Pergamon

Tetrahedron 55 (1999) 11755–11772

TETRAHEDRON

Reductive Cleavage of N-O Bonds in Hydroxylamines and Hydroxamic Acid Derivatives Using Samarium Diiodide

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Received 7 April 1999; accepted 14 May 1999

Abstract: An efficient process for the reductive cleavage of N-O bonds using samarium diiodide is detailed for a variety of structural types to define the scope and limitations of the method. The reduction is shown to be compatible with base sensitive substrates such as trifluoroacetamide derivatives, which cannot be reduced satisfactorily using aluminum amalgam or sodium amalgam. Direct quenching of the reduction mixture with acylating agents is demonstrated to provide high yields of protected amines in a one-pot process from the N-O derivatives. © 1999 Elsevier Science Ltd. All rights reserved.

Key words: SmI_2, reduction, nitrogen-oxygen bonds, chemoselective, amines

INTRODUCTION

Alkaloids (naturally occuring amines) are widely distributed in plants and animals, and have been used for medicinal purposes throughout the ages.[1] The medicinal value of alkaloids, their sometimes limited availability from natural sources, and the diversity and complexity of such structures has generated a considerable amount of interest in their total synthesis. In recent years a large number of alkaloids as well as other nitrogen containing compounds have been synthesized using electrocyclic and radical pathways *via* intermediates possessing N-O bonds. These N-O bonds are then cleaved to provide nitrogen in its more common oxidation states. Such nitrogen containing intermediates may arise from [4+2] cycloadditions of acylnitroso compounds,[2] ene reactions of acylnitroso compounds,[3] free radical additions to oxime ethers,[4] [3+2] cycloadditions utilizing nitrile oxides and nitrones,[5] [3+2] cycloaddition reactions of O- silyl nitronates,[6] and [4+2] cycloadditions of nitroalkenes[7] (Figure 1). Reductive cleavage of these compounds can be accomplished under a variety of conditions, including hydrogenolysis [(H_2/Pd, EtOH, 1 atm)[8], (H_2, Raney nickel, 1 atm)[7]], reduction with Mg(Hg)/$TiCl_4$,[9] reduction with Al(Hg) or Na(Hg),[10] reduction using $TiCl_3$,[11] and reduction by $Mo(CO)_6$.[12]

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PII: S0040-4020(99)00486-X

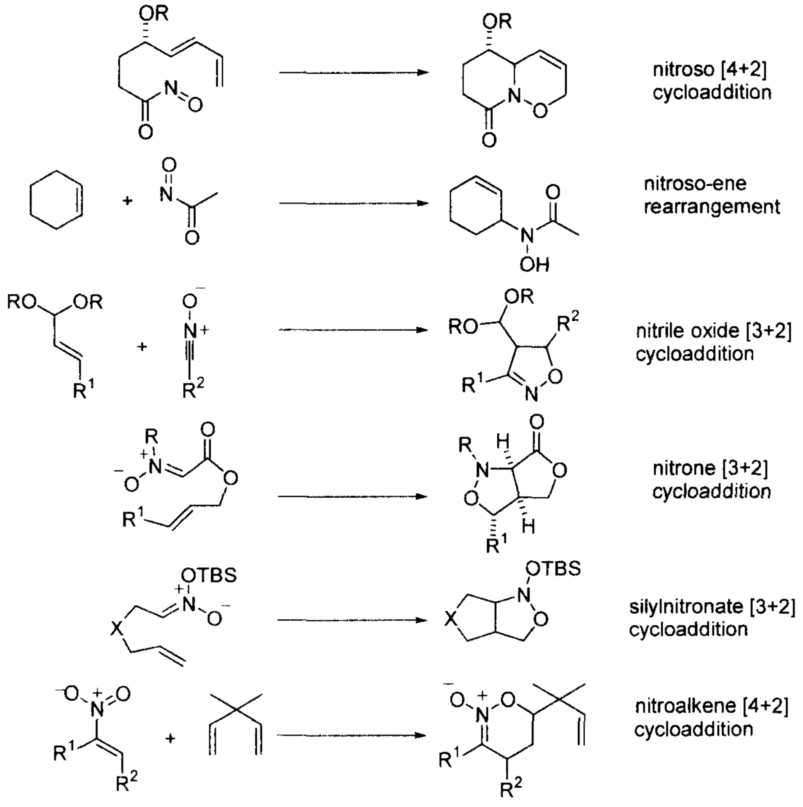
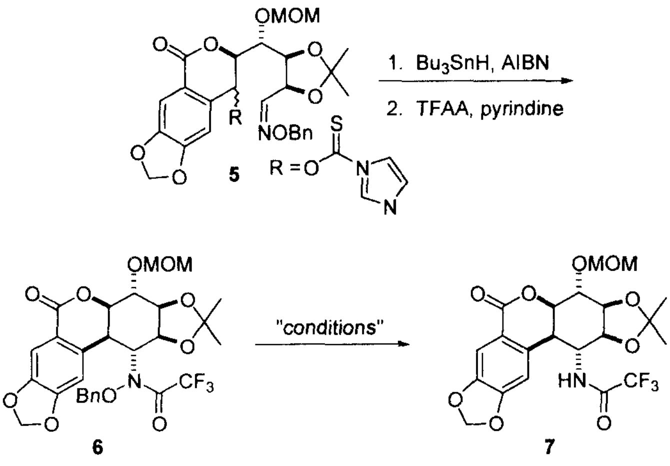


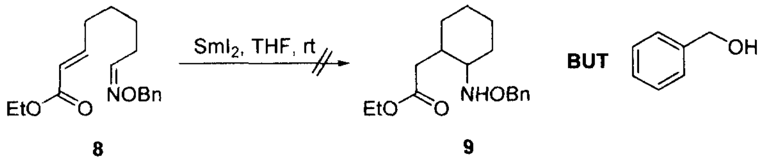
Figure 1. Processes Resulting in Compounds Possessing N-O Bonds

Recently, in our study toward the total synthesis of 7-deoxypancratistatin,[4] we needed to reductively cleave the N-O bond in the product resulting from a free radical addition to an oxime ether (Scheme 1). Specifically, we needed to reductively cleave the N-O bond of the trifluoroaceto-hydroxamic acid derivative **6**. Despite the large number of efficient methods for N-O bond reduction, we encountered limitations of the more common procedures. Using our previously developed method involving reduction with Al(Hg) or Na(Hg)[10] the desired transformation failed. Other methods such as hydrogenolysis[8a] also proved to be inefficient in the transformation of the trifluoroaceto-hydroxamic derivative **6** to the trifluoroacetamide **7**. Prior to these investigation, our group had been interested in radical additions to oxime ethers initiated by SmI_2. This research resulted in an unexpected outcome (Equation 1). When the unsaturated ester **8** was treated with SmI_2, none of the desired cyclized product **9** was obtained; however, benzyl alcohol was isolated. It was this observation which led us to consider the use of SmI_2 as a possible reducing reagent for the cleavage of N-O bonds.[13] This proved to be an effective reagent for reductive cleavage with **6**, giving the trifluoroacetamide **7** in 95% isolated yield. Although isolated reports of N-O bond cleavage promoted by

SmI_2 exist, none of them describe any general utility for such a transformation. We provide herein a full account of the scope and limitations of this reduction.



