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Hydroxyamination of Olefins Using Br-N-(CO₂Me)₂

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Abstract

The hydroxyamination reagent Br-N-(CO₂Me)₂ underwent Markovnikov addition to various olefins in the presence of catalytic BF₃·OEt₂ and provides efficient access to aminoalcohols. The reaction provided the *trans*-1-bromo, 2-*N*-bis-carbamate adduct stereoisomer in all cases. The resulting adduct underwent cyclization to give an oxazolidinone, which could be readily hydrolyzed to an oxazolidin-2-one or an amino alcohol.

Graphical Abstract

INTRODUCTION

Direct hydroxyamination of olefins is a very useful technique to synthesize amino alcohols, which are one of the most important organic building blocks. Amino alcohols are found in many natural products, such as myriocin, bestatin, and cytoxazone.¹ They are also used as ligands in asymmetric synthesis and found in numerous bioactive molecules.¹ There have been many methods developed to prepare the amino alcohol functional group; however, they often require multistep procedures. One of the better direct methods for synthesis of the amino alcohol motif from an olefin is undoubtedly the Sharpless asymmetric hydroxyamination reaction.² Although an efficient reaction, one limitation is its relative low regioselectivity and enantioselectivity depending on its substrates.³ Therefore, alternative direct and indirect methods for hydroxyamination reactions are still required to access the amino alcohol motif.^{1,4}

An example of an indirect stepwise method for hydroxyamination of an olefin is via aminohalogenation. Aminohalogenation of an olefin creates both a nitrogen–carbon bond and halogen–carbon bond adjacent to one another and may provide a method to synthesize an amino alcohol through substitution of the halogen atom with an oxygen nucleophile.

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Supporting Information

Copies of NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Notes

The authors declare no competing financial interest.

Besides an amino alcohol, aminohalogenation is a valuable tool to create a variety of different important organic building blocks, such as aziridines, dihydrooxazoles, or diamines. The reactions of an olefin with Chloramine-T,^{5,6} TsNH₂,^{7,8} TsNCl₂,^{9–11} and iodine isocyanate (INCO)¹² are examples of efficient aminohalogenation methods, which can serve as substrates for the preparation of amino alcohols.

We report herein the addition of a carbamate to an olefin as a one-pot method to access aminoalcohols. Surprisingly, the addition of a carbamate/amide^{13–17} or imide^{14,18} to an olefin has not been studied at the level of detail relative to other aminohalogenation reactions. Swern²² and others^{18–21} previously reported the addition of *N*-haloamide, *N*-halocarbamate, *N,N*-dihaloamide/carbamate, or *N*-haloimide to an olefin through a radical mechanism to give *anti*-Markovnikov products. In addition, Heasley²³ and co-workers reported that NBS underwent addition to cyclohexene, in the presence of 1 equiv of BF₃·OEt₂, to yield the *trans*-1-bromo,2-*N*-succinimide stereoisomer adduct.

Unfortunately, a succinimide as a masked nitrogen source in a hydroxyamination reaction has very little synthetic utility, because the nitrogen atom is not easily accessible for further chemical manipulation. Therefore, this intriguing report by Heasley and co-workers motivated us to explore this reaction as a new hydroxyamination methodology.

RESULTS AND DISCUSSION

We envisioned that an *N*-bromoimide containing a removable nitrogen protecting group would make the nitrogen source much more amendable for subsequent use. Design of the new *N*-bromoimide required that the nitrogen atom would be a good nucleophile and not sterically hindered and, second, that one of the nitrogen protecting groups could serve as an internal oxygen nucleophile and substitute the bromine atom in a subsequent intramolecular reaction. We found that reagent **1h** Br-N-(CO₂Me)₂ accomplished both of these requirements. *N*-Bromo bis-methyl carbamate **1h** was synthesized in a two-step procedure. First, methyl carbamate was reacted with (COCl)₂ in DCE to yield methyl carbonisocyanatide *in situ*, which was reacted with methanol to yield bis-methyl carbamate (Scheme 1).²⁵ In the second step, the bis-methyl carbamate was added to a solution of bromoacetate synthesized *in situ* from AgOAc and Br₂ in CCl₄ to yield *N*-bromo bis methyl carbamate **1h**. Compound **1h** was subsequently isolated by precipitation from CCl₄/*n*-heptane and was stable stored in the freezer for several weeks.

We investigated the first step of our hydroxyamination reaction, which was optimization of the aminohalogenation reaction of styrene with various *N*-halo reagents (**1a–h**) in the presence of the Lewis acid catalyst BF₃·OEt₂ (Table 1). The aminohalogenation of styrene in the presence of BF₃·OEt₂ using NIS, NBS, or NCS revealed that only NBS resulted in the desired product in good yields (Table 1, entries **1a–c**). Aminohalogenation of styrene with NBS provided the bromosuccinimide adduct in 83% yield. NIS gave a complex mixture of products. NCS was much less reactive and gave the desired product in trace amount yields. Therefore, the *N*-bromoimide was deemed superior to an *N*-chloroimide or *N*-iodoimide. We subsequently prepared several *N*-bromoreagents (Table 1, entries **1d–g**), none of which

resulted in the desired product formation under our reaction conditions. However, the bis-carbamate **1h** (Table 1, entry **1h**) provided the desired product in good yields (81%).

