# Surface-Mediated Reactions. 9. Selective Oxidation of Primary and Secondary Amines to Hydroxylamines<sup>1</sup>

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OXONE over silica gel or, in some cases, alumina has been found to oxidize the primary and secondary amines **3** selectively to the corresponding hydroxylamines **4**, in either the presence or absence of a solvent. Treatment of Boc-protected L-lysine (6) under the latter conditions afforded hydroxylamine 7 in excellent yield. The trialkylamine **1a** and pyridine (**1b**), in which selectivity is not an issue, were readily oxidized to the corresponding oxides 2 by OXONE over silica gel or alumina, as well as by (CH<sub>3</sub>)<sub>3</sub>COOH over silica gel. Solvent-free oxidation assisted by microwave irradiation was more forcing, while still affording the hydroxylamines 4 selectively, and is the synthetic method of choice. The mechanistic aspects of these reactions are discussed.

Oxidation of an amine initially affords the corresponding amine oxide (Scheme 1). For a tertiary amine the oxide is the final product. However, oxides derived from primary and secondary amines (R = H) rearrange to the corresponding hydroxylamines. Still possessing a pair of *n* electrons, hydroxylamines are vulnerable to further oxidation, affording a secondary product that varies depending on the structure of the amine.<sup>2</sup>

Hydroxylamines are useful synthetic intermediates and also exhibit a wide range of pharmacological and physiological activities.<sup>3</sup> However, their direct preparation by oxidation of the corresponding amines is complicated by the ease of overoxidation to secondary products. especially for primary systems.<sup>4</sup> We reported recently the selective oxidation of sulfides to sulfoxides with (CH<sub>3</sub>)<sub>3</sub>-COOH and OXONE<sup>5</sup> mediated by the surfaces of silica gel and alumina.<sup>1</sup> We report here an extension of those studies to the selective oxidation of primary and secondary amines to hydroxylamines, as well as tertiary amines to their oxides.

#### Results

Our studies began with the tertiary amine 1a. As seen in Table 1, amine 1a readily underwent oxidation to

**1989**, *19*, 3509–3522.

(4) Primary and secondary amines have been selectively oxidized to the corresponding hydroxylamines with dimethyldioxirane; see (a) ref 3. (b) Wittman, M. D.; Halcomb, R. L.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 1981–1983. However, the reagent must first be prepared (from OXONE!). Moreover, several primary and secondary

(5) OXONE is a product of the Du Pont Company consisting of a 2:1:1 mixture of the active ingredient KOSO<sub>2</sub>OOH, along with KHSO<sub>4</sub> and K<sub>2</sub>SO<sub>4</sub>, respectively.

Scheme 1

$$\begin{array}{c} & & & O^{-} & & OH \\ & & & & |_{+} & & & \\ & & & NR & & & & \\ & & & & |_{(R=H)} & & |_{-} \end{array}$$

Table 1. Oxidation of Amines 1<sup>a</sup>



			yield, %	
amine	oxidant	adsorbent	1	2
1a	(CH <sub>3</sub> ) <sub>3</sub> COOH		98	2
1a	(CH <sub>3</sub> ) <sub>3</sub> COOH	SiO <sub>2</sub>	2	93
1a	(CH <sub>3</sub> ) <sub>3</sub> COOH	$SiO_2b$	3	94
1a	(CH <sub>3</sub> ) <sub>3</sub> COOH	SiO <sub>2</sub> (OSiMe <sub>3</sub> ) <sup>c</sup>	15	85
1a	(CH <sub>3</sub> ) <sub>3</sub> COOH	$Al_2O_3$	76	12
1a	OXONE		97	$\mathbf{tr}^d$
1a	OXONE	$SiO_2$	30	63
1a	OXONE	SiO <sub>2</sub> (OSiMe <sub>3</sub> ) <sup>c</sup>	65	35
1a	OXONE	$Al_2O_3$	3	96
$1b^e$	(CH <sub>3</sub> ) <sub>3</sub> COOH		95	3
$1b^e$	(CH <sub>3</sub> ) <sub>3</sub> COOH	$SiO_2$	6	85
$1b^e$	(CH <sub>3</sub> ) <sub>3</sub> COOH	$Al_2O_3$	9	64
$\mathbf{1b}^{e}$	OXONE	$SiO_2$	10	89
$\mathbf{1b}^{e}$	OXONE	$Al_2O_3$	21	61