Scheme 1. Reductive Cleavage of the N-O Bond of Hydroxamic Derivative **6**

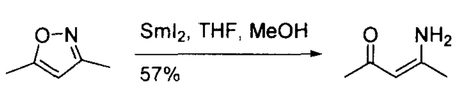


(1)

An Observation from Our Laboratories

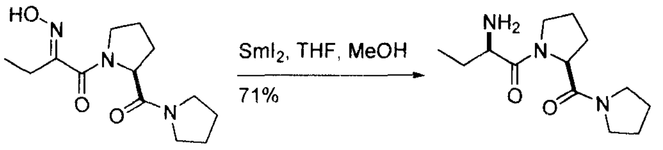
Previous Synthetic Work

In 1982 Natale[14a] reported that the N-O bonds of isoxazoles (Equation 2) could be cleaved with SmI_2 in the presence of a proton source such as methanol to give the β-amino enone as the product. More recently, Mukaiyama *et al.* (Equation 3) studied the chemo and stereoselective reductions of 2-hydroxyimino amides with SmI_2 in the presence of the proton source methanol.[14b] Interestingly, there appear to be no reports of the cleavage of N-O bonds in substrates derived from nitroso [4+2] cycloaddtions, nitroso-ene rearrangements, or from free radical or anionic additions to oxime ethers under these conditions (SmI_2).[15] With this in mind we surveyed the SmI_2 reduction of a variety of free and N-acylated O-alkylhydroxylamines and have found this reaction to be quite general. This protocol has been especially useful in cases where the substrate contained a trifluoroacetyl group since this group itself can be removed under mild alkaline condition (e.g. K_2CO_3/ MeOH). It also can be employed for the direct production of a variety of protected amines *via* directly quenching the reaction mixture with an acylating agent.



(2)

N-O Bond Cleavage of Isoxazole Using SmI_2



(3)

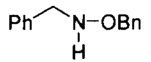
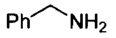
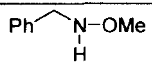
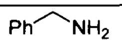
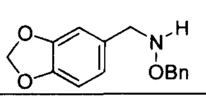
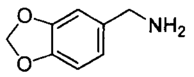
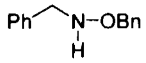
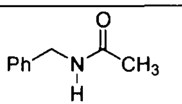
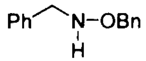
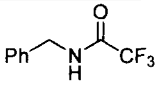
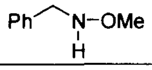
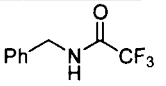
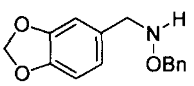
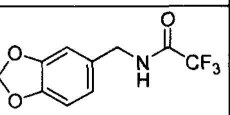
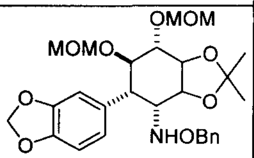
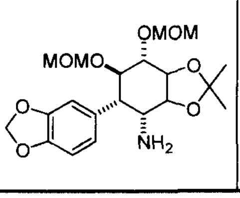
Reduction of 2-Hydroxyimino Amide by SmI_2

RESULTS AND DISCUSSION

The results obtained for the reductive cleavage of N-O bonds of simple hydroxylamines are shown in Table 1. Some of the yields reported are for the acetamide or trifluoroacetamide instead of the primary amines, due to problems arising in their isolation. For example, in the reduction of N-alkyl, O-benzylhydroxylamine derivatives, entries 1 and 3, thin layer chromatographic analysis revealed the disappearance of starting material and flash chromatography afforded a 90% isolated yield of benzyl alcohol, although no amine was isolated. Presumably the inability to isolate simple primary amines (benzylamine and piperonylamine) can be attributed to their high polarity and low molecular weight.

A solution to this isolation problem was devised. After TLC analysis indicated complete consumption of starting material, the reaction was quenched with trifluoroacetic or acetic anhydride. This resulted in good isolated yields of the acetylated products (Table 1, Entries 5-9). In order to examine the possibility of milder reduction conditions, N-benzyl-O-methylhydroxylamine (Entry 8) was treated with SmI_2 at lower temperature (-78 °C); however, this resulted in recovered starting material along with the N-benzyl-N-methoxy-2,2,2-trifluoroacetamide. Thus, the cleavage of O-alkylhydroxylamines at low temperature is not feasible. Although the direct isolation of low molecular weight amines was not practical the isolation of primary amines derived from O-alkylhydroxylamines of higher molecular weight was easily accomplished (Entry 10); in these cases, acetylation is not required for product isolation. Finally, although acetylation is not required for substrates with significantly high molecular weight, this *in situ* conversion to an amide, i.e., protection of an amine, can be employed to directly afford a protected amine if desired.

Table 1. Yields for Reductive Cleavage of N-O Bonds in O-Alkylhydroxylamines Promoted by SmI_2

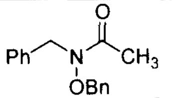
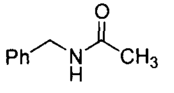
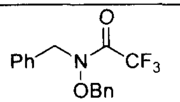
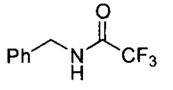
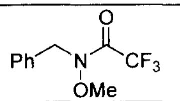
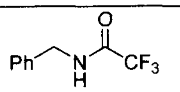
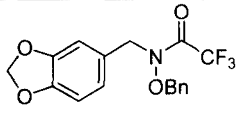
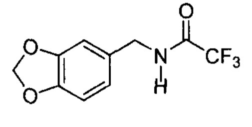
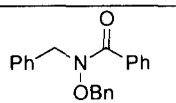
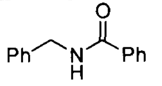
Entry	Substrate	Time (min)	Temperature (°C)	Product	Yield (%)[a]
1		15	rt		0[b]
2		15	rt		0
3		15	rt		0[b]
4		15	rt		90[c]
5		15	rt		91[d]
6		15	rt		65[d]
7		15	-23		50[d]
8		240	-78		0[d]
9		15	rt		60[d]
10		5 h	rt		69

[a]Values represent isolated yields. [b]Benzyl alcohol was isolated in 90 % yield. [c]Reaction was quenched with acetic anhydride. [d]Reaction was quenched with trifluoroacetic anhydride.