The reaction of the *N*-bromo-bis-carbamate **1h** with styrene was subsequently screened with other Lewis acids, such as $\text{Ti}(\text{O}^i\text{Pr})_4$, CuI , TiCl_4 , ZnCl_2 , $\text{Zn}(\text{OTf})_2$, and $\text{B}(\text{OPh})_3$, but none of these Lewis acids were found to be superior to $\text{BF}_3 \cdot \text{OEt}_2$ in our hands. The reaction of **1h** with styrene and stoichiometric TMSOTf did yield the aminohalide, but the reaction was much slower than when $\text{BF}_3 \cdot \text{OEt}_2$ was used. Furthermore, the reactions of **1h** with styrene and different Brønsted acids, such as TFA, CSA, and diphenyl phosphate, all resulted in debromination of compound **1h** to yield the *H*-*N*-(CO_2Me)₂, but only a trace amount of the desired product aminohalide. The reaction worked the best with $\text{BF}_3 \cdot \text{OEt}_2$ in dichloromethane (DCM) or chloroform and occurred very rapidly at room temperature (45 min). The scope of the aminobromination reaction was subsequently investigated and was found to work well with various substituted electron-rich or electron-poor styrenes and indene (Table 2, entries i–k), but provided multiple products using *cis*-stilbene.

Lower yields were obtained with aliphatic olefins, such as cyclohexene or 1-hexene (Table 2, entries l–m). The conjugated diene, (*E*)-buta-1,3-ylbenzene, provided a 2:1 mixture of the 1,4- and 1,2- adduct, respectively, at the typical reaction conditions (0.3 equiv $\text{BF}_3 \cdot \text{OEt}_2$, DCM, rt, 45 min). However, no attempts to optimize the thermodynamic versus the kinetic product by modifying the reaction conditions were pursued. Thus, the reactions of an olefin with compound **1h** yielded a *trans*-1-bromo,2-*N*-bis-carbamate stereoisomer adduct **3** and occurred at room temperature in only 45 min with catalytic $\text{BF}_3 \cdot \text{OEt}_2$. These reactions were quenched with sat. aq. NaHCO_3 and then extracted with DCM. The aminohalide **3** can be isolated in pure form following purification by silica gel chromatography.

To further investigate its potential as a hydroxyamination methodology, we subsequently focused on deprotection of one of the two methyl carbamate groups of compound **3h** and attempted a ring closure reaction to the corresponding 4,5-dihydrooxazole, by intramolecular substitution of the bromine atom by the carbamate oxygen. However, it was observed by ^1H NMR that, after 3 h, it was purified, and cyclization into an oxazolidinone **4a** slowly occurred at room temperature through loss of CH_3Br as a side product. Conversely, without purification, the crude compound **3h** underwent ring closure to yield an oxazolidinone **4a** by heating the compound neat at 75 °C (Table 3). The oxazolidinone formation is conceptually similar to the work described by Heathcock and co-workers in which iodine isocyanate (INCO) was added to olefins and cyclized using pyrolysis.¹² The current alternative hydroxyamination reaction was investigated for its scope. The two-step procedure provided the oxazolidinones of a wide range of aryl substituted olefins in moderate to good yields over the two steps (Table 3, entries a–f). Hydroxyamination with reagent **1h** also worked well with *trans*-4-octene to yield the oxazolidinone, but subsequently hydrolyzed to the oxazolidin-2-one **4g** upon workup.

The *trans* oxazolidinones were formed in all cases, as supported by ^1H NMR, NOE, and examination of the reported literature data for compound **4g**. The data for the *trans* stereoisomer of **4g** and not the *cis* stereoisomer of **4g** was verified by analysis of the chemical shifts and coupling constants of the methine CH protons of the oxazolidin-2-one

ring.²⁴ As expected, the oxazolidinone **4d** gave the *syn* stereoisomer due to the locked geometry of the indene ring.

The modest overall yields observed in some cases were dictated by low yields obtained in the aminobromination step. In all cases observed, the ring closure step of this hydroxyamination reaction occurred in near quantitative yield. This ring closure procedure rendered the protected amino alcohols from olefins in moderate to good yields. Deprotection of the oxazolidinone was accomplished via simple hydrolysis using 2 M LiOH and THF (Table 4).

The proposed mechanism of this reaction sequence involves the coordination of the $\text{BF}_3 \cdot \text{OEt}_2$ to the oxygen atom of compound **1h** to make the complex **1h'** (Scheme 2). The complex **1h'** could then react with an olefin **2** to form a bromonium ion **2'** and complex **1h''**. Complex **1h''** may subsequently attack the bromonium ion **2'** to form the *trans*-1-bromo, 2-*N*-bis-carbamate stereoisomer **3**.

Support for a bromonium ion mechanism over a radical process for the aminohalogenation step was supported by two factors. First, a mixture of regioisomers was never observed in these reactions except with 1-hexene (**2m**) and carbon–nitrogen bond formation occurred through Markovnikov-type addition to the most stable carbon in the bromonium ion intermediate **2'**. Only the Markovnikov-type regioisomer was observed by NMR analysis of compounds **3** and **4**. *Anti*-Markovnikov addition of an *N*-haloamide has been reported by Foglia and Swern to occur through a radical mechanism.²² Second, the reaction gave only the *trans*-1-bromo, 2-*N*-bis-carbamate stereoisomer **3k,l** in all cases and not a mixture of *anti* and *syn* stereoisomers, which was observed in the radical mechanism proposed by Foglia and Swern. The intramolecular ring closure reaction to yield the oxazolidinone **4** occurs through either an $\text{S}_{\text{N}}2$ or $\text{S}_{\text{N}}1$ mechanism depending on the R_2 substituent. In the case when R_2 was an H substituent, the intramolecular ring closure to yield an oxazolidinone **4** would presumably occur through an $\text{S}_{\text{N}}2$ reaction via intermediate **3'**. In the case where the *trans*-1-bromo, 2-*N*-bis-carbamate stereoisomers **3** contained an R_2 substituent that was a phenyl, benzoyl, or alkyl, the intramolecular ring closure reaction could proceed through an $\text{S}_{\text{N}}1$ reaction via intermediate **3''** or alternatively $\text{S}_{\text{N}}2$ via intermediate **3'**. In these examples, only the *trans* oxazolidinones were formed (**4e**, **4f**, **4g**) through ring closure of the precursor *trans* **3** adducts and not the *cis* oxazolidinones, which would be expected from inversion of configuration due to an $\text{S}_{\text{N}}2$ mechanism.