<sup>a</sup> Conducted for 1 h at 80 °C according to the standard procedure with solvent as described in the Experimental Section. <sup>b</sup>Run with silica gel that had been previously used and recycled five times. <sup>c</sup> Partially silylated as described previously.<sup>1</sup> <sup>d</sup> Trace. <sup>e</sup> Conducted for 5 h; pyridine (1b) and oxide 2b were isolated by washing the adsorbent with (C2H5)2O followed by CH3OH.

amine oxide 2a on treatment with (CH<sub>3</sub>)<sub>3</sub>COOH/silica gel or with OXONE/alumina at 80 °C.6 No significant oxidation occurred under similar conditions in the absence of silica gel or alumina. With (CH<sub>3</sub>)<sub>3</sub>COOH, silica gel showed no loss of activity when previously used and

<sup>(1)</sup> Part 8: Kropp, P. J.; Breton, G. W.; Fields, J. D.; Tung, J. C.; Loomis, B. R. J. Am. Chem. Soc. 2000, 122, 4280-4285

<sup>(2)</sup> For reviews of the oxidation of amines, see: (a) Challis, B. C.; Butler, A. R. In The Chemistry of the Amino Group; Patai, S., Ed.; Wiley and Sons: London, 1968; pp 320–338. (b) Rosenblatt, D. H.; Burrows, E. P. In Supplement F: The Chemistry of Amino, Nitroso, and Nitro Compounds and Their Derivatives, Patai, S.; Ed.; Wiley and Sons: Chichester, 1982; Part 2, pp 1085–1149. (c) Gilchrist, T. L. In Comprehensive Organic Chemistry, Trost, B. M., Fleming, I., Eds.; (3) See, for example, Murray, R. W.; Singh, M. Synth. Commun.

Table 2. Oxidation of Amines 3 with OXONE<sup>a</sup>

				yield, %		, )
amine	$equiv^b$	adsorbent	time, h	3	4	5
3a	1.5	$SiO_2$	8	$\mathrm{tr}^{c}$	98	
3a	3.0	$SiO_2$	24		95	$\mathbf{tr}^{c}$
3a	1.5	$Al_2O_3$	8	13	81	$\mathbf{tr}^{c}$
3b	1.5	$SiO_2$	24		100	
3b	1.5	$Al_2O_3$	24		98	$\mathbf{tr}^{c}$
3c	1.5	$SiO_2$	8	10	84	6
3c	1.5	$Al_2O_3$	6	33	50	17
3d	1.5	$SiO_2$	0.5	5	95	
3d	3.0	$SiO_2$	12		97	$\mathbf{tr}^{c}$
3d	1.5	$Al_2O_3$	2	$\mathrm{tr}^{c}$	95	

 $^a$  Conducted at 80 °C according to the standard procedure with solvent.  $^b$  [KOSO<sub>2</sub>OOH]/[**3**].  $^c$  Trace.

recycled five times. Pyridine (**1b**) afforded oxide **2b** in good yield with  $(CH_3)_3COOH/silica$  gel or OXONE/silica gel. The surface-mediated approach obviates the need to thermally dissociate the acetic acid complex encountered in the standard preparation of pyridine *N*-oxide (**2b**) using  $CH_3CO_3H$ .<sup>7</sup>

With a standard procedure in hand, attention was turned to the secondary and primary amines **3**. As seen in Table 2, the secondary amines **3a,b** and primary amines **3c,d** were readily and selectively converted to the corresponding hydroxylamines **4** on treatment with OX-ONE/silica gel at **80** °C. Indeed, amines **3a** and **3d** 



resisted oxidation beyond the hydroxylamine stage even on treatment with double the amount of oxidant. OX-ONE/alumina was about equally effective with the secondary amines **3a,b** and the substituted primary amine **3d** but afforded substantial overoxidation of the unsubstituted primary amine **3c** to the oxime **5c**. Much less selectivity and slower rates of oxidation were observed with (CH<sub>3</sub>)<sub>3</sub>COOH over either adsorbent (Table 3). The highly substituted secondary amine **3b** was unreactive toward this oxidant.<sup>8</sup> Thus, under these conditions OXONE/silica gel is the reagent of choice for selective oxidation of primary and secondary alkylamines.