Reductive cleavage of N-acyl derivatives typically afforded high isolated yields of the desired products, which ranged from 70-93% (Table 2). In contrast to results with the simple O-alkylhydroxylamines, cleavage of N-O bonds in N-acetylated O-alkylhydroxylamines at lower temperatures resulted in an increased yield (Entries 6 and 7). Thus, the carbonyl substituent allows for reduction at lower temperatures. Utilization of N-acetylated O-alkylhydroxylamines may offer some advantages over simple O-alkylhydroxylamines in cases where chemoselective reduction of an N-O bond is required in the presence of another reducible functional group.

In order to compare the mild reducing conditions of SmI_2 to that of Al(Hg) and Na(Hg), N,O-benzyl-2,2,2-trifluoroacetamide (Table 2, Entry 2) which gave a good result in the SmI_2 reduction, was also used as a substrate for attempted reduction with both Al(Hg) and Na(Hg). In neither case was the desired product obtained; in both instances the only observed product resulted from base induced cleavage of the trifluoroacetamide group. With Al(Hg) (0 °C - rt, 10 h) starting material (64%) was recovered along with 32% of the base induced cleavage product; with Na(Hg) (0 °C, 90 min) an 82% isolated yield of the base induced cleavage product was obtained. In the original Al(Hg) and Na(Hg) report from our laboratory cleavage of N-O bonds in substrates containing N-trifluoroacyl groups were not examined. Thus, the SmI_2 protocol proved to a very mild process compatible with base-labile substrates.

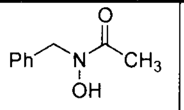
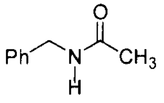
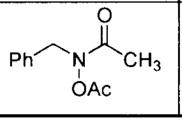
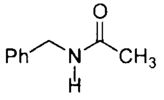
Table 2. Yields for Reductive Cleavage of N-O Bonds of N-Acyl Derivatives by SmI_2

Entry	**Substrate**	**Time (min)**	**Temperature (°C)**	**Product**	**Yield (%)^{a}**
1		20	rt		87
2 3		15 15	rt -78		80 82
4		15	rt		70
5		240	rt		93
6 7		15 20	rt -78		62 86

[a]Values represent isolated yields.

The success of these reactions using SmI_2 prompted us to examine the reductive cleavage of the N-O bond of N-benzyl-N-acetylhydroxamic acid (Table 3, Entries 1 and 2). Typically hydroxamic acids are cleaved using Mg(Hg)/$TiCl_4$. Disappointingly, when the simple hydroxamic acid was treated with SmI_2 only trace amounts of product were observed, and even under more forcing conditions (65 °C) only modest yields were obtained. However, conversion of the hydroxyamic acid to the O-acetylated derivative (Ac_2O, pyridine), followed by reaction with SmI_2 gave a high yield of the N-O bond cleavage product (Entry 3). Thus, albeit indirectly, application of SmI_2 to the cleavage of nitroso-ene type products has been investigated, and the cleavage proceeds in excellent yield for the O-acyl derivatives.

Table 3. Yields for Reductive Cleavage of N-O Bonds in Hydroxamic Acids Promoted by SmI_2

Entry	Substrate	Time (min)	Temperature (°C)	Product	Yield (%)[a]
1		50	rt		trace
2		240	65		45
3		15	rt		95
4		15	-78		50

[a]Values represent isolated yields.

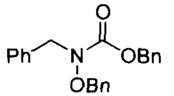
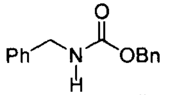
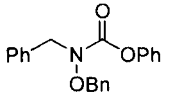
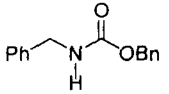
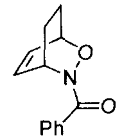
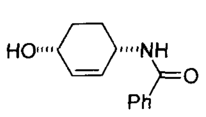
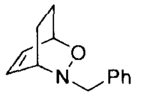
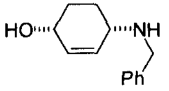
In order to broaden the scope of this procedure further we examined the cleavage of CBz protected O-alkylhydroxylamines (Table 4, Entry 1). When the N-acyl-benzyloxycarbonyl derivative was treated with SmI_2 at rt the reaction was complete within 20 min to give an excellent yield of N-benzyl-benzylcarbamate. Interestingly, upon examination of a similar substrate, an N,O-benzyl-phenyloxycarbonyl-hydroxylamine derivative, (Entries 2 and 3), none of the desired N-benzyl-phenylcarbamate was isolated. In this case the transesterified product was obtained along with recovered starting material (40%), even after long reaction times. Presumably this is a result of the leaving ability of phenoxide and the nucleophilicity of benzoxide. Thus such activated ester moieties as the phenyl ester used in this case are not compatible with this procedure.

Nitroso [4+2] cycloadditions are increasingly being used in synthetic applications.[2,3,16] We therefore examined bicyclic substrates (Table 4, entries 4 and 5), derived from an acyl nitroso [4+2] cycloaddition, which conform to the general trend that higher yields are obtained with N-acyl substrates than with N-alkyl ones; however, in this particular case (entry 5), at least part of the diminished yield can be attributed to isolation difficulties with the highly polar product.

