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Cyclic Seleninate Esters as Catalysts for the Oxidation of Sulfides to Sulfoxides, Epoxidation of Alkenes, and Conversion of Enamines to α-Hydroxyketones

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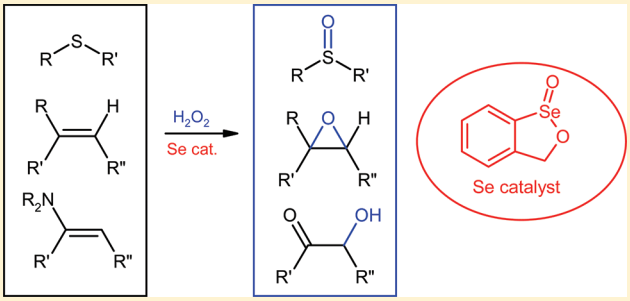
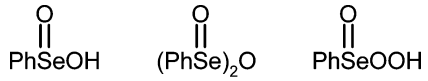
Supporting Information

ABSTRACT: Cyclic seleninate esters serve as catalysts for the rapid oxidation of sulfides to sulfoxides, alkenes to epoxides, and enamines to α-hydroxyketones. Optimal conditions were found that minimize the overoxidation of the product sulfoxides to sulfones and the hydrolysis of epoxides to diols. In some examples such as styrene derivatives, oxidative cleavage was observed instead of epoxidation. The enamine oxidations proceed via the initial formation of dimeric 2,5-diamino-1,4-dioxane species, which were hydrolyzed *in situ* to the final products. The structure of one such dimer was confirmed by X-ray crystallography.



INTRODUCTION

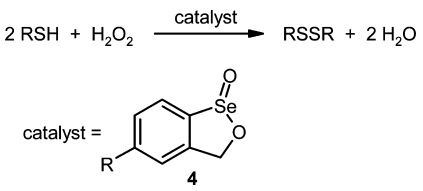
Selenium compounds have a long history as useful oxidizing agents in synthetic organic chemistry. In early examples, the element itself served as a reagent for the dehydrogenation of saturated cyclic and polycyclic hydrocarbons to afford aromatic products,[1] while selenium dioxide has found many applications as an oxidant, most notably in allylic hydroxylations and the oxidations of ketones to α-diketones.[2] More recently, benzeneseleninic acid (**1**) and anhydride (**2**) have considerably expanded the range of useful selenium-mediated oxidations.[3] Pioneering work by Barton et al. and by several other groups demonstrated that **1** and **2** can be employed in the dehydrogenation of steroidal ketones;[4] the liberation of ketones or aldehydes from their protected forms as dithioacetals,[5] diselenoacetals,[6] hydrazones, semicarbazones, and oximes;[7] and the oxidation of alcohols to aldehydes, ketones or carboxylic acids,[8] phenols to quinones,[9] amines to imines or nitriles,[10] lactams[11] and lactones[12] to their respective α,β-unsaturated derivatives and to other products,[11,13] and thiocarbonyl groups to their carbonyl analogues.[14] Benzeneseleninic acid (**1**) has been employed in the oxidation of variously substituted hydrazines to produce diimide,[15] azo compounds,[7a,15,16] selenoesters,[15] selenosulfonates,[17] and tetrazenes.[18] Seleninic acid **1** and its substituted derivatives have also been reported to effect Baeyer–Villiger oxidations,[19] oxidations of sulfides to sulfoxides,[20] and epoxidations of alkenes.[20a,21] Allylic oxidations and oxidations α to carbonyl groups were recently reported with fluorous seleninic acids.[22] In some of the above oxidations, seleninic acid **1** or its derivatives were employed catalytically in the presence of stoichiometric oxidants or generated *in situ* from the oxidation of the corresponding diselenides.[3] The peroxyseleninic acid **3** is the likely oxidizing species when hydrogen peroxide is employed as the co-oxidant with **1** or **2**. Selenoxides and other types of selenium compounds have also been investigated as reagents for oxidations.[3]



1 **2** **3**

We recently reported that cyclic seleninate esters **4** are easily prepared and function as effective mimetics of the selenoenzyme glutathione peroxidase by catalyzing the reduction of peroxides with sacrificial thiols[23] (Scheme 1). Independent

Scheme 1



4

investigations of related seleninate esters in this context were conducted by Singh et al.[24] As an extension of our previous work in this area, alternative applications of **4** were envisaged, wherein they would serve not as catalysts for the reduction of peroxides, but in the complementary sense as catalysts for the oxidation of substrates other than thiols by employing inexpensive hydrogen peroxide as a stoichiometric oxidant. We now report that seleninate esters **4** are excellent catalysts

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for the rapid and clean oxidation of sulfides to sulfoxides and alkenes to epoxides with hydrogen peroxide. We also describe the oxidations of enamines with **4** and hydrogen peroxide, resulting in their conversion to α-hydroxyketones via unexpected dimeric intermediates.

RESULTS AND DISCUSSION

Oxidation of Sulfides to Sulfoxides. The oxidation of sulfides to sulfoxides has been achieved by many methods,[2S] including the use of seleninic acids. Thus, Faehl and Kice[20b] reported a kinetic study of the reaction of dialkyl sulfides with *p*-chlorobenzeneseleninic acid, while Reich et al.[20a] employed a two-phase procedure using catalytic amounts of benzeneseleninic acid (**1**) with hydrogen peroxide as a co-oxidant in dichloromethane to prepare a variety of sulfoxides from their parent sulfides. Kim and co-workers[20c] later reported a similar process, using catalyst **1** with iodosobenzene under homogeneous conditions in acetonitrile via the proposed hypervalent iodine intermediate $PhI(OH)(PhSeO_2)$.

In order to determine whether cyclic seleninates **4** could be utilized similarly and to compare **4** with **1**, we performed several preliminary experiments in the oxidation of the representative sulfides **5a** and **5b** to the corresponding sulfoxides **6a** and **6b**, as indicated in Scheme 2 and Tables 1 and 2. Thus, thioanisole (**5a**) and benzyl phenyl sulfide (**5b**) were oxidized with 1.25 equiv of hydrogen peroxide in THF/methanol (9:1) at 19 °C in the presence of 5 mol % of benzeneseleninic acid (**1**) or cyclic seleninate **4a** under various conditions. The reactions were monitored by GC analysis, and the times required for oxidation of 50% of the sulfide ($t_{1/2}$) under various conditions are shown in Table 1. In the case of **5a**, the presence of benzeneseleninic acid as the catalyst resulted in a relatively slow reaction (entry 1). However, a dramatic effect was observed when trifluoroacetic acid (TFA, 0.1 M) was added to the reaction mixture in the presence of **1**, thereby increasing the rate ca. 30-fold (entry 2). On the other hand, alkaline conditions (entry 3) essentially stopped the reaction completely. Similar behavior was observed when **4a** was used as the catalyst instead of **1**. In the absence of TFA (entry 4), the reaction was slightly faster than was observed with **1** in entry 1, but in the presence of 0.1 M TFA, a remarkably rapid reaction again occurred with $t_{1/2}$ = 0.3 h (entry 5). A decrease in the concentration of TFA to only 0.01 M (entry 6) still afforded a considerable enhancement of rate compared to entry 4, but less so than with 0.1 M. Sulfide **5b** was oxidized more slowly than **5a** by seleninic acid **1** in the presence of TFA (entry 8), but catalyst **4a** with TFA resulted in a reaction rate too rapid to measure by GC, with the reaction being more than 50% complete after only 5 min (entry 9). Again, the reactions of both **5a** and **5b** were completely suppressed under alkaline conditions (entries 7 and 10). These results demonstrate that sulfide oxidations mediated by either **1** or **4a** are strongly accelerated by acidic conditions and that **4a** provides slightly or significantly faster rates compared to those using **1**.