Table 3. Oxidation of Amines 3 with (CH<sub>3</sub>)<sub>3</sub>COOH<sup>a</sup>

			yield, %		
amine	adsorbent	time, h	3	4	5
3a	SiO <sub>2</sub>	8	41	43	16
3a	$Al_2O_3$	8	76	12	
3b	SiO <sub>2</sub>	24	97		
3c	SiO <sub>2</sub>	6	48	27	10
3c	$Al_2O_3$	12	70	9	21
3d	$SiO_2$	4	32	50	18

<sup>a</sup> Conducted according to the standard procedure with solvent.

 Table 4.
 Solvent-Free Oxidation of Amine 1a with OXONE/Alumina<sup>a</sup>

	yiel	d, %
treatment	<b>1a</b>	2a
80 °C, 1 h	8	92
$\mu$ wave, 40 s	1	94

<sup>*a*</sup> Conducted according to the standard solvent-free procedure described in the Experimental Section.

 Table 5.
 Solvent-Free Oxidation of Amines 3 with OXONE<sup>a</sup>

			yield, %		
amine	adsorbent	time, s	3	4	5
3a	SiO <sub>2</sub>	40	$\mathbf{tr}^{b}$	97	
3b	SiO <sub>2</sub>	60	5	93	
3c	SiO <sub>2</sub>	60	8	89	3
3d	$SiO_2$	40	5	92	3
3d	$Al_2O_3$	40	6	90	$\mathbf{tr}^{b}$

 $^a$  Conducted with microwave irradiation according to the standard solvent-free procedure.  $^b$  Trace.

**Solvent-Free Oxidations.** It has become increasingly apparent that the use of a solvent in many surfacemediated reactions is unnecessary.<sup>9</sup> Thus simple mixing of a solid mixture of alumina, tertiary amine **1a**, and OXONE at 80 °C afforded oxide **2a** at a rate comparable to that observed in the presence of solvent (Table 4).<sup>10</sup> Reaction time was dramatically shortened to 40 s with microwave irradiation. Similar treatment of the secondary and primary amines **3a,c,d** afforded the corresponding hydroxylamines **4** in yields comparable with those obtained at 80 °C in the presence of solvent (Table 5). The Boc derivative of L-lysine (**6**) similarly afforded the  $\epsilon$ -hydroxylamine **7** in 93% yield, which was readily converted to the free amino acid **8**. Thus solvent-free



oxidation is more forcing without affording significant overoxidation.

## Discussion

Thus OXONE/silica gel and, in some cases, OXONE/ alumina readily oxidize primary and secondary alkylamines to the corresponding hydroxylamines with high

<sup>(6)</sup> To provide qualitative rate data, oxidations were terminated prior to total conversion. For preparative purposes, complete oxidation can be effected by using longer reaction times or employing a small excess of oxidant.

<sup>(7)</sup> Mosher, H. S.; Turner, L.; Carlsmith, A. Organic Syntheses; Wiley & Sons: New York, 1963; Collect. Vol. 4, 828-830.

<sup>(8)</sup> However, amine **3b** did afford hydroxylamine **4b** on treatment with  $3-C_6H_4CO_3H$  in solution, as described in the Experimental Section. We are indebted to D. A. Rasheed for this result.

<sup>(9)</sup> See, for example, ref 1, as well as references therein.

<sup>(10)</sup> As we recently noted,<sup>1</sup> the traditional evaporative deposition of the reagent on the substrate is not required.





selectivity, permitting their facile synthesis by direct oxidation of the amine in either the presence of absence of a solvent. The selectivity apparently arises, as described below, from the strong adsorption of hydroxylamines to the surface, protecting them from further oxidation. The trialkylamine **1a** and pyridine (**1b**), in which selectivity is not an issue, were effectively oxidized under these conditions, as well as by  $(CH_3)_3COOH/silica$  gel, which was ineffective for the primary and secondary amines **3**.