CONCLUSION

The reduction of a wide variety of compounds containing nitrogen in an uncommon oxidation state has been examined.[17,18] Treatment of these N-O bond containing compounds with SmI_2 resulted in good to excellent yields of the products in which nitrogen has been returned to a more common oxidation state. The very mild and chemoselective nature of this reaction leads to a compatibility with trifluoroacetamides,[19,20] and thus may prove to be a useful complement to a variety of existing synthetic methodology.[2-7,21]

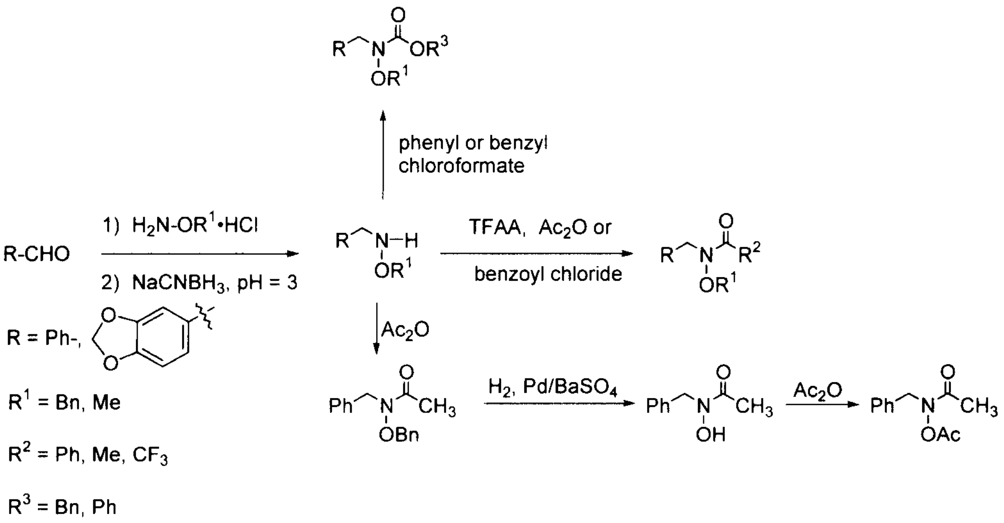
Table 4. Yields for Reductive Cleavage of N-O Bonds Promoted by SmI_2

Entry	Substrate	Time (min)	Temperature (°C)	Product	Yield (%)[a]
1		15	rt		93
2 3		20 120	rt -78 – rt		48 40
4		90	-78		93
5		15	rt		55[b]

[a]Values represent isolated yields. [b]Starting material racemic only one enantiomer is shown.

EXPERIMENTAL SECTION

All substrates used in this study are readily available from well-established chemical transformations and were synthesized as follows (Scheme 2). Benzaldehyde and piperonal were reacted with O-benzyl or O-methyl hydroxylamine hydrochloride salt, followed by reduction of the resulting oxime with sodium cyanoborohyride reduction at pH = 3.[22] Acetylation of the O-alkylhydroxylamines was accomplished using TFAA, Ac_2O or benzoyl chloride affording the corresponding N-acyl derivatives. These derivatives were treated under hydrogenolysis conditions[23] (Pd on $BaSO_4$) to yield hydroxamic acid derivatives which could ultimately be converted to the O-acetyl derivative with Ac_2O. The N-benzyl N-alkyloxycarbonyl hydroxylamines were synthesized from the O-alkylhydroxylamine and the corresponding chloroformate. A general list of compounds synthesized is provided (Figure 2).



Scheme 2. General Synthesis of Substrates

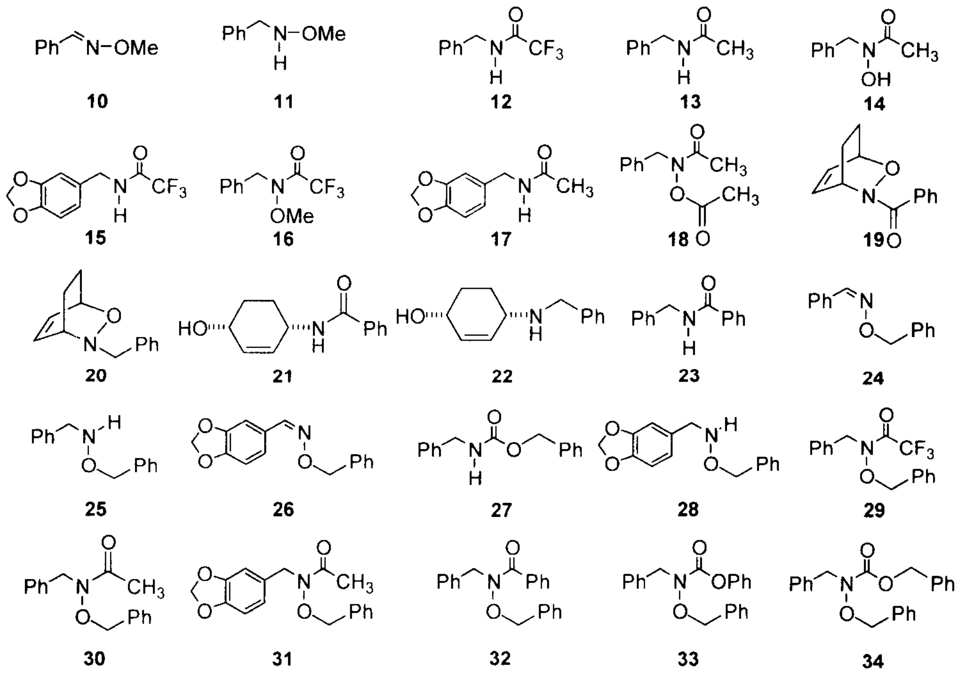


Figure 2. Structures Used in This Work

Solvents were purified according to the guidelines in Purification of Common Laboratory Chemicals (Perrin, Armarego, and Perrin, Pergamon: Oxford, 1966). Samarium diiodide (SmI_2) was prepared from samarium metal and iodine in refluxing THF,[24] or (preferably) by reaction of samarium metal with diiodomethane at rt.[25] All other reagents were purchased from Aldrich and used without further purification. Yields were calculated for material judged homogenous by thin layer chromatography and NMR. Thin layer chromatography was performed on Merck Kieselgel 60 F_{254} plates eluting with the solvents indicated, visualized by a 254 nm UV lamp, and stained with an ethanolic solution of 12-molybdophosphoric acid or p-anisaldehyde. Flash column chromatography was performed with Davisil 62 silica gel, slurry packed with 10% EtOAc / hexanes in glass columns, and flushed with hexanes prior to use. Preparative chromatography was also carried out using a Chromatotron using glass plates coated with silica gel (P. F. 254 60) of 2 and 4 mm thickness (RPLC). Nuclear magnetic resonance spectra were acquired at 300 MHz for ^1H, 75 MHz for ^{13}C, and 280 MHz for ^{19}F. Chemical shifts for proton nuclear magnetic resonance (^1H NMR) spectra are reported in parts per million downfield from tetramethylsilane (TMS). Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million downfield relative to the center line of the triplet of $CDCl_3$ at 77.0 ppm. Chemical shifts for fluorine nuclear magnetic resonance (^{19}F NMR) spectra are reported in parts per million downfield from trifluorotoluene at 130.0 ppm. The abbreviations s, d, t, q, br s, dd, dq, br t and ABq stand for the resonance multiplicity singlet, doublet, triplet, quartet, broad singlet, doublet of doublets, double of quartets, broad triplet, and AB quartet, respectively. Atlantic Microlab, Inc., Norcross, Georgia, performed analytical C and H analyses. Glassware for all reactions was oven dried at 125 °C and cooled in a desiccator prior to use. Liquid reagents and solvents were introduced by oven dried syringes through septa sealed flasks under a nitrogen atmosphere.