In conclusion, we report herein a new hydroxyamination reagent **1h**. The reaction sequence involved a Markovnikov-type addition to an olefin under catalytic Lewis acid conditions, followed by ring closure to yield the oxazolidinone **4**. The oxazolidinones (Table 4) are subsequently readily hydrolyzed to the corresponding oxazolidin-2-one (2 h hydrolysis, rt), or straight to the amino alcohol (17 h hydrolysis, reflux).

EXPERIMENTAL SECTION

General Experimental

DCM was purified through a column packed with dry alumina and was dispensed by a nitrogen pressure delivery system. THF was distilled from sodium under nitrogen. All other reagents and solvents were purchased from commercial sources and used without further purification. All flasks were oven-dried overnight and cooled under argon. All reactions were monitored by TLC with 0.25 μ M precoated silica gel plates, and UV light was used to visualize the compounds. In some cases, phosphomolybdic acid (PMA) stain or I₂ was used to visualize the compounds. Column chromatography utilized silica gel (230–400 mesh). All NMR spectra were recorded on a 500 or 300 MHz spectrometer. The mass spectrometer ionization method was ESI with a Quadrupole detector.

General Procedure to Neutralize Silica Gel

Silica gel was saturated with TEA, and the slurry was mixed for 5 min and then concentrated *in vacuo* to remove the excess TEA to give a free-flowing powder once again.

Bis-methyl Carbamate

Methyl carbonisocyanatide (water-reactive, volatile) was made and was used *in situ* by the following reaction. To a dry 500 mL round-bottom flask under nitrogen were added methyl carbamate (10 g, 0.133 mol), DCE (200 mL), and (COCl)₂ (11.43 mL, 0.133 mol). The solution was heated to reflux for 19 h and then was cooled to room temperature under nitrogen. MeOH (26.80 mL, 0.66 mol) was added all at once, and the solution was mixed for 5 h and concentrated *in vacuo* to give a white solid. The solid was triturated with ether (100 mL), filtered, and dried *in vacuo*. The product was purified by column chromatography *R_f* = 0.2 PMA stain, 100% CHCl₃. The compound has been previously synthesized.²⁵ Solid; mp = 128–130 °C; 90% yield; ¹H NMR (500 MHz) (CDCl₃) δ 3.78 (6H, s), 7.20 (1H, s, br); ¹³C NMR and DEPT (125 MHz) (CDCl₃) δ 53.0 (CH₃), 151.9 (C).

N-Bromo Bis-methyl Carbamate (1h)

Bromo-acetate was made *in situ* and was used immediately. To a 250 mL round-bottom flask wrapped in aluminum foil (light sensitive) under argon were added AgOAc (4.00 g, 0.024 mol) and CCl₄ (120 mL). The reaction flask was cooled in an ice bath for ¼ h, and then Br₂ (1.23 mL, 0.024 mol) was added neat dropwise over 2 min. After the addition of Br₂, the flask was stirred for another ½ h at 0 °C and a yellow solid formed (AgBr). The reaction solution was vacuum filtered to remove the AgBr, and the mother liquor (bromoacetate solution) was poured into a dry 500 mL round-bottom flask under argon at room temperature. Bis-methyl carbamate (1.60 g, 0.012 mol) was added neat all at once to the bromoacetate in CCl₄ at room temperature. The reaction was exothermic and was stirred for 2.5 h, and then the reaction solution was poured into a 1L Erlenmeyer flask. Hexanes (500 mL) were added, and the flask was covered with parafilm and placed in the freezer for 3 h. A precipitate formed, which was isolated by vacuum filtration and was washed with hexanes (100 mL). The white solid was briefly dried at room temperature *in vacuo* for 5 min to remove residual solvent. The product (compound **1h**) was placed in an amber bottle and was

stored in the freezer and was found to be stable for several weeks. White solid; mp = 76–78 °C; 75% yield; ¹H NMR (500 MHz) (CDCl₃) δ 3.89 (6H, s); ¹³C NMR and DEPT (125 MHz) (CDCl₃) δ 55.57 (CH₃), 152.03 (C); IR (NaCl): 1782, 1190.

General Procedure for Addition of Compound 1h to an Olefin (Table 2)

To a 10 mL round-bottom flask under argon were added DCM (4.0 mL) and the olefin (50 mg if a solid or 50 μ L in a liquid). The *N*-bromoimide **1h** (1.1 equiv) was added all at once neat, followed by immediate addition of the BF₃·OEt₂ (0.3 equiv), which was measured added using a 50 μ L syringe. The reaction was exothermic and would often form a color for about a minute from dark yellow, orange, or purple. The solution was mixed at room temperature for ³/₄ h and was then poured into a sep. funnel containing sat. aq. NaHCO₃. The solution was extracted with DCM (3 $\times$), dried with MgSO₄, vacuum filtered, and concentration *in vacuo* at room temperature. Prolonged heating of the crude product at a higher temperature when concentrating *in vacuo* caused the cyclization reaction to occur to yield an oxazolidinone **4**. The crude product was purified by silica gel chromatography.