The differences in behavior between the two oxidants OXONE and  $(CH_3)_3COOH$  can be understood in terms of their individual mechanisms, which are presumably analogous with those recently delineated for the oxidation of sulfides.<sup>1</sup> The surface of silica gel consists of two types of silanol groups: isolated (**9**) and associated (**10**).<sup>11</sup> The



latter are more acidic than their isolated counterparts and react preferentially with hexamethyldisilazane,<sup>12</sup> affording a convenient method for probing their involvement in surface-mediated reactivity. (CH<sub>3</sub>)<sub>3</sub>COOH adsorbs predominantly at the isolated sites where it can enter into reciprocal hydrogen bonding, in which both the silanol group and the hydroperoxide each serve as a hydrogen bond donor and acceptor (Scheme 2) without disrupting existing hydrogen bonding as would be required at the associated sites.<sup>1</sup> The resulting complex is poised for nucleophilic attack by the amine, resulting in a pair of proton shifts and the transfer of an oxygen atom to the amine. As expected for a process centered at the isolated sites, selective silvlation of the associated sites had no significant effect on the rate of oxidation of amine 1a (Table 1).

Once formed, the amine oxides **2** from the tertiary amine **1a** and pyridine (**1b**) should be preferentially adsorbed at the more acidic associated sites, where they would not interfere with the adsorption of  $(CH_3)_3COOH$ . By contrast, the hydroxylamines **4** from the primary and secondary amines **3** should be preferentially adsorbed at the isolated sites, where they can enter into reciprocal hydrogen bonding (Scheme 3A) in analogy with  $(CH_3)_3$ -COOH. Indeed, adsorption of hydroxylamine **4d** to silica gel was only slightly affected by partial silylation (Table 6). Thus in oxidation of primary and secondary amines



Table 6. Adsorption of Amines and Oxidation Products<sup>a</sup>

substrate	adsorbent	adsorbed, %
1a	SiO <sub>2</sub>	100
1a	SiO <sub>2</sub> (OSiMe <sub>3</sub> )	64
1a	$Al_2O_3$	8
2a	SiO <sub>2</sub>	100
2a	SiO <sub>2</sub> (OSiMe <sub>3</sub> )	43
3a	SiO <sub>2</sub>	95
3b	SiO <sub>2</sub>	100
<b>3c</b>	SiO <sub>2</sub>	90
3c	$Al_2O_3$	54
3d	SiO <sub>2</sub>	92
3d	$Al_2O_3$	45
<b>4d</b>	SiO <sub>2</sub>	100
<b>4d</b>	SiO <sub>2</sub> (OSiMe <sub>3</sub> )	84

<sup>a</sup> Conducted at 80 °C as described in the Experimental Section.



with  $(CH_3)_3COOH$  the hydroxylamine product, once formed, should compete with remaining  $(CH_3)_3COOH$  for adsorption to the isolated sites, slowing the rate of oxidation and rendering less of the oxidant activated for reaction. At the same time, this competition for the isolated sites decreases the amount of hydroxylamine that is bound and thus protected from further oxidation, thereby decreasing selectivity. Thus  $(CH_3)_3COOH/silica$ gel is effective for oxidizing tertiary amines and pyridines to their oxides, but not the selective conversion of primary and secondary amines to hydroxylamines.<sup>13</sup>

Unlike (CH<sub>3</sub>)<sub>3</sub>COOH, OXONE binds preferentially to the associated sites of silica gel (Scheme 4).<sup>1</sup> There it must thus compete with the starting amine, as well as with amine oxides emanating from tertiary amines and pyridines (Scheme 3B,C) but not with hydroxylamines formed from primary and secondary amines, which are adsorbed preferentially at the associated sites (Scheme 3A) and thereby rendered unavailable for further oxidation. Thus OXONE/silica gel is excellent for selectively oxidizing primary and secondary amines to hydroxylamines. OXONE/alumina generally exhibited similar behavior.<sup>14</sup>

In contrast with the activation of  $(CH_3)_3COOH$  through reciprocal hydrogen bonding to the isolated sites of silica gel, mediation of the oxidant OXONE by silica gel

<sup>(11)</sup> For descriptions of current models for the surfaces of alumina and silica gel, see: (a) Knözinger, H. In *The Hydrogen Bond. III. Dynamics, Thermodynamics and Special Systems*, Schuster, P., Zundel, G., Sandorfy, C., Eds.; North-Holland: Amsterdam, 1976; Chapter 27.
(b) Dufour, P.; Houtman, C.; Santini, C. C.; Nédez, C.; Basset, J. M.; Hsu, L. Y.; Shore, S. G. *J. Am. Chem. Soc.* 1992, *114*, 4248–4257.
(12) Sindorf, D. W.; Maciel, G. E. *J. Phys. Chem.* 1982, *86*, 5208–5219.