Substituent effects played an important role in determining the redox properties of cyclic seleninates **4** in our earlier studies of their ability to emulate GPx.[23b] We therefore compared derivatives **4b** and **4c**, containing an electron-withdrawing fluoro substituent or an electron-donating methoxy group, respectively, with the unsubstituted analogue **4a** as catalysts in the oxidation of thioanisole (**5a**) with hydrogen peroxide. The results were again obtained by GC analysis and are shown in Table 2. Surprisingly, both **4b** and **4c** afforded faster reactions than the unsubstituted seleninate, although the rate enhancement was more pronounced with the fluoro derivative **4b** (compare entries 1−3). We also noted that significant overoxidation of the sulfoxide product **6** to the corresponding sulfone **7** occurred in all of the reactions carried out in THF/methanol solution (entries 1−3) or in neat methanol (entry 4), with the sulfones typically comprising 5−17% of the total products. In order to suppress sulfone formation, we investigated other solvents and conditions, with and without varying amounts of added TFA. When **4a** was used in dichloromethane/methanol with only 1 equiv of hydrogen peroxide and 0.015 M TFA, we observed clean oxidation to the sulfoxide (entry 6). The fluoro derivative **4b** reacted slightly faster than **4a** in this solvent, even when only 1 mol % was employed in the absence of TFA, but again, competing sulfone formation was noted (entry 5). Finally, we found that the addition of anhydrous magnesium sulfate to the reaction mixture with **4a** increased the rate of oxidation while promoting the formation of only trace amounts of the sulfone byproduct (entry 7). The rate enhancement can be attributed either to the removal of water (introduced with the hydrogen peroxide) from the reaction mixture or possibly to the Lewis acidity of the magnesium ion.

With the above results in hand, we selected the more easily prepared catalyst **4a** and the conditions of entry 7 for the preparation of other sulfoxides, based on the minimal overoxidation and rapid reaction rate. The results are shown in Table 3, which indicates that excellent isolated yields of sulfoxides can be obtained with negligible sulfone formation. Both aryl and alkyl substituents were tolerated, along with ether, ester, and alcohol functionalities.

Scheme 2

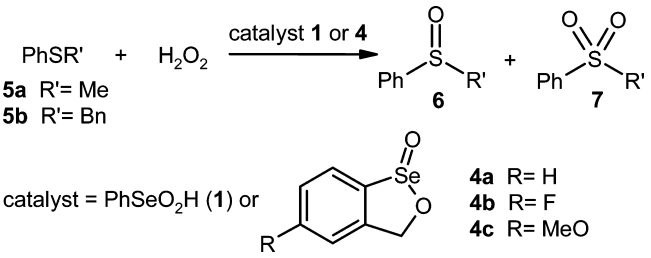

Table 1. Oxidation of Sulfides 5a and 5b in the Presence of Catalysts 1 or 4a[a]

entry	sulfide	catalyst	additive	$t_{1/2}$ (h)[b]
1	**5a**	**1**		30
2	**5a**	**1**	TFA (0.1 M)	1.0
3	**5a**	**1**	KOH (0.1 M)	NR[c]
4	**5a**	**4a**		27
5	**5a**	**4a**	TFA (0.1 M)	0.3
6	**5a**	**4a**	TFA (0.01 M)	1.7
7	**5a**	**4a**	KOH (0.1 M)	NR[c]
8	**5b**	**1**	TFA (0.1 M)	1.7
9	**5b**	**4a**	TFA (0.1 M)	<0.1
10	**5b**	**4a**	KOH (0.1 M)	NR[c]

[a]Conditions: 1.25 equiv H_2O_2, 5 mol % catalyst, THF/MeOH (9:1), 19 °C. [b]Time required for the oxidation of 50% of the sulfide. [c]NR = no reaction

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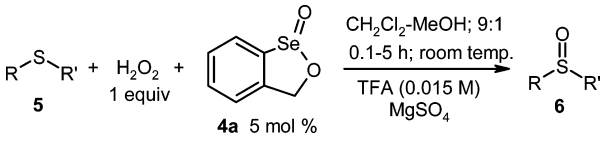
Table 2. Substituent and Solvent Effects in the Oxidation of Sulfide 5a with Catalysts 4a–4c[a,b]

entry	H_2O_2 equiv	catalyst (mol %)	solvent	additive	$t_{1/2}$ (h)[c]	ratio **6a**:**7a**
1	1.25	**4a** (5)	THF/MeOH; 9:1		27	95:5
2	1.25	**4b** (5)	THF/MeOH; 9:1		2.0	91:9
3	1.25	**4c** (5)	THF/MeOH; 9:1		11	94:6
4	1.25	**4b** (5)	MeOH		<0.1	83:17
5	1.00	**4b** (1)	CH_2Cl_2/MeOH; 9:1		0.50	95:5
6	1.00	**4a** (5)	CH_2Cl_2/MeOH; 9:1	TFA (0.015 M)	0.75	>99:1
7	1.00	**4a** (5)	CH_2Cl_2/MeOH; 9:1	TFA (0.015 M) + $MgSO_4$	0.25	98:2

[a]Reactions were performed at 19 °C. [b]A control experiment performed in the absence of **4a–4c**, with or without added TFA, afforded no significant formation of **6a** or **7a** after 6 h. [c]Time required for the oxidation of 50% of the sulfide.