1-(2-Bromo-1-phenylethyl)pyrrolidine-2,5-dione (3c)

The compound was synthesized according to the general procedure. Column chromatography 50:50 DCM:hexane; *R*_f = 0.5; solid; mp = 90–92 °C ; ¹H NMR (500 MHz) δ 2.71 (4H, s), 3.83 (1H, dd, *J*₁ = 10.5 Hz, *J*₂ = 5.5 Hz), 4.66 (1H, t, *J* = 10.5 Hz), 5.44 (1H, dd, *J*₁ = 10.5 Hz, *J*₂ = 5.5 Hz), 7.33 (3H, m), 7.48 (2H, d, *J* = 6.5 Hz); (CDCl₃) ¹³C NMR and DEPT (125 MHz) (CDCl₃) δ 28.2 (CH₂), 30.6 (CH₂), 57.7 (CH), 128.4 (CH), 129.2 (CH), 129.2 (CH), 136.9 (C), 177.2 (C). IR (NaCl): 1705, 1390, 1363, 1140. HRMS Calculated for C₁₂H₁₃BrNO₂ (M + H): 282.0130; Found 282.0128

Bis-methyl (2-Bromo-1-phenylethyl)carbamate (3h)

The compound was synthesized according to the general procedure. Column chromatography 97:3 DCM:TEA; *R*_f = 0.3; oil; 111 mg; 81% yield; ¹H NMR (500 MHz) (CDCl₃) δ 3.78 (6H, s), 4.01 (1H, dd, *J*₁ = 10.5 Hz, *J*₂ = 6.1 Hz), 4.31 (1H, t, *J* = 10.3 Hz), 5.78 (1H, dd, *J*₁ = 9.8, *J*₂ = 5.9 Hz), 7.25–7.40 (5H, m); ¹³C NMR and DEPT (125 MHz) (CDCl₃) δ 32.2 (CH₂), 54.0 (CH₃), 60.9 (CH), 127.4 (CH), 128.1 (CH), 128.4 (CH), 137.1 (CH), 154.2 (C); IR (NaCl): 2957, 1753, 1709, 1344, 1296, 1253; HRMS Calculated for C₁₂H₁₄BrNO₄ (M + H): 316.01884; Found 316.0188

Bis-methyl (2-Bromo-1-(4-methoxyphenyl)ethyl)carbamate (3i)

The compound was synthesized according to the general procedure. Column chromatography 97:3 DCM:TEA; *R*_f = 0.5; oil; 113 mg; 88% yield; ¹H NMR (500 MHz) (CDCl₃) δ 3.75 (3H, s), 3.77 (6H, s), 3.94 (1H, dd, *J*₁ = 10.3 Hz, *J*₂ = 5.9 Hz), 4.28 (1H, t, *J* = 10.3 Hz), 5.69 (1H, dd, *J*₁ = 10.3, *J*₂ = 5.4 Hz), 6.85 (2H, d, *J* = 8.1 Hz), 7.29 (1H, d, *J* = 8.1 Hz); ¹³C NMR and DEPT (125 MHz) (CDCl₃) δ 32.4 (CH₂), 54.0 (CH₃), 55.2 (CH₃), 60.7 (CH), 113.8 (CH), 129.0 (CH), 129.1 (C), 154.3 (C), 159.4 (C); IR (NaCl): 2975, 1751, 1707, 1253; HRMS Calculated for C₁₃H₁₆BrNO₅ (M + Na): 368.0106; Found 368.0110.

Bis-methyl (2-Bromo-1-(4-chlorophenyl)ethyl)carbamate (3j)

The compound was synthesized according to the general procedure. Column chromatography 97:3 DCM:TEA; R_f = 0.6; oil; 115 mg; 79% yield; ^1H NMR (500 MHz) (CDCl_3) δ 3.81 (6H, s) 3.98 (1H, dd, J_1 = 10.3 Hz, J_2 = 6.4 Hz) 4.26 (1H, dd, J_1 = 10.5, J_2 = 9.5 Hz,) 5.73 (1H, dd, J_1 = 9.5, J_2 = 6.1 Hz) 7.27–7.38 (4H, m,); ^{13}C NMR and DEPT (125 MHz) (CDCl_3) δ 31.9 (CH_2), 54.41 (CH_3), 60.7 (CH), 128.92 (CH), 129.29 (CH), 134.4 (C), 135.82 (C), 154.37 (C); IR (NaCl): 2957, 1752, 1709, 1346. HRMS Calculated for $\text{C}_{12}\text{H}_{14}\text{BrClNO}_4$ (M + H): 349.9795; Found 349.9796.

