for 4 d. The resulting crude was diluted with CH₂Cl₂ and filtered. The filtrate was 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 (28.6 mg, 88%), which was determined to be 93% ee (each diastereomer) and 1:1 dr by chiral HPLC analysis.

p-Toluene sulfinic acid (33.3 mg, 213 µmol) was added to the solution of the aldehyde (30.0 mg, 213 µmol) and carbamate (20.8 mg, 179 µmol) in toluene (0.90 ml, 0.2 M). The mixture was stirred at room temperature for 2 h, to which PBAM (166, 4.5 mg, 8.9 µmol) and K₂CO₃ (123 mg, 889 µmol) were added. The mixture was stirred at room temperature for 30 min, and then cooled to -20 °C. Bromonitromethane (90%, 29.9
mg, 213 µmol) was added. The reaction mixture was stirred at -20 °C for 4 d. The resulting crude was diluted with CH₂Cl₂ and filtered. The filtrate was 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 (48.0 mg, 71%), which was determined to be 96% ee (each diastereomer) and 1:1 dr by chiral HPLC analysis.

(2)-tert-Butyl 1-(4-chlorophenyl)-2-nitroethylcarbamate (S-5)

SnCl₂·2H₂O (17.8 mg, 79.0 µmol) was added to the solution of the α-bromo nitroalkane (20.0 mg, 52.7 µmol) in THF (0.53 mL). The reaction was stirred at room temperature for 5 min. The crude mixture was diluted with H₂O and extracted with Et₂O. The organic layer was dried with MgSO₄, filtered and concentrated. The residue was subjected to purification by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to give the nitroalkane as a white solid (15.2 mg, 96%), which was determined to be 95% ee by chiral HPLC analysis (Chiralcel AD, 10% iPrOH/hexanes, 1 mL/min, tᵣ(major) = 14.9 min, tᵣ(minor) = 11.8 min). Rₛ = 0.33 (20% EtOAc/hexanes); spectroscopic data (¹H NMR) was in complete accord with that previously reported.²³⁰

**tert-Butyl (R)-1-(4-chlorophenyl)-2-oxo-2-((R)-1-phenylethlamino)ethylcarbamate** (167)

Following General Procedure A on Page 152, the α-bromo nitroalkane (27.6 mg, 72.7 µmol) and amine (10.6 mg, 87.2 µmol) provided the amide after flash column chromatography (15-20% ethyl acetate in hexanes) as a white solid (21.5 mg, 76%). [α]$_D^{20}$ -60.1 (c 1.00, CHCl$_3$); R$_f$ = 0.12 (20% EtOAc/hexanes); mp 138-140 ºC; IR (neat) 3306, 2979, 1685, 1655, 1522, 1492, 1167 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.31-7.28 (m, 2H), 7.26-7.21 (m, 5H), 7.05-7.03 (m, 2H), 5.90 (br d, J = 7.8 Hz, 1H), 5.79 (br s, 1H), 5.10 (br s, 1H), 5.07 (dq, J = 7.1, 7.1 Hz, 1H), 1.47 (d, J = 7.0 Hz, 3H), 1.40 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 168.8, 155.2, 142.6, 136.9, 134.4, 129.2, 128.8, 128.7, 127.5, 125.8, 80.4, 58.1, 49.3, 28.4, 21.9; HRMS (CI): Exact mass calcd. for C$_{29}$H$_{25}$ClN$_2$NaO$_3$ [M+Na]$^+$ 411.1451, found 411.1459.