Table 3. Preparation of Sulfoxides



entry	sulfide	R	R′	sulfoxide (isolated yield, %)
1	**5a**	Ph	Me	**6a** (98)
2	**5b**	Ph	CH_2Ph	**6b** (97)
3	**5c**	Ph	Et	**6c** (96)
4	**5d**	$PhCH_2$	Me	**6d** (82)
5	**5e**	Ph	CH_2CO_2Me	**6e** (91)
6	**5f**	Ph	CH_2OMe	**6f** (86)
7	**5g**	$PhCH_2$	$PhCH_2$	**6g** (99)
8	**5h**	Ph	CH_2CH_2OH	**6h** (63)

A plausible mechanism for the sulfide oxidations is shown in Scheme 3. The rate enhancement observed under acidic conditions is attributed to the initial protonation of the seleninate moiety of **4a** and the correspondingly more facile formation of the required peroxyselenurane **9** or peroxyseleninate **10** from the reaction of the resulting cation with hydrogen peroxide. Additional ^{77}Se NMR experiments were performed to corroborate this mechanism. Thus, the addition of TFA (0.12 mmol) to **4a** (0.03 mmol) in $CDCl_3$ resulted in the complete disappearance of the resonance of **4a** at δ 1345.0 ppm with the formation of a new signal at δ 1292.3 ppm, tentatively assigned to the trioxyselenurane **8**. On the other hand, the reaction of **4a** with excess 30% hydrogen peroxide in the absence of TFA produced a new signal at δ 1115.4 ppm, attributed to the formation of peroxy species **9** or **10**, along with the NMR peak of unreacted **4a**. When **4a** was treated with both TFA and excess 30% hydrogen peroxide, the signal at δ1292.3 ppm from **8** was absent, whereas the one at δ 1115.4 ppm was present, along with strong new signals from unidentified selenium species at δ 1309.0 and δ 1022.5 ppm produced during the relatively lengthy acquisition time (11.3 h) of the spectrum.[26a] The observed rate enhancement by TFA and the NMR data are consistent with protonation of **4a**, followed by reaction of the resulting cation with trifluoroacetate anion in the absence of hydrogen peroxide or with hydrogen peroxide when it is present, as opposed to the slower reaction of **4a** directly with hydrogen peroxide in the absence of TFA. The Se(IV) intermediates **9** or **10** presumably serve as the active oxygen-transfer species in the subsequent oxidation of the nucleophilic sulfide substrate. The reaction of **9** with the sulfide may be facilitated by intramolecular proton transfer from the hydroperoxide substituent to the hydroxyselenurane moiety, as shown in Scheme 3. A similar mechanism based on **10** can also be envisaged. In contrast, basic conditions result in the formation of anions **11a** and/or **11b**, which are unable to generate peroxide species, resulting in failure of the reaction. The increased catalytic activity of the fluoro derivative **4b** (Table 2, entry 2) compared to the unsubstituted seleninate ester **4a** is consistent with a more electrophilic peroxide intermediate and therefore a more rapid oxygen transfer step to the sulfide. An electron-deficient seleninate ester such as **4b**

Scheme 3

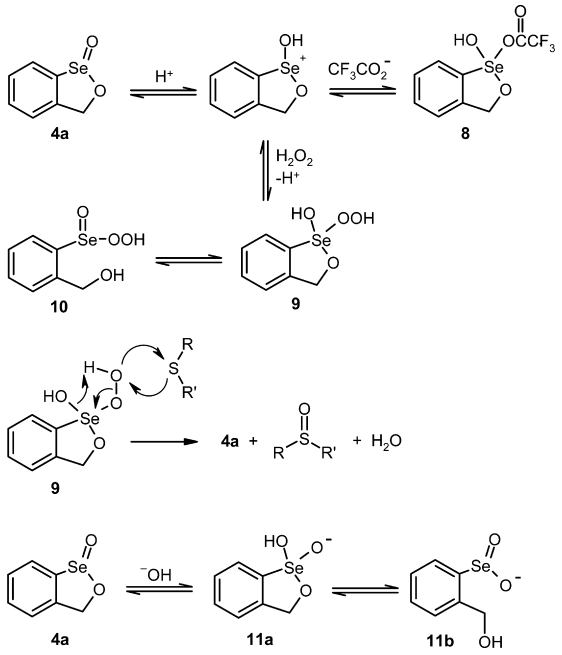


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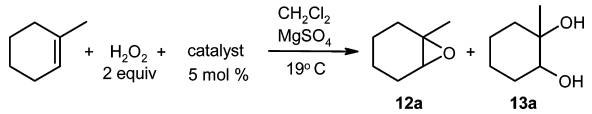
Table 4. Oxidation of 1-Methylcyclohexene with Catalysts 1 and 4a−4c[a]



entry	catalyst (mol %)	additive	rate[b]	12a:13a
1	**1** (5)		$t_{1/2}$ = 1.9 h	55:45
2	**4a** (5)		$t_{1/2}$ = 1.6 h	90:10
3	**4b** (5)		$t_{1/2}$ = 0.6 h	80:20
4	**4c** (5)		$t_{1/2}$ = 0.6 h	67:33
5	**1** (5)	TFA (0.015 M)	$t_{1/2}$ = 0.5 h	50:50
6	**4a** (5)	TFA (0.015 M)	98% complete in 15 min	90:10[c]
7	**4a** (1)	TFA (0.015 M)	65% complete in 15 min	84:16

[a]A control experiment performed in the absence of **4a−4c**, with or without added TFA, afforded no significant formation of **12a** or **13a** after 24 h. [b]$t_{1/2}$ = time required for the oxidation of 50% of the alkene. [c]A small amount of 6-oxoheptanal was also detected by GC−MS of the reaction mixture and by NMR spectroscopy of the isolated product; see Table 5, entry 1 and the NMR spectra of **12a** in the Supporting Information.

would also be expected to produce peroxide species like **9** and/or **10** more readily upon reaction of its conjugate acid with hydrogen peroxide. The reason for the smaller but nevertheless significant rate enhancement observed with the electron-donating methoxy derivative **4c** compared to **4a** (Table 2, entry1) is not clear at this time but suggests that a change in mechanism and rate-determining step may be involved.

These experiments demonstrate that the cyclic seleninate ester **4a** is an excellent catalyst for the rapid oxidation of sulfides to sulfoxides under mild conditions with minimal competing sulfone formation. Further rate enhancements are possible in the case of appropriately substituted derivatives such as **4b**.

Epoxidation of Alkenes. The epoxidation of alkenes, catalyzed by peroxyseleninic acids such as **3**, was reported in earlier studies by several groups. Reich et al.,[20a] as well as Hori and Sharpless,[21b] observed the formation of epoxides as byproducts during the oxidation and selenoxide elimination of alkyl phenyl selenides with hydrogen peroxide. They postulated that byproducts of the eliminations (e.g., PhSeOH) were oxidized in situ to the corresponding peroxyseleninic acids, which were responsible for the further oxidation of the initially formed alkene products. Grieco et al.[21a] performed epoxidations of various alkenes with stoichiometric amounts of **1** and hydrogen peroxide in a pH 7 buffer to avoid hydrolysis of the epoxides to their corresponding diols. Kametani and co-workers noted that epoxidation could be performed in tandem with oxidation and [2,3] sigmatropic rearrangement of allylic selenides.[21c,d] Subsequently, Sheldon et al.[21e] reported an improved epoxidation procedure based on trifluoromethylated derivatives of **1** that were generated *in situ* from oxidation of the corresponding diselenides, while Tiecco et al.[21f] employed the similar oxidation of diphenyl diselenide to obtain the corresponding vicinal diols by hydrolysis of the initially formed epoxides.