Bis-methyl-2-bromo-2,3-dihydro-1H-inden-1-yl)carbamate (3k)

The compound was synthesized according to the general procedure. Column chromatography 97:3 DCM:TEA; R_f = 0.5; oil; 78 mg; 52% yield; ^1H NMR (500 MHz) (CDCl_3) δ 3.32 (1H, dd, J_1 = 8.4 Hz, J_2 = 7.8 Hz), 3.71 (1H, dd, J_1 = 8.4 Hz, J_2 = 7.8 Hz), 3.76 (6H, s), 4.95 (1H, q, J = 7.8 Hz) 6.16 (1H, d, J = 7.3 Hz) 7.08 (1H, d, J = 7.3 Hz), 7.17–7.27 (3H, m); ^{13}C NMR and DEPT (125 MHz) (CDCl_3) δ 41.9 (CH_2), 49.7 (CH), 54.0 (CH_3), 70.9 (CH), 121.8 (CH), 124.4 (CH), 127.3 (CH), 128.3 (CH), 138.9 (C), 139.4 (C), 154.1 (C); IR (NaCl): 2955, 1757, 1713, 1342; HRMS Calculated for $\text{C}_{13}\text{H}_{14}\text{BrNO}_4$ (M + Na): 349.9996; Found 350.0004.

Bis-methyl (2-Bromocyclohexyl)carbamate (3l)

The compound was synthesized according to the general procedure, but 2.0 equiv of **1h** was used instead of 1.1 equiv. The crude product was dissolved in ether and was washed once with sat. aq. NaHCO_3 , dried with MgSO_4 , filtered, and concentrated *in vacuo*. Column chromatography on TEA neutralized silica gel; the crude product was loaded on the column with CHCl_3 and eluted with 100% hexane, R_f = 0.8 visualized with PMA stain; oil; 49 mg; 34% yield; ^1H NMR (500 MHz) (CDCl_3) δ 1.30–1.46 (2H, m), 1.68–1.75 (1H, m), 1.79–1.86 (2H, m), 1.87–1.94 (1H, m), 1.96–2.05 (1H, m), 2.42–2.48 (1H, m), 3.84 (6H, s), 4.30 (1H, m), 4.72 (1H, m); ^{13}C NMR and DEPT (125 MHz) (CDCl_3) δ 25.4 (CH_2), 26.7 (CH_2), 30.4 (CH_2), 38.3 (CH_2), 53.2 (CH), 53.9 (CH_3), 63.8 (CH), 154.5 (C); IR (NaCl): 2955, 1753, 1437, 1228; HRMS Calculated for $\text{C}_{10}\text{H}_{17}\text{BrNO}_4$ (M + H): 294.0341; Found 294.0339.

Bis-methyl (1-Bromohexan-2-yl)carbamate and Bis-methyl (2-Bromohexyl)carbamate (3m)

The compound was synthesized according to the general procedure, but 2.0 equiv of **1h** was used instead of 1.1 equiv. The crude product was dissolved in ether and was washed once with sat. aq. NaHCO_3 , dried with MgSO_4 , filtered, and concentrated *in vacuo*. Column chromatography on TEA neutralized silica gel; the crude product was loaded on the column with CHCl_3 and was eluted with 100% hexane, R_f = 0.8 visualized with PMA stain; oil; 44 mg; 37% yield; 52:48 ratio Regioisomer **1**: ^1H NMR (500 MHz) (CDCl_3) δ 0.80–0.91 (3H, m), 1.24–1.35 (4H, m), 1.65–1.92 (2H, m), 3.51 (1H, dd, J_1 = 10.3, J_2 = 5.9 Hz, 1 H), 3.83 (6H, s), 3.86 (1H, dd, J_1 = 10.3, J_2 = 4.9 Hz), 4.56 (1H, m). Regioisomer **2**: ^1H NMR (500 MHz) δ 0.80–0.91 (3H, m), 1.24–1.35 (4H, m), 1.65–1.92 (2H, m), 3.84 (6H, s), 3.95 (1H, dd, J_1 = 14.2, J_2 = 5.9 Hz), 4.13 (1H, dd, J_1 = 14.2, J_2 = 8.3), 4.25 (1H, m). Both Regioisomers: ^{13}C NMR and DEPT (125 MHz) (CDCl_3) δ 13.81 (CH_3), 13.83 (CH_3), 22.0

(CH₂), 22.3 (CH₂), 28.7 (CH₂), 29.5 (CH₂), 30.8 (CH₂), 33.9 (CH₂), 35.5 (CH₂), 52.5 (CH₂), 53.7 (CH), 53.9 (CH₃), 54.0 (CH₃), 59.5 (CH), 154.0 (C), 154.5 (C); IR (NaCl): 2959, 1755, 1705, 1437, 1346; HRMS Calculated for C₁₀H₁₈BrNO₄ (M + Na): 318.0315; Found 318.0317.

Bis(*E*)-methyl (4-Bromo-1-phenylbut-2-en-1-yl)carbamate and Bis(*E*)-methyl (1-Bromo-4-phenylbut-3-en-2-yl)carbamate (3n)