<sup>(13)</sup> As observed previously with sulfides,<sup>1</sup> (CH<sub>3</sub>)<sub>3</sub>COOH/alumina is generally a poor oxidant, presumably because (CH<sub>3</sub>)<sub>3</sub>COOH is deprotonated by the basic support.

<sup>(14)</sup> An exception is the oxidation of pyridine (1b), which is partially bound irreversibly to Al<sup>+</sup> sites on the alumina surface. See: Knözinger, H. *Adv. Catal.* **1976**, *25*, 184–271.

involves its dispersal on the surface through adsorption to the associated silanol sites, thereby facilitating nucleophilic attack by the amine on the bound reagent (Scheme 4).<sup>1</sup> The more highly nucleophilic tertiary amine **1a** underwent oxidation faster than the secondary and primary analogues **3a** and **3c** (Tables 1 and 2). The more highly substituted  $\alpha,\alpha$ -dimethylamine **3d** also underwent oxidation faster than its unsubstituted analogue **3c**, presumably because of increased nucleophilicity due to a larger inductive effect.

Microwave-assisted oxidation with OXONE over silica gel or alumina under solvent-free conditions effected selective oxidation of each of the primary and secondary amines **3**, as well as the tertiary amine **1a**, in high yield and short reaction time and is thus the synthetic method of choice.

We continue to study the unique and powerful synthetic utility of surface-mediated reactions, as well as the mechanisms involved.

#### **Experimental Section**

Standard Procedure with Solvent. Into a 25-mL roundbottomed flask was weighed 2.5 g of Merck 10181 silica gel or Fisher A540 alumina that had been equilibrated with the atmosphere at 120 °C for at least 48 h. The flask was stoppered, and the contents were allowed to cool to 25 °C. For oxidations with OXONE, 0.5 mL of water was added, and the adsorbent was tumbled on a rotary evaporator at atmospheric pressure until uniformly free-flowing.<sup>16</sup> A solution of 1.0 mmol each of amine and diphenylmethane, as an internal standard, in 5 mL of C<sub>6</sub>H<sub>6</sub> was added to the flask with stirring followed by 137  $\mu$ L (1.0 mmol) of 70% aqueous (CH<sub>3</sub>)<sub>3</sub>COOH or 462 mg of OXONE (1.5 mmol of KOSO<sub>2</sub>OOH). The slurry was brought to reflux and stirred at 80 °C for the specified amount of time. After cooling to 25 °C, the slurry was transferred to a 200 mL round-bottomed flask, diluted with 100 mL of CH<sub>3</sub>OH, and stirred overnight at 25 °C. The adsorbent was then removed by vacuum filtration and washed with an additional 50 mL of CH<sub>3</sub>OH. The combined filtrates were concentrated under reduced pressure, and the residue was analyzed by column chromatography or by <sup>1</sup>H NMR analysis.

**Standard Solvent-Free Procedure.** A 2.5-g portion of the adsorbent was prepared as described above. The amine was added without solvent and the resulting mixture tumbled until uniformly free-flowing. The oxidant was then added and the mixture again tumbled. After being heated for the specified period of time,<sup>17</sup> the mixture was allowed to cool to 25 °C and was stirred overnight with 100 mL of CH<sub>3</sub>OH. The adsorbent was collected by vacuum filtration and washed with an additional 50 mL of CH<sub>3</sub>OH, and the combined filtrates were concentrated under reduced pressure. The residue was weighed and analyzed by <sup>1</sup>H NMR spectroscopy.

**Preparative-Scale Procedure.** Into a 100-mL roundbottomed flask was weighed the indicated amount of Merck 10181 chromatographic silica gel or Fisher A540 alumina, which had been equilibrated to the atmosphere at 120 °C for at least 48 h. The flask was stoppered, and the contents were allowed to cool to 25 °C. A solution of 15 mL of  $C_6H_6$  and the indicated amount of substrate was added to the flask, followed by the indicated amount of 70% aqueous (CH<sub>3</sub>)<sub>3</sub>COOH or

(16) The need for this step varied from batch to batch of OXONE.(17) Microwave heating was conducted with a commercial 500-W Little Litton oven.