General Procedure for the Reductive Cleavage of N-O Bonds of O-Alkylhydroxylamines Using SmI_2/ THF Followed by TFAA or Ac_2O Addition

Preparation of N-benzylacetamide (13). To a stirring solution of N,O-benzylhydroxylamine **25** (0.10 g, 0.47 mmol) in THF was added at the desired temperature a solution of freshly prepared SmI_2 (16 mL, 0.08 M in THF) dropwise *via* syringe. After thin layer chromatography analysis indicated complete reaction (*ca.* 15 min) acetic anhydride (0.18 mL, 1.8 mmol) (or TFAA for 2,2,2-trifluoroacetyl derivatives) was added *via* syringe. The resulting mixture was stirred for 15 min before being diluted with CH_2Cl_2 (30 mL) and quenched with a 10% solution of $Na_2S_2O_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x25 mL). The combined organic layers were dried over $MgSO_4$ and then filtered under reduced pressure through a compressed pad of Celite (2 mm). The filter pad was washed with CH_2Cl_2, and the filtrate concentrated *in vacuo*. Purification of this material was accomplished by RPLC, using a 2 mm plate, eluting with a gradient solvent of 20% acetone/ hexanes through 70% acetone/ hexanes. The product fractions were combined and concentrated to give **13** (0.06 g, 90% yield) as a colorless solid: mp 51 °C; R*f* 0.22 (30% acetone/ 30% Et_2O/ 40% hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 7.34-7.24 (m, 5H), 6.43 (br s, 1H), 4.37 (d, *J* = 5.9 Hz, 2H), 1.97 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) 170.4, 138.3, 128.7, 127.9, 127.5, 43.8, 23.2; IR ($CHCl_3$) 3448 (broad), 3020, 1675, 1520, 1215 cm^{-1}; Anal. Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.17; H, 7.52; N, 9.19.

Analytical data for 2,2,2-trifluoro-N-benzylacetamide (12). mp 66 °C; R*f* 0.50 (75% Et_2O/ hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 7.36-7.25 (m, 5H), 6.91 (s, 1H), 4.46 (d, *J* = 5.9 Hz, 2H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 157.6 (q, $J_{C\text{-}F}$ = 37.1 Hz), 136.0, 128.5, 128.2, 120.8, 115.6 (q, $J_{C\text{-}F}$ = 285.7 Hz), 44.1; 280 MHz ^{19}F NMR ($CDCl_3$) 117.7; IR ($CHCl_3$) 3435 (broad), 3020, 1725, 1530, 1215 cm^{-1}; Anal. Calcd for C_9H_8NO: C, 53.21; H, 3.97; N, 6.89. Found: C, 53.05; H, 3.98; N, 6.83.

Analytical data for N-(2H-benzo[3,4-d]1,3-dioxolen-5-ylmethyl)-2,2,2-trifluoroacetamide (15). mp 75 °C; R*f* 0.45 (40% acetone/ hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 6.75 (br s, 1H), 5.93 (s, 3H), 4.39 (d, *J* = 5.9 Hz, 2H), 4.37 (s, 2H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 157.3 (q, $J_{C\text{-}F}$ = 37.1 Hz), 148.3, 147.7, 129.8, 121.7, 116.0 (q, $J_{C\text{-}F}$ = 286.2 Hz), 108.6, 109.6, 101.4, 43.9; 280 MHz ^{19}F NMR ($CDCl_3$) δ 117.7; IR ($CHCl_3$) 3435 (broad), 3020, 1726, 1531 cm^{-1}; Anal. Calcd for $C_{19}H_8F_3NO_3$: C, 48.59; H, 3.26; N, 5.67. Found: C, 48.57; H, 3.26; N, 5.66.

General Procedure for the Reductive Cleavage of N-O Bonds of N-Acylhydroxamic Acid Derivatives Using SmI$_2$/ THF

Preparation of N-benzylacetamide (13). To a stirring solution of N,O-benzyl-N-benzyloxyacetamide **30** (0.20 g, 0.78 mmol) in THF was added at the desired temperature a solution of freshly prepared SmI_2 (21 mL, 0.070 M in THF), dropwise *via* syringe. After thin layer chromatography analysis indicated completion the reaction was diluted with CH_2Cl_2 (50 mL) and then quenched with a 10% solution of $Na_2S_2O_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x20 mL) . The combined organic layers were dried over $MgSO_4$ and then filtered under reduced pressure through a compressed pad of Celite (2 mm) and $MgSO_4$ (2 mm). The filter pad was washed with CH_2Cl_2 and the filtrate was concentrated *in vacuo*. Purification of this material was accomplished by RPLC, using a 2 mm disk, eluting with a solvent gradient of 25% acetone/ hexanes through 50% acetone/ hexanes. The product containing fractions were combined and concentrated *in vacuo* to give the acetamide **13** (0.10 g, 87% yield) as a colorless solid: mp 51 °C; R*f* 0.22 (30% acetone/ 30% Et_2O/ 40% hexanes); 300 MHz ^1H and 75 MHz ^{13}C NMR ($CDCl_3$) δ were consistent with the product obtained from the cleavage of the N-O bond of N,O-benzyl hydroxylamine **25** followed by Ac_2O quench.

Analytical data for N-(2H-benzo[3,4-d]1,3-dioxolen-5-ylmethyl)acetamide (17). mp 83-85 °C; R*f* 0.14 (30% acetone/ 30% Et_2O/ 40% hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 6.75-6.70 (m, 3H), 6.28 (br s, 1H), 5.92 (s, 2H), 4.28 (d, *J* = 5.7 Hz, 2H), 1.98 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 170.2, 147.9, 147.0, 132.3, 121.2, 108.5, 108.4, 101.1, 43.6, 23.3; IR (CHCl3) 3447 (broad), 2930, 1665, 1505 cm^{-1}; Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.25; H, 5.70; N, 7.21.