The compound was synthesized according to the general procedure. Column chromatography 100% DCM, *R_f* = 0.45; oil; 63 mg; 50% yield; ¹H NMR (500 MHz) (CDCl₃) δ Regioisomer **1** (1,4-addition product) ¹H NMR (500 MHz) (CDCl₃) δ 3.75 (6H, s), 4.04 (2H, d, *J* = 7.34 Hz), 5.98–6.08 (1H, m), 6.11 (1H, d, *J* = 8.30 Hz), 6.36 (1H, dd, *J*₁ = 16.0 Hz, *J*₂ = 8.30 Hz), 7.29–7.40 (5H, m); Regioisomer **2** (1,2- addition product) ¹H NMR (500 MHz) (CDCl₃) δ 3.67 (1H, dd, *J*₁ = 10.3 Hz, *J*₂ = 6.4 Hz), 3.87 (6H, s), 3.99 (1H, t, *J* = 9.8 Hz), 5.30 (1H, m), 6.40 (1H, m), 6.67 (1H, d, *J* = 16 Hz), 7.25–7.40 (5H, m); ¹³C NMR and DEPT (Both Regioisomers) (125 MHz) (CDCl₃) δ 31.42 (CH₂), 32.82 (CH₂), 53.88 (CH₃), 54.12 (CH₃), 60.74 (CH), 60.8 (CH), 124.34 (CH), 126.41(CH), 126.7 (CH), 127.42 (CH), 128.32 (CH), 128.41 (CH), 128.62 (CH), 131.36 (CH), 131.8 (CH), 135.15 (CH), 135.91 (C), 139.05 (C), 154.02 (C), 154.06 (C); IR (NaCl): 2953, 1753, 1707, 1282, 1259; HRMS Calculated for C₁₄H₁₆BrNO₄ (M + Na): 364.0161; Found 364.0160.

General Procedure for Synthesis of Oxazolidinones (Table 3)

To a 10 mL round-bottom flask under argon were added DCM (4.0 mL) and the olefin (50 mg if a solid or 50 μL in a liquid). BF₃·OEt₂ (0.3 equiv) was measured with a 50 μL syringe and set aside. The *N*-bromoimide **1h** (1.1 equiv) was added all at once neat, followed by immediate addition of the BF₃·O(Et)₂. The solution was exothermic and would often form a color for about a minute from dark yellow, orange, or purple. The solution was mixed at room temperature for ¾ h and was then poured into a sep. funnel containing sat. aq. NaHCO₃. The solution was extracted with DCM (3×), dried with MgSO₄, vacuum filtered, and concentrated *in vacuo*. The crude compound was transferred into a 20 mL glass vial, and the solvent was removed *in vacuo* to yield a residue. The crude product was heated in the glass vial neat under a nitrogen atmosphere with an oil bath to 75 °C for 3 h unless otherwise indicated. The crude product could be dissolved in ether and washed with water to remove residual H-N(CO₂Me)₂ side product if needed. The crude methyl-2-oxazolidinone-3-carboxylate was purified by silica gel chromatography.

Methyl 2-Oxo-4-phenyloxazolidine-3-carboxylate (4a)

The compound was made by the general procedure above. The crude product was purified by column chromatography; 98:2 DCM:TEA; *R_f* = 0.32; solid mp = 79–82 °C; 78 mg; 81% yield; ¹H NMR (500 MHz) (CDCl₃) δ 3.76 (3H, s), 4.23 (1H, dd, *J*₁ = *J*₂ 8.80 Hz), 4.68 (1H, t, *J* = 8.80 Hz), 5.29 (1H, dd, *J*₁ = 8.80, *J*₂ = 4.40 Hz), 7.31 (2H, d, *J* = 6.85), 7.33–7.40 (3H, m); ¹³C NMR and DEPT (125 MHz) (CDCl₃) δ 53.9 (CH₃), 58.4 (CH), 69.5 (CH₂), 125.8 (CH), 128.8 (CH), 129.1 (CH), 138.8 (C), 151.1 (C), 151.9 (C); IR (NaCl): 2959, 1882, 1734, 1342, 1080; HRMS Calculated for C₁₁H₁₁NO₄ (M + Na): 244.0586; Found 244.0586.

Methyl 4-(4-Chlorophenyl)-2-oxazolidinone-3-carboxylate (4b)

The compound was made by the general procedure above. The crude product was purified by column chromatography; 50:50:2 DCM:Hexane:TEA; R_f = 0.5; oil; 81 mg; 76% yield; ^1H NMR (500 MHz) (CDCl_3) δ 3.81 (3H, s), 4.24 (1H, dd, J_1 = 9.3 Hz, J_2 = 3.9 Hz), 4.70 (1H, t, J = 9.05 Hz), 5.15–5.50 (1H, dd, J_1 = 8.8 Hz, J_2 = 4.4 Hz), 7.27 (2H, d, J = 8.3 Hz), 7.39 (2H, d, J = 8.3 Hz), ^{13}C NMR and DEPT (125 MHz) (CDCl_3) δ 54.19 (CH_3), 57.95 (CH), 69.33 (CH_2), 127.36 (CH), 127.43 (CH), 129.50 (CH), 134.97 (C), 137.28 (C), 151.19 (C), 151.63 (C); IR (NaCl): 2959, 1828, 1734, 1340, 1084; HRMS Calculated for $\text{C}_{11}\text{H}_{11}\text{ClNO}_4$ (M + H): 256.0372; Found 256.0377.

Methyl 4-(4-Fluorophenyl)-2-oxazolidinone-3-carboxylate (4c)