OXONE. This slurry was brought to reflux and stirred at 80 °C for the specified amount of time. After cooling to 25 °C, the slurry was transferred to a 200-mL round-bottomed flask and stirred overnight at 25 °C with 100 mL of CH<sub>3</sub>OH. The adsorbent was then removed by vacuum filtration and washed with an additional 50 mL of CH<sub>3</sub>OH. After filtration the solvents were removed under vacuum and the residue chromatographed on a silica gel or alumina column by elution with diethyl ether and CH<sub>3</sub>OH.

*N,N*-Dimethyloctylamine *N*-oxide (2a). According to the preparative-scale procedure, 0.472 g (3.0 mmol) of amine **1a** was treated with 0.270 g (3.0 mmol) of  $(CH_3)_3COOH$  and 7.5 g of silica gel for 4 h. Separation of the residue on a chromatographic silica gel column afforded 0.468 g (90% yield) of *N*-oxide **2a** as a colorless solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.88 (t, 3 H, J = 6.8 Hz), 1.31 (m, 10 H) 1.88 (m, 2 H) 3.23 (m, 8 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  13.95, 22.40, 23.76, 26.49, 28.88, 29.10, 31.51, 58.50, 71.64; lit.<sup>18</sup> no spectral data.

**Pyridine N-Oxide (2b).** According to the preparative-scale procedure, 0.237 g (3.0 mmol) of pyridine (**1b**) was treated with 0.270 g (3.0 mmol) of (CH<sub>3</sub>)<sub>3</sub>COOH and 7.5 g of silica gel for 24 h. Separation of the residue on a chromatographic silica gel column afforded 0.214 g (75% yield) of oxide **2b** as a colorless solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.27 (m, 3 H), 8.22 (m, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  125.30, 126.93, 137.88; lit.<sup>19</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  125.59, 126.79, 138.86.

*N,N*-Dibutylhydroxylamine (4a). According to the preparative-scale procedure, 0.387 g (3.0 mmol) of amine **3a** was treated with 1.39 g (2.25 mmol) of OXONE and 7.5 g of silica gel for 24 h. Separation of the residue on a chromatographic alumina column afforded 0.414 g (95% yield) of hydroxylamine **4a** as a clear, yellow liquid: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.87 (t, 6 H, *J* = 7.3 Hz), 1.38 (m, 4 H), 1.72 (m, 4 H), 2.97 (m, 4 H);<sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  13.30, 19.60, 27.55, 47.74; lit.<sup>20</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ 0.93 (t, 6 H, *J* = 6 Hz), 1.48 (m, 8 H), 2.69 (t, 4 H, *J* = 8 Hz).

**2,2,6,6-Tetramethylpiperidin-1-ol (4b).** Treatment of 0.424 g (3.0 mmol) of amine **3b** with 0.812 g (4.0 mmol) of 55% 3-ClC<sub>6</sub>H<sub>4</sub>CO<sub>3</sub>H in 15 mL of refluxing C<sub>6</sub>H<sub>6</sub> for 24 h afforded 0.425 g (99% yield) of hydroxylamine **4b** upon separation of the residue on a chromatographic alumina column as a clear, yellow liquid having spectral properties consistent with those of material obtained by solvent-free oxidation (Table 5): IR (neat) 3445, 2974, 2938, 1714, 1466, 1360, 1242, 1130, 976, 733 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.45 (s, 12 H), 1.55 (s, 6 H), 4.08 (s, 1 H); lit.<sup>21</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.22 (s, 12 H), 1.56 (s, 6 H), 4.03 (s, 1 H).

**N-(1-Octyl)hydroxylamine (4c).** According to the preparative-scale procedure, 0.388 g (3.0 mmol) of amine **3c** was treated with 1.39 g (2.25 mmol) of OXONE and 7.5 g of silica gel for 24 h. Separation of the residue on a chromatographic silica gel column afforded 0.331 g (76% yield) of hydroxylamine **4c** as a colorless solid: IR (KBr) 3264, 3160, 2922, 2853, 1508, 1468, 1381, 1152, 1061, 892, 721, 548 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.88 (t, 3 H, J = 6.6 Hz), 1.32 (m, 12 H), 1.65 (m, 2 H), 2.94 (t, 2 H, J = 7.2 Hz);<sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  14.06, 22.62, 26.96, 27.13, 29.19, 29.48, 31.79, 53.93; lit.<sup>22</sup> no spectral data.