We first compared the cyclic seleninates **4a−4c** with benzeneseleninic acid (**1**) in their ability to catalyze the epoxidation of 1-methylcyclohexene with hydrogen peroxide in dichloromethane in the presence of magnesium sulfate, which accelerated the reaction and suppressed epoxide hydrolysis (Table 4). The results indicated that seleninate **4a** provided a modest increase in reaction rate compared with benzeneseleninic acid (**1**) (entries 1 and 2). A further increase was again observed with both the fluoro and methoxy derivatives **4b** and **4c** (entries 3 and 4), respectively. The addition of TFA provided a dramatic increase in the rate for both **1** and **4a**, even when the amount of the latter catalyst was decreased from the usual 5 mol % to only 1 mol % (entry 7). Indeed, the reactions in entries 6 and 7 proved too rapid to monitor by GC analysis, and the yields of products were simply measured after 15 min. It was also evident from these experiments that the use of benzeneseleninic acid (**1**) resulted in considerable hydrolysis of epoxide **12a** to diol **13a**, even in the presence of magnesium sulfate (entries 1 and 5). This was suppressed when seleninate esters **4a−4c** were employed instead of **1**, particularly in the case of **4a** (entries 2, 6, and 7). Interestingly, the presence of TFA did not significantly affect the ratio of **12a**:**13a**. The slightly lower reaction rate observed with 1 mol % of **4a** compared to the use of 5 mol % was accompanied by a slight decrease in the ratio of epoxide to diol (entries 6 and 7).

On the basis of the results shown in Table 4, we chose the conditions of entry 6, which offered the fastest reaction rate with minimal diol formation for the epoxidation of a variety of other alkenes (Table 5). As expected, more highly substituted substrates such as 1-methylcyclohexene and the citronellol derivative **12g** (entries 1 and 7) reacted faster than less substituted (entries 2−6) or resonance-stabilized alkenes (entries 8 and 9). *Trans* and *cis* alkenes gave comparable results (entries 5 and 6), while **12g** produced a ca. 1:1 mixture of diastereomers. Epoxide **12a** was accompanied by the formation of a small amount of the oxidative cleavage product 6-oxoheptanal (entry 1 and *vide infra*), while **12h** was obtained in the ratio of 74:26 with 2-indanone[26b] (entry 8). In general, good to excellent isolated yields of epoxides were obtained, while traces of the corresponding diols were observed but were not isolated. A poor yield and unusually slow reaction was encountered in the case of the highly conjugated alkene *trans*-stilbene (entry 9). The mechanism of the epoxidation is presumably similar to that postulated for the oxidation of sulfides (Scheme 3), except that the π-system of the alkene serves as the nucleophile instead of the sulfide sulfur atom in the reaction with peroxy species **9** or **10**.

During the course of these investigations, several anomalous results were observed. Electron-deficient alkenes such as methyl methacrylate and methyl 1-cylohexenecarboxylate failed to react under the above conditions. This reflects the electrophilic nature of the postulated peroxy species **9** or **10** that are required in the oxygen-transfer step and their low reactivity toward electron-poor alkenes. As in the case of the oxidative cleavage of 1-methylcyclohexene to produce the byproduct keto

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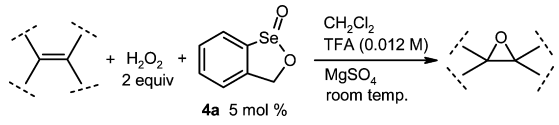
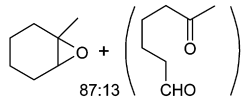
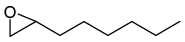
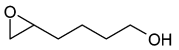
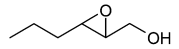
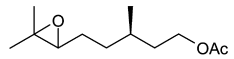
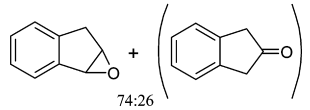
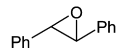
Table 5. Preparation of Epoxides



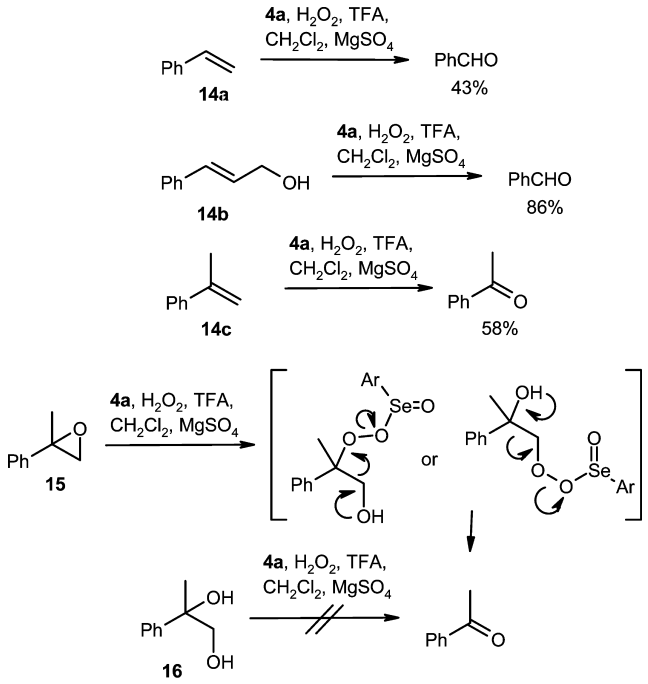
entry	epoxide	structure of product(s)	time (h)	isolated yield (%)
1	**12a**	 87:13	0.25	53 (69[a])
2	**12b**		0.75	90
3	**12c**		7	91
4	**12d**		2	72
5	**12e**		2	90
6	**12f**		2	92
7	**12g**		0.25	89
8	**12h**	 74:26	13	71
9	**12i**		24	48

[a]10 mol % of catalyst **4a** was employed.

aldehyde in entry 1 of Table 5, but in contrast to indene and *trans*-stilbene (entries 8 and 9), styryl derivatives **14a**–**14c** underwent oxidative cleavage to benzaldehyde or acetophenone (Scheme 4) instead of epoxidation. Further experiments with **14c** indicated that an authentic sample of the corresponding epoxide **15** produced acetophenone in 50% yield in 45 min when subjected to the conditions of Table 5, including the catalyst **4a**. A similar yield of 52% of acetophenone was obtained in the absence of **4a**, but a much longer reaction time of 29 h was required. However, when the experiment was repeated with diol **16**, with or without the presence of **4a**, no reaction was observed. This rules out the diol as an intermediate in the oxidative cleavage of the alkene **14c** and suggests the mechanism shown in Scheme 4.[26c] It is therefore evident that cyclic seleninate **4a** is an efficient catalyst for the epoxidation of variously substituted alkenes, with the exception of electron-deficient substrates and some styryl derivatives. The optimized conditions employed in Table 5 afford rapid conversions and minimal hydrolysis to the corresponding diols.