**tert-Butyl (R)-1-(4-chlorophenyl)-2-oxo-2-((R)-1-phenylethlamino)ethylcarbamate** (167) and **tert-Butyl (S)-1-(4-chlorophenyl)-2-oxo-2-((R)-1-phenylethlamino)ethylcarbamate** (S-6)
Following General Procedure A on Page 152, the racemic α-bromo nitroalkane (29.0 mg, 76.4 µmol) and amine (11.1 mg, 91.7 µmol) provided the amides after flash column chromatography (15-20% ethyl acetate in hexanes) as two separable diastereomers (22.6 mg combined, 76% yield). \((R,R)\)-diastereomer: as reported above; \((S,R)\) diastereomer: a white solid. \([\alpha]_D^{20} -48.7 (c 0.30, \text{CHCl}_3); R_f = 0.22 \text{ (20% EtOAc/hexanes); mp 138-140 }^\circ\text{C}; \)\(^1\)H NMR (400 MHz, \text{CDCl}_3) \(\delta 7.31-7.29 \text{ (m, 2H), 7.26-7.21 \text{ (m, 5H), 7.06-7.03 \text{ (m, 2H), 5.83 \text{ (br d, J = 7.7 Hz, 1H), 5.78 \text{ (br s, 1H), 5.10 \text{ (br s, 1H), 5.08 \text{ (dq, J = 7.1, 7.1 Hz, 1H), 1.47 \text{ (d, J = 6.9 Hz, 3H), 1.40 \text{ (s, 9H); \)\(^1\)C NMR (100 MHz, \text{CDCl}_3) ppm 168.7, 155.2, 142.5, 137.0, 134.4, 129.3, 128.8, 128.7, 127.5, 125.8, 80.3, 58.1, 49.3, 28.4, 21.9.}

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\text{\(N\)-Boc-4-Cl-Phenylglycine-Ala-Phe-OMe (168) \)
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Following General Procedure B on Page 152, with an additional base wash (saturated aqueous \(\text{K}_2\text{CO}_3\)) before chromatography, the α-bromo nitroalkane (24.0 mg, 63.2 µmol) and ammonium salt (21.8 mg, 75.9 µmol) provided the amide after flash column chromatography (30-50% ethyl acetate in hexanes) as a white solid (23.5 mg, 72%). \([\alpha]_D^{20} -38.0 (c 1.00, \text{CHCl}_3); R_f = 0.16 \text{ (40\% EtOAc/hexanes); mp 207-208 }^\circ\text{C; IR (neat) 3282, 3072, 2980, 1747, 1693, 1671, 1644, 1549, 1368 cm}^{-1}; \)\(^1\)H NMR (400 MHz, \text{CDCl}_3) \(\delta 7.32-7.29 \text{ (m, 5H), 7.27-7.21 \text{ (m, 2H), 7.09-7.07 \text{ (m, 2H), 6.58 \text{ (br s, 2H), 5.80 \text{ (br s, 1H), 5.13 \text{ (br s, 1H), 4.80 \text{ (ddd, J = 7.6, 6.2, 6.2 Hz, 1H), 4.45 \text{ (dq, J = 7.1, 7.1 Hz, \)\text{)}

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1H), 3.71 (s, 3H), 3.12 (dd, \( J = 13.9, 5.8 \) Hz, 1H), 3.03 (dd, \( J = 13.9, 6.5 \) Hz, 1H), 1.41 (s, 9H), 1.21 (d, \( J = 7.0 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) ppm 171.7, 171.4, 169.6, 155.1, 136.8, 135.7, 134.4, 129.3, 129.3, 128.7, 128.6, 127.3, 80.5, 58.0, 53.5, 52.5, 49.0, 37.8, 28.4, 18.1; HRMS (ESI): Exact mass calcd. for C\(_{26}\)H\(_{32}\)Cl\(_2\)N\(_3\)O\(_6\) [M+Cl]\(^+\) 552.1668, found 552.1649.

\[ \text{N-Boc-4-Cl-Phenylglycine-Pro-OMe (170)} \]

Following General Procedure B, the \( \alpha \)-bromo nitroalkane (20.0 mg, 52.7 µmol) and ammonium salt of 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%). \([\alpha]\)\(^D\) = -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\(^{-1}\); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) major rotamer: \( \delta \) 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\(_2\)NaO\(_5\) [M+Na]\(^+\) 419.1350, found 419.1356.