Catalytic Epoxidation of Alkenes with Oxone

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A practical, general and efficient protocol for the catalytic epoxidation of alkenes has been developed. The *in situ* generation of reactive dioxiranes capable of epoxidizing a variety of alkenes under biphasic conditions has been accomplished using phase transfer catalysts bearing a carbonyl group. Optimal epoxidation conditions employ 10 mol % of 1-dodecyl-1-methyl-4-oxopiperidinium triflate (**8d**$^+$OTf$^-$) in a CH_2Cl_2/pH 7.5–8.0 biphase using potassium monoperoxosulfate (Oxone) as the oxidant. Optimization of the conditions identified (1) slow addition rate, (2) pH 7.5–8.0, (3) *N*-dodecyl chain, and (4) the triflate salt as key experimental and structural variables. A selection of nine olefins was successfully oxidized to the corresponding epoxides in 83–96% yield.

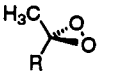
Introduction

The epoxidation of alkenes represents one of the most useful synthetic transformations for the introduction of functionality into organic molecules.[1] Indeed, some of the most spectacular advances in synthetic methodology in the past decade involve the asymmetric oxygenation of alkenes.[2] Accordingly, many powerful methods for the epoxidation of olefins have been developed. In the family of non-metal-catalyzed epoxiding reagents, the most familiar members are peracids,[3] peroxides,[4] and oxaziridines.[5] In recent years, a new and powerful member of this group, dioxiranes, has risen to prominence. The historical evolution, structural characterization, mechanism of action, and synthetic utility of dioxiranes has been the subject of several contemporary reviews.[6]

Background

Mechanism of Action and Synthetic Utility. For use in synthesis the two most useful dioxiranes are dimethyldioxirane (**1a**)[7] and methyl(trifluoromethyl)-dioxirane (**1b**) (Chart 1).[8] Both reagents are generated from potassium peroxomonosulfate (Oxone)[9] and the parent ketone and are used either *in situ*[7b,10,11] or in solution as an isolated species.[12] Indeed, for preparative oxidations, the *in situ* generation of dioxirane is recommended. Under biphasic conditions (benzene or CH_2Cl_2/H_2O) using excess acetone, Oxone, an appropriate buffer, and a phase transfer catalyst (18-crown-6 or $Bu_4N^+HSO_4^-$),[13] this protocol has been successfully applied to the oxidation of three main classes of substrates:[6] (1) unsaturated functions, such as, alkenes,[7a,10–12,14] alkynes,[15] and allenes,[16] (2) nucleophiles containing lone pairs including amines,[17] sulfides,[18] and low valent organo-

Chart 1



1

a : R = CH_3 dimethyldioxirane
b : R = CF_3 methyltrifluoromethyldioxirane

[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1995.

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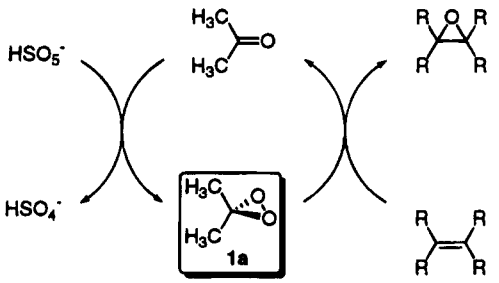
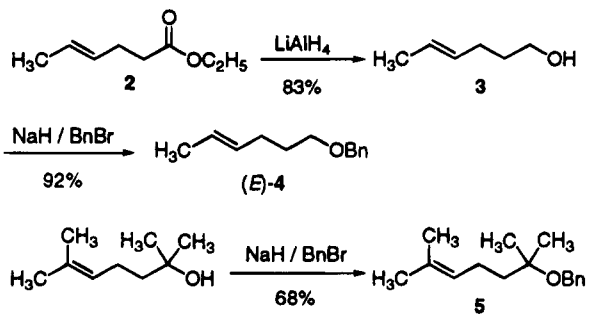
0022-3263/95/1960-1391$09.00/0

Scheme 1



Scheme 2



metallic species,[19] and (3) saturated hydrocarbons which undergo C–H insertion processes.[8a,20]

The isolation method for dioxirane use was developed for instances where either the substrate or the product are not stable under biphasic oxidation conditions. This method is a modification to the acetone/Oxone system where the dioxirane intermediate is physically removed from the generation medium and transferred to a receiver containing the parent ketone.[12,21] In solutions of the dioxiranes prepared by this method, spectroscopic examination has confirmed the existence of a cyclic peroxide.[7c,d,12a,c,14a,22,23]

Both processes involve the formation of a dioxirane by nucleophilic attack of Oxone at the carbonyl carbon with subsequent loss of potassium hydrogen sulfate (Scheme 1). The mechanistic details of the formation and the effects of structure and pH have been extensively discussed.[11a,24] The transfer of oxygen to the substrate (either in a biphasic medium with a PTC or in a homogeneous system) forms the oxidized product and regenerates the initial ketone. With formation of the parent ketone, the generation of more dioxirane from Oxone becomes possible and thus, the epoxidation can, in principle, be catalytic in ketone.[24] While this constitutes no advantage for dimethyldioxirane itself, the potential for catalytic, asymmetric epoxidation using a chiral ketone becomes clear. There exists a single report on record of the asymmetric epoxidation of olefins using simple chiral ketones but the enantiomeric excesses were very low (9–12.5%).[25] To improve the selectivity of the epoxidation would require the preparation of a specially designed ketone,[26] which would ideally be used in catalytic quantities, thus necessitating the development of a highly efficient catalytic protocol. We report herein the development of an efficient method for the catalytic epoxidation of alkenes with Oxone.[27]

Since the majority of likely organic substrates for such a catalytic epoxidation of alkenes are not water soluble, and since we wanted to use a cheap, readily available inorganic persulfate, we employed the biphasic oxidation procedure with the following objectives in mind: (1) identify and optimize key experimental variables for biphasic reaction conditions using acetone as the promoter, (2) survey ketone structure/reactivity models for potential catalysts, (3) optimize promoters that exhibit high levels of activity, and (4) demonstrate the generality of the procedure with a variety of olefinic substrates.