The compound was made by the general procedure for the intermediate 1-bromo, 2-*N*imide and was purified by column chromatography. Oil; R_f = 0.5; 100% DCM; the intermediate was heated neat at 75 °C for 3 h to yield compound **4c** and did not require any further purification. Solid mp = 67–68 °C; 42 mg; 43% yield; ^1H NMR (500 MHz) (CDCl_3) δ 3.79 (3H, s), 4.23 (1H, dd, J_1 = 9.05 Hz, J_2 = 4.16 Hz), 4.69 (1H, t, J = 8.80 Hz), 5.30 (1H, dd, J = 8.56, J_2 = 4.16 Hz), 7.09 (2H, t, J = 8.56 Hz), 7.30–7.45 (2H, m); ^{13}C NMR and DEPT (125 MHz) (CDCl_3) δ 54.08 (CH_3), 57.87 (CH), 69.48 (CH_2), 116.13 (d, $^2J_{\text{CF}}$ = 22.50 Hz), (CH), 127.86 (d, $^3J_{\text{CF}}$ = 8.75 Hz), (CH), 134.60 (d, $^4J_{\text{CF}}$ = 3.80 Hz), (C), 151.17 (C), 151.69 (C), 161.84 (d, $^1J_{\text{CF}}$ = 246.30 Hz), (C); IR NaCl: 1819, 1734, 1336, 1080; HRMS Calculated for $\text{C}_{11}\text{H}_{10}\text{NO}_4\text{F}$ (M + Na): 262.0497; Found 262.0492.

cis-Methyl 2-Oxo-8,8a-dihydro-2*H*-indeno[1,2-*d*]oxazole-3-(3*aH*)-carboxylate (4d)

The compound was made by the general procedure above. The crude product was dissolved in ether and was washed with sat. aq. NaHCO_3 , and the ether layer was dried with MgSO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography 1:1 ether:hexane; R_f = 0.5; solid mp = 98–100 °C; 48 mg; 48% yield; ^1H NMR (500 MHz) (CDCl_3) δ 3.38 (2H, m), 4.00 (3H, s), 5.31 (1H, m), 5.79 (1H, d, J = 6.85 Hz), 7.29 (2H, d, J = 5.4 Hz), 7.37 (1H, t, J = 7.3 Hz), 7.66 (2H, d, J = 7.83 Hz); ^{13}C NMR and DEPT (125 MHz) (CDCl_3) δ 38.0 (CH_2), 54.2 (CH_3), 63.7 (CH), 77.7 (CH), 125.3 (CH), 126.7 (CH), 128.1 (CH), 130.1 (CH), 138.4 (C), 139.6 (C), 151.2 (C), 152.2 (C); IR (NaCl): 1824, 1734, 1334, 1253, 1068; HRMS Calculated for $\text{C}_{12}\text{H}_{11}\text{NO}_4$ (M + Na): 256.0586; Found 256.0586.

trans-Methyl 2-Oxo-4,5-diphenyloxazolidine-3-carboxylate (4e)

The compound was made by the general procedure above except that the residue only had to be heated at 75 °C for 1 h to yield **4e**. The crude product was purified by column chromatography 1:1 ether:hexane; R_f = 0.28; solid; mp = 120–122 °C; 30 mg; 36% yield; ^1H NMR (500 MHz) (CDCl_3) δ 3.78 (3H, s), 5.13 (1H, d, J = 4.89 Hz), 5.34 (1H, d, J = 4.89 Hz), 7.33 (4H, m), 7.43 (6H, m); ^{13}C NMR and DEPT (125 MHz) (CDCl_3) δ 54.1 (CH_3), 66.6 (CH), 82.4 (CH), 125.2 (CH), 126.0 (CH), 129.1 (CH), 129.2 (CH), 129.4 (CH), 129.4 (CH), 137.2 (C), 138.4 (C), 151.2 (C), 151.6 (C); IR (NaCl): 1824, 1797, 1327, 1074; HRMS Calculated for $\text{C}_{17}\text{H}_{15}\text{NO}_4$ (M + Na): 320.0901; Found 320.0899.

trans-Methyl 5-Benzoyl-4-(4-methoxyphenyl)-2-oxazolidinone-3-carboxylate (4f)

The compound was made by the general procedure above except that the residue only had to be heated at 75 °C for 1 h to yield **4f**. The crude product was dissolved in ether and was washed with sat. aq. NaHCO₃, and the ether layer was dried with MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography 40:57:3 EtOAc:hexane:TEA; *R_f* = 0.45; oil; 34 mg; 50% yield; ¹H NMR (500 MHz) (CDCl₃) δ 3.77 (3H, s), 3.83 (3H, s), 5.48 (1H, d, *J* = 2.93), 5.55 (1H, d, *J* = 2.93 Hz), 6.96 (2H, d, *J* = 8.80 Hz), 7.32 (2H, d, *J* = 8.31 Hz), 7.51 (1H, t, *J* = 7.58 Hz), 7.66 (1H, t, *J* = 7.34 Hz), 7.91 (2H, d, *J* = 7.85 Hz); ¹³C NMR and DEPT (125 MHz) (CDCl₃) δ 54.1 (CH₃), 55.4 (CH₃), 59.5 (CH), 79.9 (CH), 114.8 (CH), 127.7 (CH), 129.1 (CH), 129.1 (CH), 129.8 (C), 132.8 (CH), 134.8 (C), 150.5 (C), 150.8 (C), 160.3 (C), 191.3 (C); IR (NaCl): 1821, 1792, 1728, 1369, 1082; HRMS Calculated for C₁₉H₁₇NO₆ (M + Na): 378.0959; Found 378.0954.

trans-4,5-Dipropylloxazolidin-2-one (4g)