Oxidations of Enamines. The electrophilic nature of the peroxy species derived from cyclic seleninates and hydrogen peroxide suggested that the catalytic oxidation of electron-rich enamines might be especially facile. Among the possible products that were envisaged, α-hydroxy ketones were of special interest because of their common occurrence in numerous natural products and as intermediates in synthetic schemes directed toward various other types of target compounds. Current methods for the overall α-hydroxylation of ketones include the peracid oxidation of enol silyl ethers

Scheme 4



(Rubottom oxidation)[27] or their reaction with chromyl chloride (CrO_2Cl_2),[28] as well as the reactions of ketone enolates with MoO_5·py·HMPA (MoOPH),[29] dimethyldioxirane (DMDO),[30] and *N*-sulfonyloxaziridines.[31] The use of hypervalent iodine species[32] in the direct oxidation of ketones, the enantioselective oxidation of aldehydes with nitrosobenzene in the presence of catalytic amounts of proline,[33] and the microwave-assisted reaction of α-halo ketones with water[34] are examples of alternative approaches to these compounds. The angular hydroxylations of several terpenoid ketones with anhydride **2** have also been reported.[35]

The sensitivity of enamines toward hydrolysis, especially in the presence of acids, precluded the use of TFA to accelerate the oxidation and again required the presence of a drying agent. Preliminary experiments with enamine **17** indicated that anhydrous calcium sulfate was more effective than magnesium sulfate for suppressing hydrolysis, while the inclusion of potassium carbonate was also beneficial, despite the retarding effect of the stronger base potassium hydroxide that we had observed in sulfide oxidations (see Table 1). Under these conditions, the oxidation of **17** with hydrogen peroxide and 5 mol % of **4a** afforded the dimeric product **18**, which was isolated in 91% yield, while a small amount of cyclohexanone (**20**) was identified in the reaction mixture by GC–MS, presumably from hydrolysis of the starting enamine. In contrast, the use of benzeneseleninic acid (**1**) instead of **4a** resulted almost exclusively in hydrolysis of the enamine to cyclohexanone (**20**) under the same oxidation conditions (Scheme 5). A control experiment with enamine **17** and hydrogen peroxide in the absence of **4a** resulted only in the gradual hydrolysis of the enamine to cyclohexanone over a period of 19 h. Furthermore, when a sample of the mixture of diastereomers of **18** was subjected to hydrolysis with 1 M HCl, it was quantitatively converted into the desired α-hydroxycyclohexanone (**19**). Thus, by combining the oxidation step and a workup with 1 M HCl in a separate experiment, the α-

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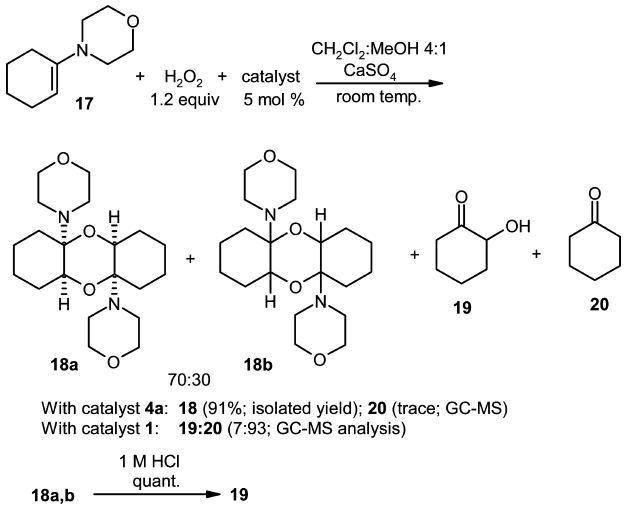
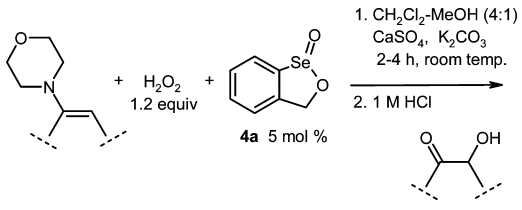
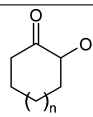
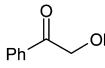
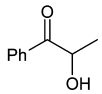
Scheme 5



hydroxyketone **19** was obtained in one pot in 94% yield (Table 6, entry 1). Product **18** was isolated as a mixture of the *cis-syn-*

Table 6. Isolated Yields of α-Hydroxyketones[a]



entry	compound	structure	isolated yield (%)
1	**19** n= 1		94
2	**22** n= 2		67
3	**23** n= 3		65
4	**24**		87
5	**25**		85

cis diastereomer **18a** with a second diastereomer **18b** of unknown configuration in the ratio of 70:30, and the structure of the major isomer was confirmed by X-ray crystallography (Figure 1). This revealed a slightly distorted boat conformation for the central 1,4-dioxane ring with the two tertiary hydrogens occupying flagpole positions and the two *cis* morpholine substituents attached pseudoequatorially to the dioxane ring. This conformation relieves 1,3-diaxial interactions that exist between a pair of respective cyclohexane methylene groups in either flip form of the corresponding chair conformation of the 1,4-dioxane ring. Formally, dimers **18** are produced from the addition of the alkoxy group (or hydroxyl group if protonated) from each of two molecules of intermediate **21** to the iminium moiety of the other (Scheme 6).[36,37]

The extension of the one-pot oxidation and hydrolysis of enamine **17** with seleninate **4a** as the catalyst to several other systems was also investigated. In each case, this was followed by

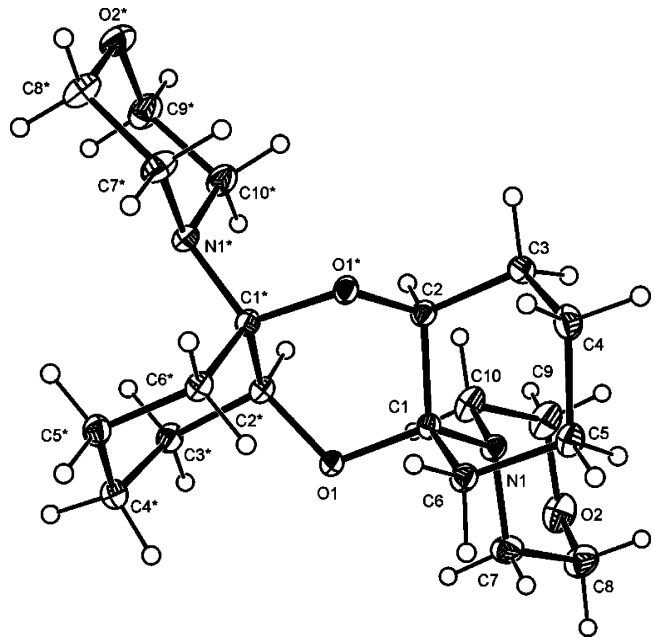
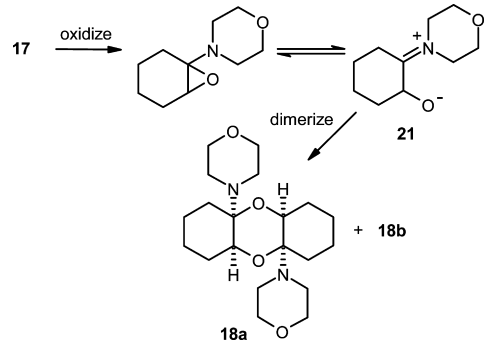