Results

Preparation of Substrates. For the exploratory survey of key experimental variables we employed the alkene (*E*)-**4** as the test substrate. The alkene (*E*)-**4** was prepared in three steps from commercially available 3-buten-2-ol. Johnson orthoester Claisen rearrangement[28] with triethyl orthoformate afforded ester **2** in an *E*/*Z* ratio of 98/2. The ester was subsequently reduced with $LiAlH_4$ to alcohol **3** which was then protected with benzyl bromide to yield the desired *E*-isomer in 76% overall yield (Scheme 2). The trisubstituted alkene **5** was

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(26) One of the elements of that design is an accurate knowledge of the preferred geometry of oxygen transfer in the transition state of dioxirane oxidations. We are currently investigating this issue independently (J. S. DePue, unpublished results). For a recent theoretical treatment of this problem see: Bach, R. D.; Andrés, J. L.; Owensby, A. L.; Schlegel, H. B.; McDouall, J. J. W. *J. Am. Chem. Soc.* **1992**, *114*, 7207.

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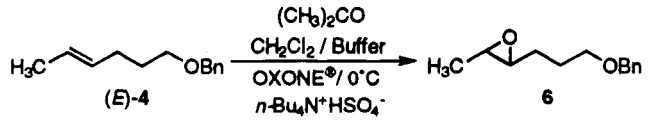
Table 1. Optimization of Oxidation Stoichiometry for (*E*)-4[a]



entry	Oxone[b] (equiv)	n-$Bu_4N^+HSO_4^-$ (equiv)	acetone (equiv)	epoxide/olefin ratio GC	epoxide/olefin ratio isolated (recovery, %)[c]
1	10	0.1	1	50/50	42/58 (82)
2	20	0.1	1		37/63 (84)
3	42	0.1	1	44/56	44/56 (96)
4	10	0.25	1	45/55	46/54
5	10	1.0	1	32/68	41/59
6	10	0.1	10	100/0	99/1 (87)
7	10	0.1	0	2/98	2/98 (95)

[a] All reactions done in CH_2Cl_2/H_2O (pH 7.8) at 0 °C for 24 h. [b] 0.4 M solution. [c] Yield of chromatographically homogeneous material.

prepared from the known alcohol[29] by benzylation, Scheme 2.

Optimization of Reaction Variables. A. Stoichiometry. The systematic optimization of all the experimental variables described below involved the determination of substrate conversion in terms of the epoxide/olefin ratio by GC analysis as well as isolation. All stoichiometry experiments were performed at 0 °C in a CH_2Cl_2/H_2O biphase containing (*E*)-**4** (1−2 mmol), n-$Bu_4N^+HSO_4^-$ as phase transfer catalyst (PTC), and acetone as the dioxirane precursor. Since early studies[10,11a,24] and our own results shown below documented a critical sensitivity of oxidation rate to certain reaction parameters, all reactions were performed using a pH stat[30] and a syringe pump for controlled addition of standardized Oxone solution. The experimental variables examined in the acetone-catalyzed epoxidations of (*E*)-**4** were (1) the stoichiometry of oxidant, PTC, and acetone and (2) rate of oxidant delivery. Since we subsequently discovered that many of these variables are interdependent, it was not possible to systematically examine all permutations.

Previous studies involving biphasic epoxidations commonly employed a large excess of both oxidant and ketone[11,12] so we examined these most critical variables first. The results are collected in Table 1. For this study we arbitrarily set certain boundary conditions: (1) all reactions would be run at 0 °C and pH 7.8 and (2) an addition rate of 1 min/equiv of Oxone solution (0.4 M) would be used. Orienting experiments showed that with 1 equiv of acetone and 0.1 equiv of PTC, a maximum conversion of about 50% could be accomplished with 10 equiv of Oxone. Interestingly, neither additional oxidant (up to 42 equiv) nor additional PTC (up to 1.0 equiv) affected the conversion. However, the stoichiometry of acetone had a dramatic effect on the overall oxidation efficiency (entries 1 and 6). To confirm that the oxidation is indeed a dioxirane-mediated process[31] a control experiment in the absence of acetone was carried out (entry 7) which gave less than 2% conversion to **6**. Thus, it was established that the efficiency of epoxidation is most sensitive to the stoichiometry of acetone and that at rapid addition rates, increasing the amount of oxidant does not improve conversion.

Scheme 3

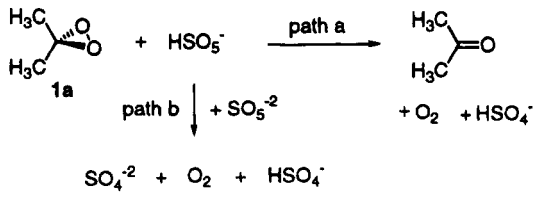
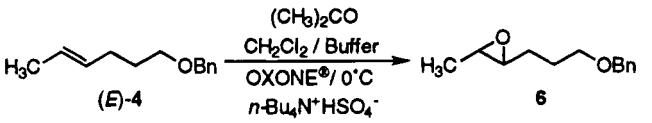


Table 2. Optimization of Rate of Oxone Addition[a]



entry	Oxone[b] equiv	Oxone[b] addition time, min	acetone (equiv)	epoxide/olefin ratio GC	epoxide/olefin ratio isolated (recovery, %)[c]
1	10	10	1	50/50	42/58 (82)
2	10	120	1	60/40	58/42 (94)
3	10	480	1	75/25	71/29 (87)
4	10	120	2	63/37	63/37 (93)
5	10	240	2	88/12	85/15 (92)
6	10	480	2	88/12	87/13 (92)

[a] All reactions done in CH_2Cl_2/H_2O (pH 7.8) with 10 mol % of n-$Bu_4N^+HSO_4^-$ at 0 °C for 24 h. [b] 0.4 M solution. [c] Yield of chromatographically homogeneous material.