The methyl-2-oxazolidinone-3-carboxylate was made by the general procedure above for compounds in Table 3 except 2.0 equiv of **1h** was used. The oxazolidinone was unstable on silica gel, so the crude product was hydrolyzed to *trans*-4,5-dipropylloxazolidin-2-one **4g** by dissolving in THF (2.0 mL) and cooling the crude reaction to 0 °C. 2 M LiOH (1.0 mL) was added, and the solution was mixed fast to cause an emulsion for 2 h while warming slowly to room temperature. The crude product was extracted with EtOAc, dried with MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography; 100% DCM; *R_f* = 0.2 (PMA stain); oil; 20 mg; 36% yield (over 3 steps). The compound matched the reported literature data.²⁶ ¹H NMR (500 MHz) (CDCl₃) δ 0.94 (6H, m), 1.28–1.73 (8H, m), 3.42 (1H, q, *J* = 6.03 Hz), 4.15 (1H, dt, *J* = 7.95, 5.07 Hz), 6.21 (1H, s, br.); ¹³C NMR and DEPT (125 MHz) (CDCl₃) δ 13.75 (CH₃), 13.83 (CH₃), 18.15 (CH₂), 18.74 (CH₂), 36.88 (CH₂), 37.51 (CH₂), 57.85 (CH), 82.50 (CH), 159.56 (C).

4-Phenylloxazolidin-2-one (5a)

Compound **4a** (50 mg) was dissolved in THF (2.0 mL), and 2 M LiOH (1.0 mL) was added. The solution was mixed fast to cause an emulsion for 2 h at room temperature. The crude reaction was poured into a sep. funnel containing water. The product was extracted with EtOAc (3×), dried with MgSO₄, filtered, and concentrated *in vacuo* to give a solid. The solid was triturated with 50:50 ether:hexane (3 mL) and was placed in the fridge for 1 h. The solvent was removed from the crystals with a pipet, and the crystals were dried *in vacuo*. The compound was consistent with the previously reported literature data.²⁷ Solid mp = 132–133 °C; 30 mg; 81% yield; ¹H NMR (500 MHz) (CDCl₃) δ 4.19 (1H, dd, *J*₁ = 8.56, *J*₂ = 7.09 Hz), 4.74 (1H, t, *J* = 8.80 Hz), 4.96 (1H, t, *J* = 7.83 Hz), 5.76 (1H, s, br), 7.31–7.43 (5H, m); ¹³C NMR and DEPT (125 MHz) (CDCl₃) δ 56.36 (CH), 72.52 (CH₂), 126.03 (CH), 128.87 (CH), 129.21 (CH), 139.40 (C), 159.49 (C).

2-Hydroxy-1-phenylethanaminium Chloride (5b)

Compound **4a** (100 mg) was dissolved in THF (4.0 mL), and 2 M LiOH (2.0 mL) was added. The solution was refluxed for 17 h. The crude reaction was cooled to room temperature and was extracted with DCM (5 × 10 mL), dried with MgSO₄, filtered, and

concentrated *in vacuo* to give an oil. The oil was suspended in ether, and an excess of HCl (g) was bubbled into the ether for 2 min. Solids instantly crystallized out, and the solution was left to stand at room temperature for 30 min. The ether was removed with a pipet, and the crystals were dried. The compound was consistent with the previously reported literature data.²⁸ Solid, 55 mg; mp = 148–150 °C; 70% yield; ¹H NMR (500 MHz) (DMSO) δ 3.70 (2H, s), 4.22 (1H, s), 5.52 (1H, s), 7.3 (3H, s), 7.49 (2H, s), 8.61 (3H, s); ¹³C NMR and DEPT (125 MHz) (DMSO) δ 56.56 (CH), 63.44 (CH₂), 128.07 (CH), 128.86 (CH), 128.93 (CH), 136.28 (C).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Synthesis of Br-N(CO₂Me)₂, **1h**

Scheme 2.

Proposed Mechanism for Hydroxyamination of an Olefin with $\text{Br-N}(\text{CO}_2\text{Me})_2$ To Yield a *trans* Oxazolidinone

Table 1

Reaction of *N*-Halo Reagents with Styrene

$$\begin{array}{c}
 R_1-N(R_2)-X \\
 \text{1a-h}
 \end{array}
 + \text{Ph-CH=CH}_2
 \xrightarrow[\text{DCM, rt, 45min.}]{\text{BF}_3 \cdot \text{OEt}_2 \text{ 0.3 equiv.}}
 \begin{array}{c}
 R_1-N(R_2)-CH(Ph)-CH_2-X \\
 \text{3a-h}
 \end{array}$$

entry	1 <i>N</i> -halo reagent	3 product	3 yield (%)
a			0
b			trace
c			83
d			0
e			0
f			0
g			0
h			81

Table 2

Aminobromination of Olefin 2 with Reagent 1h^{a,b,c}

entry	2 substrate	3 product	3 yield (%)
i			88
j			79
k			52
l			34 ^a
m			37 ^{a, b}
n			50 ^c

^a2.0 equiv of **1h** was used.^bRxn yielded a 52:48 mixture of regioisomers.^c2:1 ratio of 1,4-addition to 1,2-addition to the terminal alkene.

Table 3

Hydroxyamination of Olefin 2 with Reagent 1h^{a,b}

entry	2 substrate	4 product	4 yield
a			81
b			76
c			43 ^b
d			48
e			36
f			50
g	Trans-octene		36 ^b

^aThe intermediate **3** was purified before cyclization to **4**.^bThe oxazolidinone was hydrolyzed to *trans*-4,5-dipropyloxazolidin-2-one, reported yield was for 3 steps.

Table 4Selective Deprotection of the Aminoalcohols^{a,b}

entry	4 substrate	5 product	5 yield (%)
a			81 ^a
b			70 ^b

^aHydrolysis with 2 M LiOH/THF at rt for 2 h.^bHydrolysis by refluxing in 2 M LiOH/THF overnight.