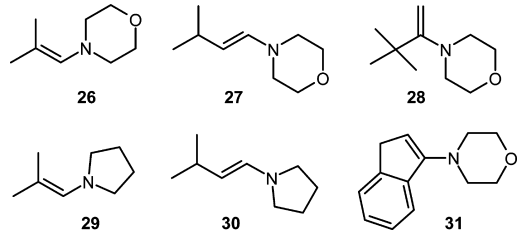
Figure 1. ORTEP diagram of **18a**.

Scheme 6



workup with hydrochloric acid in order to convert dimeric products analogous to **18** directly to the desired α-hydroxyketones. The results are shown in Table 6, which indicates that the method is applicable to morpholine-based enamines of cyclic and acyclic ketones, affording the corresponding products **19** and **22**–**25** in good to excellent isolated yields. On the other hand, the similar reaction of the more hindered enamines **26**–**30**, including the pyrrolidine derivatives **29** and **30**, as well as of 1-(morpholino)indene (**31**) (Chart 1), failed under these conditions. The corresponding enamine of cyclopentanone afforded the α-aminoketone **32** in 79% yield, instead of the expected α-hydroxy derivative (Scheme 7).[38] Finally, the enamine derived from phenyl-

Chart 1



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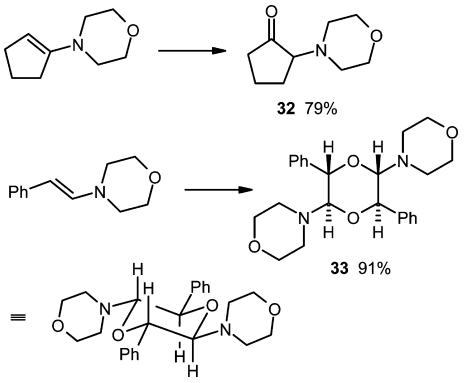
Scheme 7



acetaldehyde furnished the corresponding dimeric product in 91% yield as a single diastereomer, tentatively assigned structure **33** on the basis of the coupling constant J_{trans} = 8.7 Hz between the vicinal methine hydrogen atoms, as well as on the expected preference of phenyl and morpholino substituents to occupy equatorial positions on the 1,4-dioxane ring (Scheme 7). Attempted hydrolysis of the latter in the usual manner afforded mixtures from which the corresponding α-hydroxyaldehyde could not be isolated.

CONCLUSIONS

Cyclic seleninate esters **4** serve as effective catalysts for the oxidation of sulfides to sulfoxides, alkenes to epoxides, and enamines to α-hydroxyketones. Although the fluoro derivative **4b** showed the highest catalytic activity, the more easily prepared unsubstituted seleninate **4a**[23] provided the best overall performance, as it minimized overoxidation to sulfones, hydrolysis of epoxides to diols, and hydrolysis of enamines to their parent ketones. The oxidations of sulfides and alkenes were strongly catalyzed by TFA, presumably via activation of the seleninate moiety by protonation of the selenoxide oxygen atom and facilitation of the formation of required peroxyseleninic species. Catalyst **4a** provided slightly faster rates than benzeneseleninic acid (**1**) in the sulfide oxidations and considerably enhanced rates in epoxidations, as well as higher selectivity for the desired sulfoxide and epoxide products relative to sulfone and diol byproducts, respectively. Seleninate **4a** also proved effective in the oxidation of several enamines to α-hydroxyketones via the unexpected formation of stable and isolable dimeric species such as **18**, although the scope of this transformation appears to be more limited than that of sulfoxide and epoxide formation. To our knowledge, the transformation of enamines to α-hydroxyketones in this manner has not been previously effected with other selenium-based reagents. Cyclic seleninate esters also provide the potential for enantioselective variations of these processes and investigations of chiral derivatives for this purpose are underway.

EXPERIMENTAL SECTION

General Experimental. Cyclic seleninate esters **4a**–**4c** were prepared as described previously.[23] Hydrogen peroxide was titrated prior to use.[39] All sulfide and alkene starting materials were commercially available except for methyl α-(phenylthio) acetate[40] and citronellyl acetate,[41] which were prepared by literature methods. 1-Morpholino-1-cyclohexene was obtained commercially, while other enamines were obtained from morpholine or pyrrolidine and the corresponding commercially available ketones by the method of White and Weingarten.[42] Optimization experiments were monitored by GC analysis, with naphthalene as an internal standard. NMR spectra were recorded at either 300 or 400 MHz for proton spectra and at 75 or 100 MHz for ^{13}C NMR spectra, as indicated for specific compounds below. The ^{77}Se NMR spectra were obtained at 76 MHz and are referenced to dimethyl selenide at 0.00 ppm. Mass spectra were obtained by ESI or CI techniques, as indicated for specific compounds below.

Typical Procedure for the Oxidation of Sulfides (Table 3, entry 1). Preparation of Methyl Phenyl Sulfoxide (6a).[43] Catalyst **4a** (6.0 mg, 0.030 mmol) was dissolved in 10 mL of dichloromethane/methanol (9:1) containing 11 μL (0.15 mmol) of TFA. Hydrogen peroxide (30%, 0.60 mmol) and 500 mg of $MgSO_4$ were then added, and the mixture was stirred at room temperature for 10 min, followed by the addition of methyl phenyl sulfide (74 mg, 0.60 mmol). The reaction was monitored by TLC until completion. The mixture was then filtered, evaporated *in vacuo*, and purified by flash chromatography (ethyl acetate–hexanes) to afford 82 mg (98%) of sulfoxide **6a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66–7.63 (m, 2 H), 7.54–7.50 (m, 3 H), 2.72 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 131.0, 129.3, 123.5, 44.0.

The yields of the other sulfoxides that were prepared in this manner are listed in Table 3, and their NMR spectra are provided in the Supporting Information. All of the sulfoxides are known compounds with spectra matching those reported in the literature.

Benzyl Phenyl Sulfoxide (6b).[43] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.44 (m, 5 H), 7.40–7.24 (m, 3 H), 7.00–6.97 (m, 2 H), 4.09 (d, J = 12.6 Hz, 1 H), 4.00 (d, J = 12.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 131.2, 130.4, 129.2, 128.9, 128.5, 128.3, 124.5, 63.7.

Ethyl Phenyl Sulfoxide (6c).[44] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62–7.60 (m, 2 H), 7.54–7.49 (m, 3 H), 2.90 (m, 1 H), 2.76 (m, 1 H), 1.20 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 130.9, 129.1, 124.2, 50.3, 5.9.