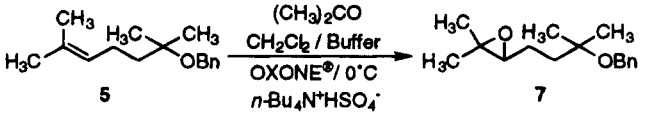
B. Addition Rate. The failure to achieve complete conversion of (*E*)-**4** even with large excess of Oxone suggested that a nonproductive consumption of the oxidant was competitive under these conditions. Indeed, Edwards and Curci demonstrated that the presence of dimethyldioxirane (**1a**) in an Oxone rich environment resulted in both oxygen and potassium hydrogen sulfate generation (Scheme 3).[10] This nonproductive pathway (path a) documented via ^{18}O-labeling studies occurred when SO_5^{-2} was consumed by **1a** and is therefore pH dependent (vide infra). In addition, keeping the Oxone concentration low during the oxidation will suppress the uproductive consumption of oxidant by the autodecomposition at the higher pH (path b).

The results of Oxone addition rate on conversion are collected in Table 2. Under the boundary conditions used in the stoichiometry study, (10 equiv of Oxone, 1 equiv of acetone, 24 h reaction time) the rate of addition displayed a dramatic effect. The slower addition rates led to higher conversions for both 1 and 2 equiv of acetone. Interestingly, monitoring the reactions revealed that the oxidation was still proceeding long after the addition of Oxone was complete. To allow for sufficient conversion to evaluate the effects of the other variables, we chose to use 2 equiv of ketone in the standard protocol, entry 6.

C. pH. The rate of dioxirane formation from Oxone has been shown to exhibit a strong pH dependence with a maximum at 7.5−8.0.[7a,10,24] The control of pH is critical throughout the oxidation since formation of dioxirane involves the generation of acid. For efficient conversion of substrate to product, strict control of the reaction pH must be maintained as well as careful introduction of the oxidant when higher pH values are mandated. We have carried out a number of pH optimizations for biphasic

(29) Kennedy, J. P.; Melby, E. G. *J. Org. Chem.* **1975**, *40*, 1099.
(30) All Oxone reactions were carried out using a Brinkman pH stat apparatus which consists of a Brinkman pH meter E512, a Brinkman Impulsomat 473, and a Brinkman Dosimat E412. See Experimental Section for a more complete description.
(31) The epoxidation of alkenes by Oxone in methanol without added ketones has been reported. Bloch, R.; Abecassis, J.; Hassan, D. *J. Org. Chem.* **1985**, *50*, 1544.

Table 3. Optimization of pH[a]



5 7

entry	pH	acetone (equiv)	ratio epoxide/ olefin GC
1	6.5	1	8/92
2	7.0	1	19/81
3	7.5	1	30/70
4	7.8	1	48/52
5	8.0	1	58/42
6	8.5	1	2/98
7	9.0	1	0/100
8	7.8	0	0/100

[a] All reactions done in CH_2Cl_2/H_2O with 10 equiv of Oxone (5 mL/min) and 10 mol % of n-$Bu_4N^+HSO_4^-$ at 0 °C for 6.5 h.

Table 4. Survey of Ketone Structure in the Epoxidation of (*E*)-4[a]

entry	ketone	epoxide/olefin ratio (recovery, %)[b]
1	acetone	87/13 (92)
2	2-butanone	40/60 (92)
3	3-pentanone	5/95 (86)
4	cyclobutanone	2/98 (99)
5	cyclopentanone	3/97 (96)
6	cyclohexanone	67/33 (89)
7	1,1,1-trifluoroacetone	29/71 (95)
8	hexafluoroacetone	2/98 (94)
9	**8a**$^+NO_3^-$	2/98 (94)

[a] All reactions done in CH_2Cl_2/H_2O (pH 7.8) with 2 equiv of ketone and 10 mol % of n-$Bu_4N^+HSO_4^-$ at 0 °C for 24 h. [b] Isolated, chromatographically homogeneous material.

reactions using various ketones and substrates by determining both olefin conversion and concentration of oxidant (by iodometric titrations of the aqueous phase). An early study for acetone employed the trisubstituted alkene **5** using a slightly different protocol (20 min addition). The results shown in Table 3, clearly show a narrow window with the optimal pH between 7.8–8.0. It was difficult to assure the constancy of the pH (±0.2) at these addition rates. Nevertheless, moving a few tenths of a unit away from the 7.8–8.0 region resulted in either Oxone self-destruction at higher pH values (Scheme 3, path b) or loss in reactivity (Oxone preservation) at lower pH values (see Discussion).[32] The pH dependence was reexamined later with more active catalysts (vide infra).

Optimization of Promoter Structure. A. Ketone Type. Having addressed the critical reaction variables and having selected a standard oxidation protocol (10 equiv of Oxone (8 h addition), 2 equiv of ketone, 0.1 equiv of PTC, 24 h reaction at 0 °C, pH 7.8), we were in a position to survey the relationship of ketone structure to efficiency of epoxidation.[12a,24,27,33] The results in Table 4 reveal several interesting trends when compared to acetone. First, for acyclic ketones, α-substitution significantly decreased epoxidation efficiency (entries 1–3). Second, for cyclic ketones, oxidation efficiency was found to be strongly ring size dependent; only cyclohexanone promoted the formation of **6** in a yield comparable to