Analytical data for N-((4SR,1RS)-4-hydroxycyclohex-2-enyl)benzamide (21). R*f* 0.38 (8% MeOH/ $CHCl_3$); 300 MHz ^1H NMR ($CDCl_3$) δ 7.76-7.73, (m, 2H), 7.50-7.27 (m, 3H), 6.52 (d, *J* = 8.1 Hz, 2H) 5.94 (app. dq, *J* = 10.0, *J* = 1.7 Hz, 1H) 5.78 (dd, *J* = 10.2, *J* =2.6 Hz, 1H), 4.68-4.58 (m, 1H), 4.23-4.16 (m, 1H), 3.08 (br s, 1H), 1.94-1.70 (m, 4H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 167.2, 134.5, 133.3, 131.7, 130.4, 128.7, 127.1, 64.5, 45.3, 29.1, 25.5; IR (neat) 3360 (broad), 2945, 1640, 1330, 1270, 1080 cm^{-1}; HR FABMS Calcd for $C_{13}H_{15}NO_2$: 217.1102. Found: 217.1097.

Analytical data for (1SR,4RS)-4-[benzylamino]cyclohex-2-en-1-ol (22). R*f* 0.20 (12% MeOH/ $CHCl_3$); 300 MHz ^1H NMR ($CDCl_3$) δ 7.42-7.23 (m, 5H), 5.87 (s, 2H), 4.14 (br s, 1H), 3.91 (ABq, $\Delta\nu$ = 10.1 Hz, *J* = 13.1 Hz, 2H), 3.24 (br s, 1H), 3.05 (br s, 2H), 1.87-1.73 (m, 4H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 138.4, 132.0, 132.5, 130.6, 128.8, 127.7, 64.7, 52.4, 50.7, 29.2, 24.4; IR (neat) 3355 (broad), 3020, 2945, 1455, 1215 cm^{-1}; HR FABMS Calcd. for $C_{13}H_{17}NO$: 203.1310. Found: 203.1309.

Analytical data for phenyl-N-benzylcarboxamide (23). mp 115 °C; R*f* = 0.18 (60% Et_2O/ hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 7.84-7.76 (m, 2H), 7.53-7.26 (m, 8H), 6.63 (br s, 1H), 4.61 (d, *J* = 5.6 Hz, 2H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 167.6, 138.4, 134.5, 131.7, 128.9, 128.7, 128.1, 127.7, 127.2, 44.3; IR ($CHCl_3$) 3684 (broad), 3020, 1520, 1420 cm^{-1}.

Analytical data for (phenylmethoxy)-N-benzylcarboxamide (27). mp 55-56 °C; R*f* 0.34 (35% EtOAc/ hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 7.32-7.23 (m, 10H), 5.18 (br s, 1H), 5.10 (s, 2H), 4.33 (d, *J* = 6.1 Hz, 2H); 75 MHz ^{13}C NMR ($CDCl_3$) 156.6, 138.6, 136.7, 128.8, 128.6, 128.2, 127.6, 66.9, 45.3; IR ($CHCl_3$) 3450 (broad), 3020, 2955, 1715, 1515 cm^{-1}.

General Procedure for the Preparation of Oximes

Preparation of benzaldehyde O-benzyloxime (24). To a stirring solution of benzaldehyde (10.2 g, 96.2 mmol) in 280 mL of pyridine was added O-benzylhydroxylamine hydrochloride salt (20.0 g, 125 mmol) in one portion. After 17 h the solvent was removed *in vacuo* and the residue was diluted with EtOAc (400 mL), then washed with a saturated solution of copper sulfate (3x200 mL) and finally with H_2O (2x100 mL). The organic layer was dried over $MgSO_4$, and then filtered under reduced pressure through a compressed pad of Celite (2 mm) and $MgSO_4$ (2 mm). The filter pad was washed with CH_2Cl_2 and the filtrate was concentrated *in vacuo*. Purification of this material was accomplished by flash column chromatography using a (4x24) cm column, eluting with a gradient solvent of hexanes through 10% EtOAc/ hexanes. The product containing fractions were combined and concentrated *in vacuo* to give **24** (18.4 g, 90% yield) as a clear colorless oil: R*f* = 0.70 (35% EtOAc/ hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.17 (s, 1H) 7.63-7.59 (m, 2H), 7.48-7.33 (m, 8H), 5.21 (s, 2H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 149.2, 137.7, 132.4, 130.0, 128.9, 128.7, 128.6, 128.2, 127.3, 76.6; IR (neat) 3030, 2930, 1880, 1810, 1755, 1495, 1445, 1020 cm^{-1}; Anal. Calcd for $C_{14}H_{12}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.83; H, 6.30; N, 6.50.

Analytical data for benzaldehyde O-methyloxime (10). R*f* 0.67 (35% EtOAc/ hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.03 (s, 1H), 7.56-7.51 (m, 2H), 7.34-7.28 (m, 3H), 3.94 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 148.5, 132.4, 129.8, 128.7, 127.1, 62.0.

Analytical data for piperonal O-benzyloxime (26). mp 39 °C; R*f* 0.60 (35% EtOAc/ hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.97 (s, 1H), 7.39-7.23 (m, 5H), 7.14, (d, *J* = 1.4 Hz, 1H), 6.81 (dd, *J* = 8.1, 1.7, 1H), 6.65 (d, *J* = 8.1, 1H), 5.77, (s, 2H), 5.13 (s, 2H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 149.2, 148.5, 148.1, 137.7, 128.4, 128.0, 127.9, 126.5, 122.9, 108.2, 105.6, 101.3, 76.3; IR ($CHCl_3$) 3030, 2900, 1625, 1490, 1045 cm^{-1}; Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13. Found: C, 70.70; H, 5.16.