Benzyl Methyl Sulfoxide (6d).[43] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.22 (m, 5 H), 3.99 (d, J = 12.8 Hz, 1 H), 3.88 (d, J = 12.8 Hz, 1 H), 2.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.1, 129.7, 129.0, 128.5, 60.3, 37.3.

Methyl (Phenylsulfinyl)acetate (6e).[45] ^{1}H NMR (400) MHz, $CDCl_3$) δ 7.72–7.70 (m, 2 H), 7.58–7.55 (m, 3 H), 3.86 (d, J = 13.6 Hz, 1 H), 3.72 (s, 3 H), 3.68 (d, J = 13.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 143.1, 131.9, 129.5, 124.2, 61.7, 52.9.

Methoxymethyl Phenyl Sulfoxide (6f).[46] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63–7.60 (m, 2 H), 7.54–7.50 (m, 3 H), 4.41 (d, J = 10.1 Hz, 1 H), 4.36 (d, J = 10.1 Hz, 1 H), 3.65 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.3, 129.3, 124.3, 94.3, 61.0.

Dibenzyl Sulfoxide (6g).[43] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.24 (m, 10 H), 3.91 (d, J = 13.0 Hz, 2 H), 3.85 (d, J = 13.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.3, 130.2, 129.1, 128.4, 57.4.

2-(Phenysulfinyl)ethanol (6h).[47] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.67 (m, 2 H), 7.44–7.56 (m, 3 H), 3.99–4.18 (br s, overlapping with m, 2 H), 3.94 (dt, J = 12.1, 4.7 Hz, 1 H), 3.10 (ddd, J = 13.4, 8.9, 4.4 Hz, 1 H), 2.90 (ddd, J = 13.4, 5.0, 3.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 131.2, 129.5, 124.0, 59.3, 56.5.

Typical Procedure for the Epoxidation of Alkenes (Table 5, entry 1). Preparation of 1,2-Epoxy-1-methylcyclohexane (12a).[48] Catalyst **4a** (6.2 mg, 0.031 mmol) was dissolved in 10 mL of dichloromethane containing 9.0 μL (0.12 mmol) of TFA. Hydrogen peroxide (30%, 1.2 mmol) and 500 mg of $MgSO_4$ were then added, and the mixture was stirred at room temperature for 30 min, followed by the addition of 1-methylcyclohexene (73 μL, 0.61 mmol). After 15 min, GC analysis indicated that the reaction was complete. The mixture was then filtered, washed with aqueous pH 7.4 phosphate buffer, dried, and evaporated *in vacuo* to afford 36 mg (53%) of an 87:13 mixture of epoxide **12a**[48a] and 6-oxo-heptanal[48b] (NMR integration). ^{1}H NMR (300 MHz, $CDCl_3$) peaks from the major product **12a**: δ 2.93–2.92 (m, 1 H), 1.86–1.82 (m, 3 H), 1.66–1.63 (m, 2 H), 1.40–1.35 (m, 3 H), 1.26 (s, 3 H, CH_3); peaks from the minor product 6-oxo-heptanal: δ 9.75 (t, J = 1.6 Hz), 2.13 (s). ^{13}C NMR (100 MHz, $CDCl_3$) peaks from the major product **12a**: δ 59.7, 57.7, 30.0, 24.9, 24.1, 20.2, 19.8; peaks from the minor product 6-oxo-heptanal: 43.8, 43.4, 23.3, 21.6. Attempts at further purification by

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chromatography were unsuccessful, in part due to further decomposition. A slightly higher yield of 69% of a similar mixture of the two products was obtained when the procedure was repeated with 10 mol % of catalyst **4a**.

The other epoxides listed in Table 5 were prepared similarly, except that the yields are reported on products that were isolated by flash chromatography over silica gel (ethyl acetate−hexanes). Their NMR spectra are provided in the Supporting Information. All of the epoxides are known compounds with spectra matching those reported in the literature.

1,2-Epoxycyclohexane (12b).[49] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12 (m, 2 H), 1.98−1.92 (m, 2 H), 1.85−1.78 (m, 2 H), 1.47−1.41 (m, 2 H), 1.27−1.19 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.1, 24.4, 19.4.

1,2-Epoxyoctane (12c).[49] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.94−2.89 (m, 1 H), 2.75 (dd, J = 5.0, 4.4 Hz, 1 H), 2.47 (dd, J = 5.0, 2.8 Hz, 1 H), 1.55−1.29 (m, 10 H), 0.90 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 47.1, 32.5, 31.8, 29.1, 25.9, 22.6, 14.0.

5,6-Epoxyhexan-1-ol (12d).[50] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03−4.00 (m, 1 H), 3.59−3.43 (m, 4 H), 2.25 (br s, 1 H), 1.88−1.83 (m, 1 H), 1.57−1.40 (m, 1 H), 1.45−1.25 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.2, 68.3, 66.4, 27.4, 26.0, 22.9.

***trans*-2,3-Epoxyhexan-1-ol (12e).**[51] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (d, J = 12.4 Hz, 1 H), 3.63 (dt, J = 12.5, 5.0 Hz, 1 H), 2.99−2.92 (m, 2 H), 1.79 (br s, 1 H), 1.60−1.40 (m, 4 H), 0.97 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.7, 58.4, 55.8, 33.6, 19.2, 13.7.

***cis*-2,3-Epoxyhexan-1-ol (12f).**[51] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (dd, J = 12.1, 4.0 Hz, 1 H), 3.69 (dd, J = 12.1, 7.0 Hz, 1 H), 3.17 (dt, J = 6.9, 4.3, 1 H), 3.07−3.05 (m, 1 H), 1.75 (br s, 1 H), 1.57−1.45 (m, 4 H), 0.95 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.0, 57.2, 56.7, 29.9, 19.9, 13.9.

6,7-Epoxycitronellyl Acetate (12g).[52] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04−4.17 (m, 2 H), 2.69 (t, J = 6.2 Hz, 1 H), 2.04 (s, 3 H), 1.34−1.75 (m, 7 H), 1.31 (s, 3 H), 1.26 (s, 3 H), 0.93 (d, J = 4.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 64.4, 64.3, 62.70, 62.67, 58.2, 58.1, 35.4, 35.2, 33.5, 33.4, 29.7, 29.6, 26.3, 26.2, 24.8, 20.9, 19.3, 19.2, 18.6, 18.6.

1,2-Epoxyindane[53] **(12h) and 2-Indanone.**[54] Ratio of epoxide:ketone = 74:26. 1,2-Epoxyindane: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.4 Hz, 1 H), 7.35−7.15 (m, 3 H), 4.28 (dd, J = 2.8, 1.2 Hz, 1 H), 4.15 (t, J = 2.9 Hz, 1 H), 3.23 (d, J = 17.6 Hz, 1 H), 3.00 (dd, J = 17.6, 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 140.9, 128.5, 126.2, 126.1, 125.0, 59.1, 57.6, 34.6. 2-Indanone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.15 (m, 4 H), 3.52 (s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9, 137.8, 127.4, 125.2, 44.1.