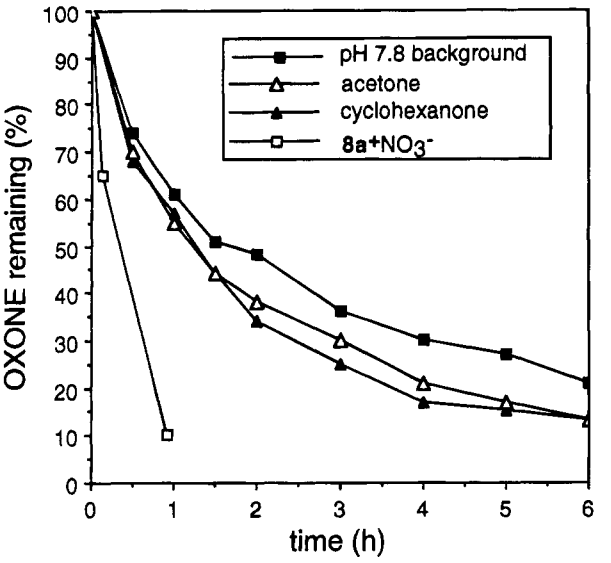


Figure 1. Rate of Oxone consumption by ketones.

acetone (entries 1, 4, 5, and 6). Third, increasing the electrophilicity of the ketone had a detrimental effect on the epoxidation efficiency (entries 1, 7, and 8).[27] Finally, the highly hydrophilic ketone, 1,1-dimethyl-4-oxopiperidinium nitrate (**8a**$^+NO_3^-$) failed to promote the epoxidation of (*E*)-**4**. We included this ketone in the survey because Montgomery found that in the homogeneous oxidation of chloride ion by Oxone, **8a**$^+NO_3^-$ was more efficient than acetone by a factor of 1300.[24]

The ability of a ketone to serve as a promoter for epoxidation involves two critical features, (1) the ability to efficiently form a dioxirane and (2) the ability to efficiently transfer the oxygen to the substrate. To evaluate the ability of a ketone to be converted to a dioxirane we examined the consumption of Oxone in the absence of olefin. As shown in Figure 1, using the conditions described in Table 3 (with **5**), after 1 h the consumption of Oxone was the following: by acetone (45%), cyclohexanone (43%), and **8a**$^+OTf^-$ (0.1 equiv) (90%). The extremely rapid consumption of Oxone but low epoxidation efficiency with **8a**$^+OTf^-$ indicated the ability to convert monoperoxosulfate to a dioxirane, but not to transfer the oxygen efficiently to **5**. Thus, it is clear that in biphasic oxidations, factors other than ease of formation and reactivity of the dioxirane must be considered.

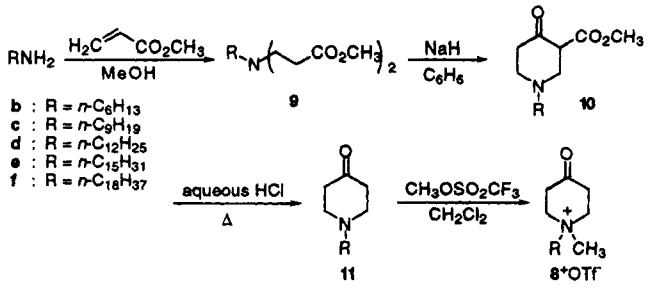
B. Chain Length Dependence. Stoichiometric. Given the ability of **8a**$^+NO_3^-$ to decompose Oxone and its potential to serve as a phase transfer catalyst we surveyed the oxidation efficiency of a series of 4-oxopiperidinium salts as a function of *N*-substituent under the standard reaction protocol. Our initial study compared the efficiency of *n*-hexyl, methyl (**8b**$^+OTf^-$) and *n*-dodecyl, methyl (**8d**$^+OTf^-$) derivatives as their triflate salts. The synthesis of the piperidinones follows a general procedure described by McElvain and Rorig[34] and the results are summarized in Table 5. Treatment of the appropriate primary amine with 2 equiv of methyl acrylate afforded the diester **9** which underwent Dieckmann cyclization to afford the desired β-keto ester **10**. Saponification and thermolysis of **10** produced the requisite *N*-alkylpiperidinone **11** which was converted to the

(32) The concentration of Oxone, as determined by iodometric titration, in aqueous solution (pH 7.8) without ketone promoter dropped from 0.4 M to 0.075 M over 4 h at 0 °C. At higher reaction temperatures, the rate of oxidant decomposition is significantly higher.

(33) Murray, R. W.; Singh, M.; Jeyaraman, R. *J. Am. Chem. Soc.* **1992**, *114*, 1346.

(34) McElvain, S. M.; Rorig, K. *J. Am. Chem. Soc.* **1948**, *70*, 1820 and references sited therein.

Table 5. Preparation of *N*-Alkyl, *N*-Methyl Piperidinium Triflates 8b⁺–8f⁺



series	9 (yield, %)[a]	10 (yield, %)[a]	11 (yield, %)[a]	8⁺OTf⁻ (yield, %)[b]	mp, °C
b	**9b** (98)	**10b** (43)	**11b** (79)	**8b**⁺ (80)	115–116
c	**9c** (96)	**10c** (89)	**11c** (49)	**8c**⁺ (48)	148–150
d	**9d** (98)	**10d** (83)	**11d** (82)	**8d**⁺ (96)	168–169
e	**9e** (63)	**10e** (64)	**11e** (35)	**8e**⁺ (68)	163–166
f	**9f** (95)	**10f** (98)	**11f** (16)	**8f**⁺ (68)	179–181

[a] Isolated, chromatographically homogeneous material. [b] Recrystallized.