This material was spectrally consistent with a specimen prepared independently by a modification of the general procedure<sup>23</sup> To a solution of 0.423 g (3.0 mmol) of oxime **5c** in 100 mL of CH<sub>3</sub>OH was added 2 mL of a 1.0 M solution of NaBH<sub>3</sub>CN in tetrahydrofuran, along with a trace of methyl orange to give a yellow solution. A 1.0 M solution of HCl in diethyl ether was added via syringe to achieve pH 3 (indicated

<sup>(15)</sup> The more forcing effect of solvent-free conditions is apparently not due to the involvement of higher bulk temperatures under microwave irradiation since the temperature of the reaction mixture did not exceed 52 °C. Moreover, the survival of the Boc protecting group of the L-lysine derivative **6** under these conditions indicates that the maximum localized temperature was no higher than 150 °C, as the group cleaves just above that temperature: Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6141–6142. (16) The need for this step varied from batch to batch of OXONE.

<sup>(18)</sup> Lawson, K. D. J. Phys. Chem. 1965, 69, 3204-3205.

<sup>(19)</sup> Murray, R. W.; Singh, M.; Jeyaraman, R. J. Am. Chem. Soc. 1992, 114, 1346-1351.

<sup>(20)</sup> Wawzonek, S.; Kempf, J. V. Org. Prep. Proced. Int. **1972**, *4*, 135–151. See also, Yaouanc, J. J.; Masse, G.; Sturtz, G. Synthesis **1985**, 807–810.

<sup>(21)</sup> Bordwell, F. G.; Liu, W.-Z. J. Am. Chem. 1996, 118, 10819-10823.

<sup>(22)</sup> Doleschall, G. Tetrahedron Lett. 1987, 28, 2993-2994.

 <sup>(23)</sup> Borch, R. F.; Bernstein, M. D.; Durst, H. D. J. Am. Chem. Soc.
 1971, 93, 2897–2904.

by red color). The solvents were removed under aspirator vacuum, and the resulting yellow residue was dissolved in 20 mL of H<sub>2</sub>O, adjusted to pH 9 with 6 N NaOH, extracted with  $3 \times 50$  mL of CHCl<sub>3</sub>, and backwashed with 50 mL of H<sub>2</sub>O. The combined organic layers were dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated to afford a pale yellow solid, which on recrystallization from hexanes afforded colorless flakes: mp 70-71 °C; lit.<sup>24</sup> mp 73.5 °C.

Octanal Oxime (5c). According to the preparative-scale procedure, 0.388 g (3.0 mmol) of amine 3c was treated with 0.541 g (6.0 mmol) of (CH<sub>3</sub>)<sub>3</sub>COOH and 7.5 g of alumina for 48 h. Separation of the residue on a chromatographic silica gel column afforded 0.232 g (54% yield) of oxime 5c as a colorless solid: IR (CCl<sub>4</sub>) 3603, 3271, 3104, 2934, 2859, 1549, 1466, 1254, 905, 781 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.85 (t, 3 H, J = 6.6 Hz), 1.38 (m, 10 H), 2.26 (dt, 2 H, J = 7.4, 5.6) 6.70 (t, 1 H); lit.<sup>25</sup> 3280, 2960, 2920, 2860, 1670, 1470, 1380, 1350, 900 cm $^{-1}$ ; lit. $^{26}$   $^1\mathrm{H}$  NMR (CDCl\_3)  $\delta$  1.20–1.80 (m, 12 H), 2.10–2.60 (m, 3 H), 6.68-6.99 (t, 1 H), 9.01-9.47 (s, 1 H).

This material was spectrally consistent with a specimen prepared independently. To a solution of 25 g (360 mmol) of hydroxylamine hydrochloride in 150 mL of water was added 10 g (78 mmol) of 1-octanal, 100 mL of 10% NaOH, and 250 mL of CH<sub>3</sub>CH<sub>2</sub>OH. The resulting solution was heated on a steam bath for 2 h, allowed to cool, and allowed to stand overnight. The resulting colorless crystals were dried for 2 h under vacuum: mp 57-59 °C; lit.<sup>26</sup> mp 59-60 °C.