General Procedure for the Reduction of Oximes Using Sodium Cyanoborohydride

Preparation of N,O-benzylhydroxylamine (25). To a stirring solution of benzaldehyde O-benzyl oxime **24** (5.00 g, 23.5 mmol) in 47 mL of CH_2Cl_2 was added sodium cyanoborohydride (2.50 g, 37.9 mmol) in one portion followed by a solution of ca 2 N HCl-MeOH (34 mL, solution prepared by addition of 16.6 mL of conc HCl to 100 mL of MeOH) dropwise over a 10 min period (pH = 3). After 20 h the solvent was removed *in vacuo* and the residue was taken up in CH_2Cl_2 (25 mL). The reaction mixture was then made basic to pH = 9 using a 1 N aqueous NaOH solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried over $MgSO_4$, then filtered under reduced pressure through a compressed pad of Celite (2 mm) and $MgSO_4$ (2 mm). The filter pad was washed with CH_2Cl_2 and the filtrate was concentrated *in vacuo*. Purification of this material was accomplished by flash column chromatography using a 4x24 cm column, eluting with a solvent gradient of hexanes through 30% EtOAc/ hexanes. The product containing fractions were combined and concentrated *in vacuo* to give **25** (3.50 g 70% yield) as a clear colorless oil: R*f* 0.65 (35% EtOAc/ hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ

7.35-7.21 (m, 10H), 5.72 (br s, 1H), 4.65 (s, 2H), 4.04 (s, 2H); 75 MHz ^{13}C NMR (CDCl$_3$) δ 138.0, 137.8, 129.2, 128.7, 128.6, 128.5, 128.0, 127.6, 76.5, 56.7; IR (neat) 3261 (broad), 3030, 2910, 1950, 1890, 1810, 1495, 995 cm^{-1}; Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.69; H, 7.06; N, 6.63.

Analytical data for N-benzyl-O-methyl-hydroxylamine (11). R*f* 0.43 (35% EtOAc/ hexanes); 300 MHz ^{1}H NMR (CDCl$_3$) δ 7.31-7.23 (m, 5H), 5.71 (s, 1H), 3.98 (s, 2H), 3.46 (s, 3H); 75 MHz ^{13}C NMR (CDCl$_3$) δ 137.7, 128.8, 128.4, 127.4, 61.7, 56.2; IR (neat) 3300 (broad), 3100, 2940, 1950, 1880, 1810, 1740, 1465, 1060 cm^{-1}; Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.99; H, 8.09; N, 10.19.

Analytical data for (2H-benzo[3,4-d]1,3-dioxolen-5-ylmethyl)(phenylmethoxy)amine (28). R*f* 0.50 (35% EtOAc/ hexanes); 300-MHz ^{1}H NMR (CDCl$_3$) δ 7.38-7.28 (m, 5H), 6.83 (s, 1H), 6.75 (s, 2H), 5.92 (s, 2H), 5.82 (br s, 1H), 4.65 (s, 2H), 3.94 (s, 2H); 75 MHz ^{13}C NMR (CDCl$_3$) δ 147.8, 147.1, 138.0, 131.6, 128.7, 128.5, 128.0, 122.4, 109.6, 108.3, 101.1, 76.5, 56.5; IR (CHCl$_3$) 3263 (broad), 3030, 2900, 1500, 1250, 1040 cm^{-1}; Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.74; H, 5.90; N, 5.65.

General Procedure for the Preparation of N-Acyl N,O-Alkylhydroxylamines

Preparation of N-(phenylmethoxy)-N-benzylacetamide (30). To a stirring solution of **25** (1.0 g, 4.7 mmol) in 94 mL of CH_2Cl_2 was added DMAP (0.30 g, 2.3 mmol), pyridine (0.76 mL, 9.4 mmol) and Ac_2O (0.66 mL, 7.0 mmol). After 2 h the reaction was diluted with CH_2Cl_2 (100 mL), then washed with a saturated solution of $NaHCO_3$ (100 mL). The layers were separated and the organic layer was dried over $MgSO_4$, then filtered under reduced pressure through a compressed pad of Celite (2 mm) and $MgSO_4$ (2 mm). The filter pad was washed with CH_2Cl_2 and the filtrate was concentrated *in vacuo*. Purification of this material was accomplished by RPLC using a 4 mm disk, eluting with a solvent gradient of 10% EtOAc/ hexanes through 50% EtOAc/ hexanes. The product containing fractions were combined and concentrated *in vacuo* to give **30** (1.1 g, 95% yield) as a colorless solid: mp 41-42 °C; R*f* 0.30 (35% EtOAc/ hexanes); 300 MHz ^{1}H NMR (CDCl$_3$) δ 7.37-7.28 (m, 10H), 4.79 (s, 2H), 4.71 (s, 2H), 2.13 (s, 3H); 75 MHz ^{13}C NMR (CDCl$_3$) δ 172.4, 136.6, 134.5, 129.3, 129.0, 128.8, 128.7, 127.8, 76.6, 50.2, 20.7; IR (CHCl$_3$) 3015, 1660, 1340, 1215 cm^{-1}; Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.29; H, 6.70; N, 5.48.

Analytical data for 2,2,2-trifluoro-N-methoxy-N-benzylacetamide (16). R*f* 0.60 (35% EtOAc/ hexanes); 300 MHz ^{1}H NMR (CDCl$_3$) δ 7.36-7.28 (s, 5H), 4.81 (s, 2H), 3.67 (s. 3H); 75 MHz ^{13}C NMR (CDCl$_3$) δ 158.0 (q, $J_{C\text{-}F}$ = 36.8 Hz), 134.4, 128.9, 128.4, 128.3, 116.3 (q, $J_{C\text{-}F}$ = 284.6 Hz), 62.9, 49.8; 280 MHz ^{19}F NMR (CDCl$_3$) δ 121.6; IR (neat) 3035, 2950, 1705, 1455, 1200, 985 cm^{-1}.

Analytical data for (N-benzylacetylamino) acetate (18). R*f* 0.58 (100% Et_2O); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.36-7.26 (m, 5H), 4.86 (s, 2H), 2.09 (s, 3H), 2.08 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 168.4, 135.2, 128.7, 128.5, 128.0, 45.6, 20.4, 18.4; IR (neat) 3035, 1705, 1455, 1215, 970 cm^{-1}; Anal. Calcd for $C_{12}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.47; H, 6.34; N, 6.60.

Analytical data for 2,2,2-trifluoro-N-(phenylmethoxy)-N-benzylacetamide (29). R*f* 0.58 (35% EtOAc/ hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.41-7.25 (m, 10H), 4.83 (s, 4H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 158.0 (q, $J_{C\text{-}F}$ = 37.1 Hz), 134.5, 133.5, 129.4, 129.1, 129.0, 128.8, 128.5, 128.5, 116.4 (q, $J_{C\text{-}F}$ = 285.0 Hz), 78.3, 51.3; 280 MHz ^{19}F NMR ($CDCl_3$) δ 121.4; IR (neat) 3034, 2953, 1705, 1454, 1213, 968 cm^{-1}.