Table 6. Epoxidation of (*E*)-4 Catalyzed by 4-Oxopiperidinium Salts[a]

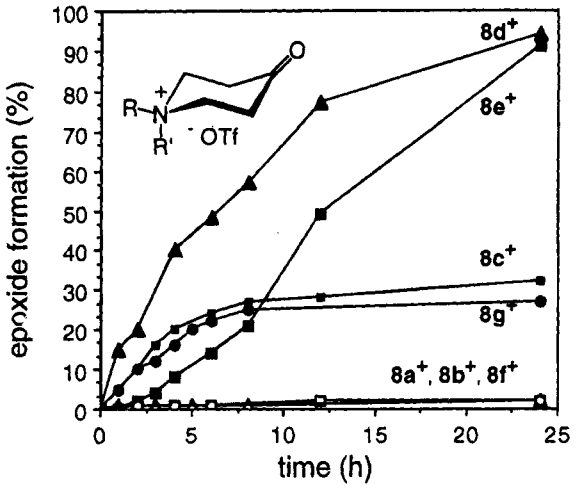
entry	ketone	equiv	epoxide/olefin ratio (recovery, %)[c]
1	acetone[b]	2	87/13 (92)
2	**8b**⁺OTf⁻	2	100/0 (91)
3	**8b**⁺OTf⁻	1	44/56 (89)
4	**8d**⁺OTf⁻	1	100/0 (92)
5	**8d**⁺OTf⁻	0.1	94/6[d] (91)

[a] All reactions done in CH_2Cl_2/H_2O (pH 7.8) at 0 °C for 24 h. [b] 10 mol % of n-$Bu_4N^+HSO_4^-$. [c] Isolated, chromatographically homogeneous material. [d] GC ratio.

salt by alkylation with excess methyl trifluoromethanesulfonate. Purification of the salts by recrystallization provided the *n*-alkyl, methyl piperidinium salts (**8**⁺OTf⁻) in analytically pure form.[35]

With a series of dialkyl triflate salts at hand, we evaluated their ability to epoxidize substrate (*E*)-**4** and the results are compiled in Table 6. We were delighted to find that at equal loadings, *n*-hexyl, methyl (**8b**⁺OTf⁻, 2.0 equiv) is more efficient than acetone affording quantitative epoxidation of (*E*)-**4** after 24 h. However, the efficiency drops significantly with less promoter. On the other hand, only 1 equiv of the *n*-dodecyl, methyl analog **8d**⁺OTf⁻ was required for the quantitative conversion of (*E*)-**4** to **6**. Most remarkable, however, was the nearly complete consumption of (*E*)-**4** promoted by a catalytic quantity of **8d**⁺OTf⁻!

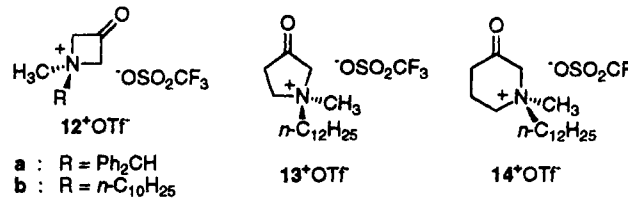
C. Chain Length Dependence. Catalytic. Clearly, the lipophilicity of the ketone was crucial for success, which suggested a more careful tuning of chain length. On the basis of previous studies above and the potential for catalysis, we chose ketone **8**⁺ for additional optimization. The graph in Figure 2 shows the rate of epoxide formation using the standard protocol with only 10 mol % of 4-oxopiperidinium salts **8**⁺OTf⁻. Both highly hydrophilic (**8a**⁺OTf⁻) and highly lipophilic (**8f**⁺OTf⁻) ketones are inactive; chain length (not just carbon count) is important as the symmetrical di(*n*-hexyl) derivative



icon	promoter	R	R'
△	**8a**⁺NO_3^-	CH_3	CH_3
□	**8b**⁺OTf⁻	n-C_6H_{13}	CH_3
⊞	**8c**⁺OTf⁻	n-C_9H_{19}	CH_3
▲	**8d**⁺OTf⁻	n-$C_{12}H_{25}$	CH_3
■	**8e**⁺OTf⁻	n-$C_{15}H_{31}$	CH_3
○	**8f**⁺OTf⁻	n-$C_{18}H_{37}$	CH_3
●	**8g**⁺OTf⁻	n-C_6H_{13}	n-C_6H_{13}

Figure 2. Chain length dependence of epoxidation of (*E*)-**4** with **8**⁺.

Chart 2



8g⁺OTf⁻[36] is inferior to **8d**⁺OTf⁻. Thus, both **8d**⁺OTf⁻ and **8e**⁺OTf⁻ give near quantitative conversion, though **8d**⁺OTf⁻ is markedly faster.

D. Structural Variations of Keto Ammonium Salts. The successful results with the 4-oxopiperidinium salts underscored the importance of uniting the dioxirane precursor (carbonyl group) with the phase transfer catalyst. We therefore extended our survey of promoter structures to evaluate other heterocyclic keto ammonium salts, Chart 2. Several structural types were assayed which incorporated the ammonium site at various locations with respect to the carbonyl moiety. The first series was designed to reevaluate the effect of ring size (see Section A, above) and the location of the ammonium group. Each modification was compared to **8d**⁺OTf⁻ as the benchmark standard.

D. 1. 3-Oxoazetidinium Series. Despite the failure of cyclobutanone to promote the oxidation and its propensity for Baeyer–Villiger oxidation,[10] we tested the keto azetidinium salt **12**⁺OTf⁻ prepared as shown in Scheme 4. Treatment of benzhydrylamine with epichlorohydrin[37] afforded the azetidinol **15** which was subsequently oxidized affording the desired *N*-substituted azetidinone **16**. The *N*-benzhydrylazetidinone could be

(35) An alternative procedure for formation of *N*-alkyl, *N*-methyl piperidinium salts was later developed which involved quaternization of commercially available *N*-methyl-4-piperidinone with the appropriate *n*-alkyl triflate. For the preparation of alkyl triflates see: Beard, C. D.; Baum, K. *J. Org. Chem.* **1974**, *39*, 3875.

(36) The synthesis of **8g**⁺OTf⁻ was accomplished via *n*-hexylation of *N*-hexyl-4-piperidinone in 66% yield after recrystallization.

(37) (a) Chatterjee, S. S.; Triggle, D. J. *J. Chem. Soc., Chem. Commun.* **1968**, 93. (b) Gaertner, V. R. *Tetrahedron Lett.* **1966**, 4691. (c) Gaertner, V. R. *Tetrahedron* **1967**, *23*, 2123. (d) Gaertner, V. R. *J. Org. Chem.* **1967**, *32*, 2972.