N-(1,1,3,3-Tetramethylbutyl)hydroxylamine (4d). According to the preparative-scale procedure, 0.388 g (3.0 mmol) of amine 3d was treated with 1.39 g (2.25 mmol) of OXONE and 7.5 g of silica gel for 24 h. Separation of the residue on a chromatographic alumina column afforded 0.363 g (83% yield) of hydroxylamine 4d as a colorless, amorphous solid: mp 228-231 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.02 (s, 9 H), 1.48 (s, 6 H), 1.72 (s, 2 H), 3.72 (s, 1 H), 7.5 (br s, 1 H);  $^{13}\mathrm{C}$  NMR (CDCl<sub>3</sub>)  $\delta$  26.84, 31.13, 50.01, 52.05, 56.98; lit.<sup>27</sup> <sup>1</sup> H NMR (CDCl<sub>3</sub>)  $\delta$  1.00 (s, 9 H), 1.17 (s, 6 H), 1.48 (s, 2 H), 5.52 (s, 1 H).

2,2,4-Trimethyl-4-nitrosopentane (5d). According to the preparative-scale procedure, 0.388 g (3.0 mmol) of amine 3d was treated with 0.541 g (6.0 mmol) of (CH<sub>3</sub>)<sub>3</sub>COOH and 7.5 g of silica gel for 48 h. Separation of the residue on a chromatographic alumina column afforded hydroxylamine 4d as a colorless solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.942 (s, 9 H), 1.62 (s,

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6 H), 2.01 (s, 2 H); lit.28 1H NMR (CCl<sub>4</sub>) & 0.82 (s, 9 H), 1.04 (s, 6 H), 2.34 (s, 2 H).

Oxidation of N<sub>1</sub>-(tert-Butoxycarbonyl)-L-lysine (6). A solution of 256 mg (1.0 mmol) of amino acid 6 in 0.5 mL of water was adsorbed on silica gel and treated with OXONE for 60 s under microwave heating according to the standard solvent-free procedure. Isolation in the usual way afforded 249 mg (92% yield) of N1-(tert-butyoxycarbonyl)-N6-hydroxy-Llysine (7), which was dissolved in 100 mL of CH<sub>3</sub>OH along with 342 mg (3.0 mmol) of CF<sub>3</sub>COOH. After being stirred at 25 °C for 3 h, the solution was concentrated under reduced pressure to give  $N_6$ -hydroxy-L-lysine (8) as a colorless solid, which was recrystallized from aqueous CH3CH2OH to afford colorless rods: mp 218–220 °C (dec); <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  3.89 (t, 1 H, J = 6.2 Hz), 3.02 (t, 2 H, J = 7.5 Hz), 1.92 (m, 2 H), 1.73 (m, 2 H), 1.51 (m, 2 H); lit.<sup>29</sup> mp 223-225 °C (dec); lit.<sup>30</sup> <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  3.35 (t, 1 H, J = 5.7 Hz), 2.86 (t, 2 H, J = 7.3Hz), 1.46 (m, 2 H), 1.35 (m, 2 H), 1.06 (m, 2 H).

Adsorption Studies. Into a 25-mL round-bottomed flask was weighed 2.5 g of Merck 10181 chromatographic silica gel or Fisher A540 chromatographic alumina that had been equilibrated to the atmosphere at 120 °C for at least 48 h. The flask was stoppered, and the contents were allowed to cool to 25 °C. A solution of 1.0 mmol each of substrate and a known amount of diphenylmethane, as an internal standard, in 5 mL of C<sub>6</sub>H<sub>6</sub> was added to the flask with stirring. After 5 min 137  $\mu$ L (1.0 mmol) of 70% aqueous (CH<sub>3</sub>)<sub>3</sub>COOH (with amine **1a**) or 462 mg of OXONE (with other amines) was added. The slurry was heated at reflux for 5 min, after which a 250-µL aliquot of the supernatant liquid was removed, evaporated to dryness, and analyzed by <sup>1</sup>H NMR spectroscopy.

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