Analytical data for N-(2H-benzo[3,4-d]1,3-dioxolen-5-ylmethyl)-N-(phenylmethoxy)acetamide (31). mp 70-72 °C; R*f* 0.24 (35% EtOAc/ hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.37-7.30 (m, 5H), 6.83-6.75 (m, 3H), 5.89 (s, 2H), 4.07 (d, *J* = 7.1 Hz, 2H), 2.11 (s, 3H); IR ($CHCl_3$) 3015, 2935, 1660, 1490, 1250 cm^{-1}; Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.13; H, 5.80; N, 4.61.

Analytical data for phenyl-N-(phenylmethoxy)-N-benzylcarboxamide (32). mp 58 °C; R*f* 0.46 (35% EtOAc/ hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.66-7.63 (m, 2H), 7.39-7.15 (m, 11H), 6.91-6.88 (m, 2H), 4.88 (s, 2H) 4.49 (s, 2H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 169.8, 136.2, 134.2,133.8, 130.3, 129.3, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.6, 76.7, 51.1; IR ($CHCl_3$) 3016, 1637, 1404 cm^{-1}; Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.51, H, 6.10; N, 4.49.

Preparation of N-hydroxy-N-benzylacetamide (14). To a stirring solution of acetamide **21** (0.40 g, 1.6 mmol) in 16 mL of MeOH was added a catalytic amount of palladium on barium sulfate (0.40 g, 5% Pd content). The reaction vessel was deoxygenated and fitted with a hydrogen filled balloon under static pressure. After 2 h the reaction was filtered through a pad of Celite (2 mm) and concentrated *in vacuo* to yield an off-white solid which was used without further purification: mp 108-109 °C; R*f* 0.21 (100% Et_2O); 300 MHz ^{1}H NMR (CD_3OD) δ 7.22-7.26 (m, 5H), 4.87 (s, 2H), 3.26 (s, H), 2.05 (s, 3H); 75 MHz ^{13}C NMR (CD_3OD) δ 174.3, 138.4, 130.1, 130.0, 129.2, 53.4, 20.9; IR ($CHCl_3$) 3370, 3020, 1660 cm^{-1}; Anal. Calcd for $C_9H_{11}NO_2$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.47; H, 6.34; N, 6.60.

General Preparation of N-Alkyloxycarbonyl, and N,O-Dialkylhydroxylamines

Preparation of (phenylmethoxy)-N-(phenylmethoxy)-N-benzylcarboxamide (34). To a stirring solution of **25** (1.95 g, 9.15 mmol) in 91 mL of CH_2Cl_2 was added pyridine (1.50 mL, 18.3 mmol), DMAP (0.560 g, 0.500 mmol), and benzyl chloroformate (2.00 mL, 13.7 mmol). After 16 h the reaction was quenched with a saturated solution of $NaHCO_3$ (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x70 mL). The combined organic layers were dried over $MgSO_4$, then filtered under reduced pressure through a compressed pad of Celite (0.2 mm) and $MgSO_4$ (0.2 mm). Purification of this material was accomplished by RPLC using a 4 mm plate, eluting with a solvent gradient of 5% EtOAc/ hexanes through 10% EtOAc/hexanes. The product containing fractions were combined and concentrated to give **34** (2.80 g, 90% yield) as a clear colorless oil which solidified upon standing. mp 54 °C; R_f 0.61 (35% EtOAc/ hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 7.32-7.18 (m, 15H), 5.20 (s, 2H), 4.67 (s, 2H), 4.56 (s, 2H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 157.5, 136.5, 136.2, 135.4, 129.6, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 127.9, 77.8, 68.1, 54.2; IR ($CHCl_3$) 3065, 3030, 2945, 1710, 1455, 1090 cm^{-1}; Anal. Calcd for $C_{21}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 75.79; H, 6.06; N, 3.96.

Analytical data for N-(phenylmethoxy)-N-benzylphenoxycarboxamide (33). R_f 0.56 (35% EtOAc/ hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 7.43-7.31 (m, 11H), 7.23-7.18 (m, 2H), 7.13-7.10 (m, 2H), 4.83 (s, 2H), 4.71 (s, 2H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 155.7, 151.1, 136.2, 135.1, 129.7, 128.9, 128.8, 128.7, 128.6, 128.1, 125.9, 121.7, 77.9, 54.2; IR ($CHCl_3$) 3020, 2940, 1720, 1495, 1060 cm^{-1}; Anal. Calcd for $C_{22}H_{21}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.63; H, 5.77; N, 4.25.

Preparation or Data for Nitroso (4 + 2) Hydroxamic Acid Derivatives

Preparation of 3-aza-2-oxa-3-benzylbicyclo[2.2.2]oct-5-ene (20). To a stirring solution of hydroxamic acid derivative **19**[10] (0.44 g, 2.0 mmol) in 100 mL of Et_2O was added a solution of DIBAL (5.3 mL, 1.5 M in hexanes) at rt. After 20 min the reaction was slowly quenched with MeOH (10 mL), then diluted with CH_2Cl_2 (50 mL) and washed with a saturated solution of Na and K tartrates, (Rochelle salts) (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were dried over $MgSO_4$, then filtered under reduced pressure through a compressed pad of Celite (2 mm) and $MgSO_4$ (2 mm). The filter pad was washed with CH_2Cl_2, and the filtrate was concentrated *in vacuo*. Purification of this material was accomplished by RPLC, using a 4 mm disk, eluting with 30% Et_2O/ hexanes. The product containing fractions were combined and concentrated *in vacuo* to give **20** (0.26 g 64% yield) as a viscous liquid: R_f 0.64 (100% Et_2O); 300 MHz ^1H NMR ($CDCl_3$) δ 7.36-7.21 (m, 5H), 6.72-6.66 (m, 1H), 6.35-6.30 (m, 1H), 4.43-4.41 (m, 1H), 3.68 (ABq, $\Delta\nu$ = 48.4 Hz, J = 12.5 Hz, 2H), 3.57-3.54 (m, 1H), 2.12-2.00 (m, 2H), 1.44-1.23 (m, 2H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 137.1, 132.9, 129.6, 129.5, 128.5, 127.4, 68.3, 61.5, 52.9, 23.8, 22.1; IR (neat) 3018, 1521, 1215, 931 cm^{-1}; Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.40; H, 7.47; N, 7.04.

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