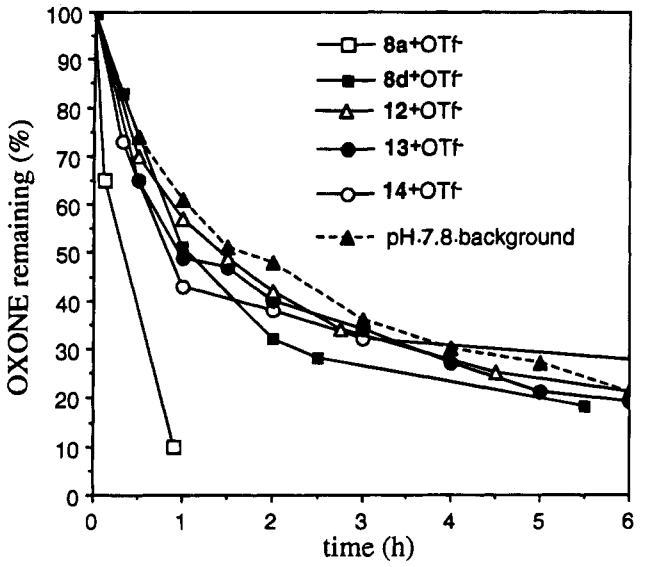
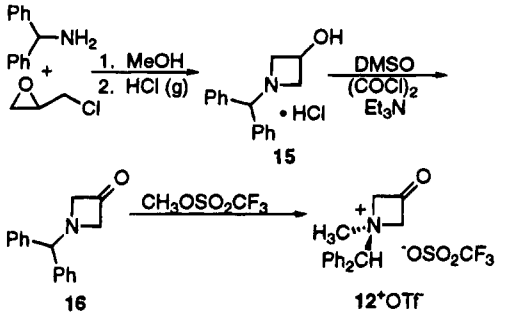


Figure 3. Rate of Oxone consumption by keto ammonium salts at pH 7.8.

Scheme 4

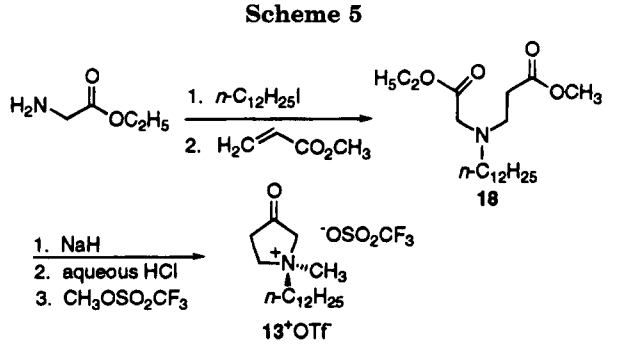


quaternerized directly with methyl triflate to afford **12**$^+$OTf$^-$.[38] Attempted oxidation of (*E*)-**4** with this salt under the standard protocol resulted in no epoxide formation. In addition, the results of Oxone titration experiments with **12**$^+$OTf$^-$ (Figure 3) showed a rate only slightly faster than background consumption. We conclude that **12**$^+$OTf$^-$ was inefficient in forming a dioxirane due to competitive destruction by Baeyer–Villiger oxidation.

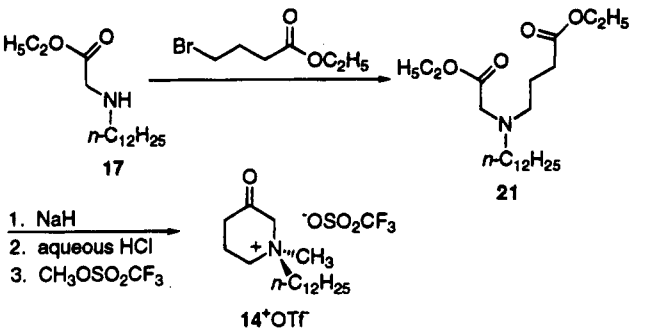
D. 2. 3-Oxopyrrolidinium Series. To relieve ring strain, we next examined the five-membered ring analog in the 3-oxopyrrolidinium series **13**$^+$OTf$^-$. The synthesis of **13**$^+$OTf$^-$ was easily accomplished by a modification of the McElvain approach[34] for the synthesis of *N*-substituted piperidinones, Scheme 5. *N*-Alkylation of ethyl glycinate with 1-iodododecane afforded a monoalkylation product **17** which underwent Michael addition to methyl acrylate to afford the tertiary amine **18**. The acyclic precursor was next treated with NaH in hot benzene and then was saponified, decarboxylated, and finally quaternerized with methyl triflate to afford **13**$^+$OTf$^-$. Unfortunately, no epoxidation of (*E*)-**4** was observed using **13**$^+$OTf$^-$ under the standard protocol. Interestingly, Oxone titration experiments (Figure 3) with **13**$^+$OTf$^-$ showed it to be less effective than **8d**$^+$OTf$^-$ at promoting the consumption of oxidant. Thus, again, the failure of **13**$^+$OTf$^-$ resides in its diminished ability to form a dioxirane.

(38) All attempts to prepare an *n*-dodecyl, methyl derivative analogous to **8d**$^+$OTf$^-$ were unsuccessful.

Scheme 5



Scheme 6



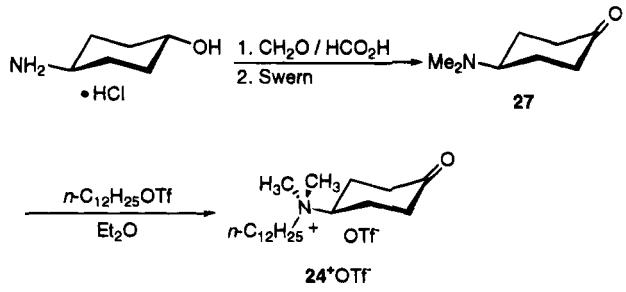
D. 3. 3-Oxopiperidinium Series. Having little success in finding oxidation promoters of smaller ring size, we returned to the piperidinium series and assayed the effect of moving the carbonyl group to the 3-position. Preparation of the unsymmetrical *n*-dodecyl, methyl 3-oxopiperidinium salt **14**$^+$OTf$^-$ began by alkylation of **17** (see above) with ethyl bromobutyrate, Scheme 6. The acyclic precursor **21** was then subjected to the same reaction sequence as previously described (Scheme 5).