***trans*-Stilbene Oxide (12i).**[48] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.38 (m, 10 H), 3.92 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 128.6, 128.4, 125.6, 62.9.

Typical Procedure for the Oxidation of Enamines (Table 6, entry 1). Preparation of α-Hydroxycyclohexanone (19).[55] Catalyst **4a** (3.0 mg, 0.015 mmol) was dissolved in 10 mL of 4:1 dichloromethane/methanol containing 500 mg of crushed anhydrous $CaSO_4$ (500 mg) and 20 mg of K_2CO_3. Hydrogen peroxide (30%, 0.36 mmol) was added, and the mixture was stirred for 30 min. 1-Morpholinocyclohexene (50 mg, 0.30 mmol) was added, and stirring was continued for 4 h, after which the mixture was filtered and the solvent removed *in vacuo*. The crude residue was stirred for 2 h at room temperature in 5 mL of 1 M HCl prior to extraction with dichloromethane and purification by flash chromatography over silica gel (ethyl acetate−hexanes) to afford 32 mg (94%) of **19**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (ddd, J = 12.5, 6.9, 1.3 Hz, 1 H), 3.25 (br s, 1 H,), 2.61−2.31 (m, 3 H); 2.17−2.07 (m, 1 H), 1.95−1.85 (m, 1 H), 1.81−1.43 (3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.4, 75.3, 39.5, 36.7, 27.6, 23.4.

The yields of the other α-hydroxy ketones that were prepared in this manner are listed in Table 6, and their NMR spectra are provided in the Supporting Information. All of the products are known compounds with spectra matching those reported in the literature.

Preparation of Dimeric Hemiaminal 18. Hemiaminal **18** was prepared as described above from 1-morpholinocyclohexene, except that after the oxidation and removal of the solvent, the crude mixture was flash chromatographed over silica gel (ethyl acetate/hexanes, 2:1) and the product was isolated as a white solid, consisting of two isomers in the ratio of 70:30 in a combined yield of 91%: IR (KBr) 2965, 2933, 2849, 1202, 1121, 1020 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) major isomer: δ 4.11 (s, 2 H), 3.67 (t, J = 4.9 Hz, 8 H), 2.90−2.70 (m, 8 H), 2.39−2.26 (m, 2 H), 1.90−1.65 (m, 2 H), 1.60−1.33 (m, 12 H); minor isomer: δ 4.36 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: δ 87.4, 67.8, 66.9, 44.8, 28.6, 25.0, 22.5, 20.6; minor isomer: δ 89.6, 67.6, 66.1, 45.2, 30.6, 27.2, 22.1, 20.3; mass spectrum, m/z (ESI) 389.2 (M^+ + Na); exact mass calcd for $C_{20}H_{35}N_2O_4$ 367.2591 (M^+ + H), found 367.2586. Recrystallization from THF afforded the major isomer **18a**, mp 180−182 °C (dec), which was subjected to X-ray diffraction (see the Supporting Information).

α-Hydroxycycloheptanone (22).[56] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (dd, J = 9.6, 3.6 Hz, 1 H), 3.78 (br s, 1 H), 2.60−2.75 (m, 1 H), 2.45 (ddd, J = 17.4, 11.0, 3.5 Hz, 1 H), 1.96−2.09 (m, 1 H), 1.48−1.94 (m, 5 H), 1.18−1.40 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.9, 77.2, 40.2, 34.0, 29.7, 26.8, 23.6.

α-Hydroxycyclooctanone (23).[56] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (d, J = 6.4 Hz, 1 H), 3.72 (br s, 1 H), 2.71 (td, J = 12.2, 3.8 Hz, 1 H), 2.44−2.29 (m, 2 H), 2.08−1.91 (m, 2 H), 1.87−1.62 (m, 4 H), 1.45−1.32 (m, 2 H), 0.98−0.84 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.4, 76.2, 37.3, 29.2, 28.7, 25.5, 24.5, 22.1.

α-Hydroxyacetophenone (24).[57] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 8.6 Hz, 2 H), 7.67 (t, J = 7.5 Hz, 1 H), 7.54 (t, J = 7.5 Hz, 2 H), 4.91 (d, J = 4.7 Hz, 2 H), 3.53 (t, J = 4.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 134.3, 133.4, 129.0, 127.7, 65.5.

2-Hydroxy-1-phenyl-1-propanone (25).[58] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96−7.93 (m, 2 H), 7.64 (tt, J = 7.4, 1.3 Hz, 1 H), 7.52 (m, 2 H), 5.21−5.13 (m, 1 H), 3.78 (d, J = 6.3 Hz, 1 H), 1.47 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 134.0, 133.4, 128.9, 128.7, 69.3, 22.3.

Preparation of α-Morpholinocyclopentanone (32).[59] The oxidation of 1-morpholinocyclopentene was carried out as in the preparation of **19**, except that after the oxidation was complete, the solvent was evaporated and the crude mixture was chromatographed over silica gel (ethyl acetate/hexanes, 3:1), affording 79% of **32**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (t, J = 4.7 Hz, 4 H,), 3.71−3.58 (m, 1 H), 3.03−2.94 (m, 1 H), 2.84−2.73 (m, 2 H), 2.56−2.46 (m, 2 H), 2.39−1.65 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.4, 71.1, 67.1, 50.6, 37.3, 24.4, 18.2; mass spectrum (CI), m/z (relative intensity) 170 (M^+ + H, 20), 168 (100), 133 (10), 119 (10).

Preparation of Dimeric Hemiaminal 33. The oxidation of 1-morpholino-2-phenylethylene was carried out as described for the preparation of **18**, except that after the oxidation and removal of the solvent, the crude mixture was recrystallized from ethyl acetate, affording a 91% yield of the product as a white solid, mp 197−199 °C (dec) in the form of a single diastereomer: IR (KBr) 2968, 2880, 2849, 1450, 1118, 1055 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, J = 7.9, 1.5 Hz, 4 H), 7.42−7.32 (m, 6 H), 4.81 (d, J = 8.7 Hz, 2 H), 4.06 (d, J = 8.7 Hz, 2 H), 3.60 (m, 8 H), 3.03 (m, 4 H), 2.70 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 127.9, 127.8, 127.2, 95.2, 77.0, 67.1, 48.7; mass spectrum (ESI), m/z (relative intensity) 449 (M^+ + K, 5), 433 (M^+ + Na, 50), 411 (M^+ + H, 5); exact mass calcd for $C_{24}H_{31}N_2O_4$ (M^+ + H) 411.2278, found 411.2274.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of final products; ^{77}Se NMR spectra of **4a** with H_2O_2 and/or TFA; X-ray crystallographic data for **18a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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