Employment of **14**$^+$OTf$^-$ as promoter (10 mol %) was only modestly successful for the conversion of olefin to epoxide. After 24 h, the ratio of **6**/(*E*)-**4** was 22/78 with an 80% recovery. Increasing the loading to 50% of **14**$^+$OTf$^-$ had little effect; the ratio of **6**/(*E*)-**4** was 34/66 (GC analysis). The Oxone titration curve for this promoter (Figure 3) also shows a rapid initial rate even greater than **8d**$^+$OTf$^-$ and then a flattening of the slope. This behavior indicates that the promoter is active, but it undergoes destruction within 1 h of reaction. That the consumption of **14**$^+$OTf$^-$ involved a Baeyer–Villiger oxidation was supported by the observation of a lactone peak at 177 ppm in the ^{13}C NMR spectrum of the recovered catalyst.

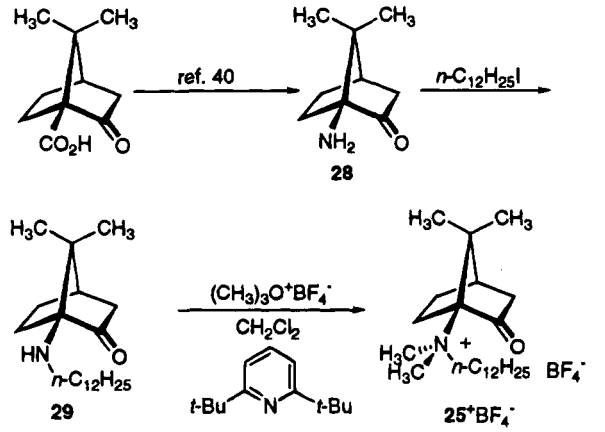
D. 4. Exo-Ammonium Series. All of the previously examined salts were based on heterocyclic ketones. As an alternative, we next evaluated carbocyclic ketones bearing ammonium substituents at different locations. In this series the inductive effect due to the ammonium center is separated from the central framework. In **24**$^+$OTf$^-$ (Scheme 7), the ammonium group is one atom removed compared to **8d**$^+$OTf$^-$ but also enjoys greater conformational freedom. In **25**$^+$BF$_4^-$ (Scheme 8) the ammonium group is attached to the α-carbon in an exocyclic fashion reinforcing the dipole of the carbonyl group.

The preparation of these promoters involved a related strategy of quaternization of the parent amino ketones. The precursor amino ketone **27** was obtained by Eschweiler–Clark methylation of the commercially available

Scheme 7



Scheme 8



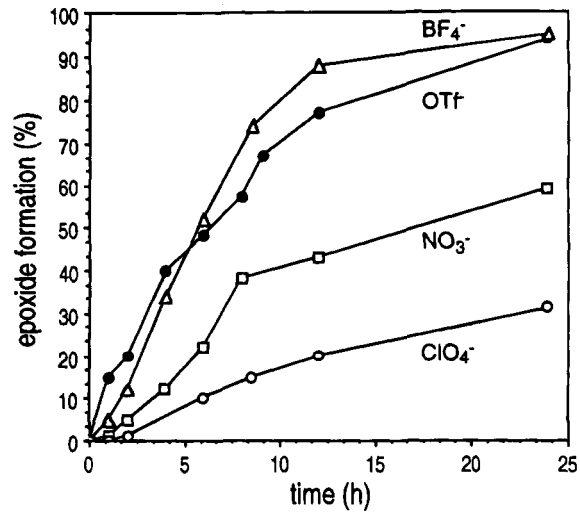
amino alcohol followed by Dess–Martin periodinane[39] or Swern oxidation, Scheme 7. Quaternization with *n*-dodecyl triflate afforded the salt **24**$^+$OTf$^-$ as a waxy solid. The bicyclic keto ammonium salt was prepared by *N*-dodecylation of amino ketone **28**, itself obtained by Curtius degradation of ketopinic acid.[40] Permethylation of **29** with trimethyloxonium tetrafluoroborate afforded the salt **25**$^+$BF$_4^-$, Scheme 8.

Both promoters were evaluated under the standard oxidation protocol using (*E*)-**4** as the test olefin. The salts behaved quite differently. The dimethyl, *n*-dodecyl ammonium cyclohexanone salt **24**$^+$OTf$^-$ displayed modest activity as an epoxidation promoter in catalytic quantities affording ratio of **6**/(*E*)-**4** of 47/53 with a 90% recovery. This is consistent with its activity for Oxone consumption which parallels that of **8d**$^+$OTf$^-$. With stoichiometric amounts of **24**$^+$OTf$^-$, the conversion was complete and an 86% yield of **6** was obtained.

The bicyclic catalyst **25**$^+$BF$_4^-$ was less successful. Even with a full equivalent of the promoter, none of the epoxidation product was detected by GC analysis after 9 h. Moreover, it was also ineffective as an Oxone decomposition promoter.

To summarize the results of this initial optimization, we found that (1) slow addition of Oxone solution to the substrate while maintaining a pH between 7.8 and 8.0 was critical for efficient epoxidation, (2) the 4-oxopiperidinium salts provided the best framework examined for efficient dioxirane formation and oxygen transfer though the (4-oxocyclohexyl)ammonium salts were also effective, and (3) the *n*-dodecyl group provided optimal phase transfer properties allowing efficient epoxidation even with catalytic amounts of the promoter. The following optimization studies further refined the efficiency of the catalyst.

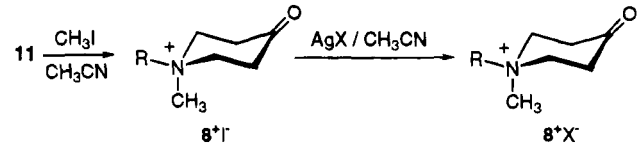
(39) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(40) (a) Beak, P.; Harris, B. R. *J. Am. Chem. Soc.* **1974**, *96*, 6363. (b) Bartlett, P. D.; Knox, L. H. *Org. Synth.* **1965**, *45*, 55.



		% formation of **6**			
		pH = 7.8		pH = 8.0	
icon	catalyst	12 h	24 h	12 h	24 h
–△–	**8d**$^+$BF$_4^-$	88	95	41	71
–●–	**8d**$^+$OTf$^-$	77	94	91	95
–□–	**8d**$^+$NO$_3^-$	43	59	-	-
–○–	**8d**$^+$ClO$_4^-$	20	31	-	-

Figure 4. Counterion dependence of epoxidation of (*E*)-**4** with **8**$^+$ at pH 7.8.

Scheme 9



8a$^+$NO$_3^-$ (81%); **8d**$^+$I$^-$ (92%); **8d**$^+$BF$_4^-$ (79%); **8d**$^+$OTf$^-$ (96%); **8d**$^+$NO$_3^-$ (73%); **8d**$^+$ClO$_4^-$ (70%)

E. Counterion Dependence. Having settled on a basic catalyst structure (**8d**$^+$OTf$^-$) and reaction protocol, the influence of counterion was next examined. Interestingly, the nature of the counterion greatly influenced the overall outcome in the epoxidation of substrate (*E*)-**4**. Three additional counterions were surveyed. Preparation of each salt (except the triflate which arose from direct alkylation) was accomplished by anionic exchange of the requisite ammonium iodide salt (**8d**$^+$I$^-$) in an acetonitrile solution at 0 °C with the appropriate silver salt, Scheme 9. Under the standard protocol (**8d**$^+$X$^-$) (10 mol %), the conversion of (*E*)-**4** to **6** after 24 h was found to be strongly counterion dependent in the following order: BF$_4^-$ (95%), CF$_3$SO$_3^-$ (94%), NO$_3^-$ (59%), and ClO$_4^-$ (31%), Figure 4. We also noted the influence of pH on the counter ion dependence. By examining the epoxidation of (*E*)-**4** with **8d**$^+$OTf$^-$ and **8d**$^+$BF$_4^-$ at pH 7.8 and 8.0, we found that **8d**$^+$OTf$^-$ is significantly faster at pH 8.0 than at pH 7.8 and the **8d**$^+$BF$_4^-$ is significantly slower at pH 8.0 than at pH 7.8.

F. pH Dependence. Although a pH optimization was carried out earlier for acetone, we felt it necessary to reexamine the pH dependence with the phase transfer catalyst **8d**$^+$OTf$^-$. The pH rate profile was examined over a narrow range (pH 7.0–8.5) under the standard oxidation conditions (10 mol % **8d**$^+$OTf$^-$) with (*E*)-**4** as the substrate. This range was selected on the basis of our initial pH study with acetone. The results in Figure

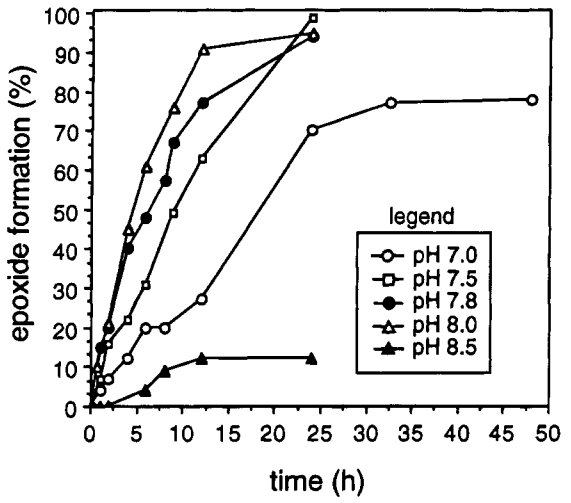


Figure 5. pH Dependence of epoxidation of (*E*)-**4** with **8d**$^+$OTf$^-$.

Table 7. Catalytic Epoxidation of Selected Olefins[a]

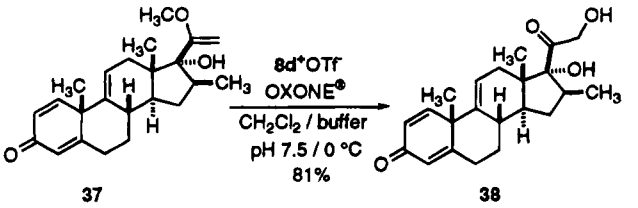
alkene	pH	product	conversion, %[b]	yield, %[c]
1-octene	7.5	**30**	100	91
cyclohexene	8.0	**31**	100	92[d]
(*E*)-**4**	8.0	**6**	99	91
5[e]	8.0	**7**	100	90[d]
$\Delta^{9,10}$-octalin	8.0	**32**	100	87
(*E*)-2-methylstyrene	7.5	**33**	100	96
(*Z*)-2-methylstyrene	7.5	**34**	100	93
(*E*)-cinnamyl alcohol	7.5	**35**	100	83
2-cyclohexen-1-ol	8.0	**36**[f]	96	83[d]

[a] All reactions done in CH_2Cl_2/H_2O with 10 mol% of **8d**$^+$OTf$^-$ at 0 °C for 24 h. [b] GC analysis. [c] Analytically pure material. [d] Chromatographically homogeneous material. [e] 2,6-Dimethyl-6-phenylmethoxy-2-heptene. [f] Syn-**36**/anti-**36**, 53/47 by GC analysis.

5 show clearly that the maximum rate is found between 7.5 and 8.0.[10,24] While all oxidations in this range proceed to completion after 24 h, the rates are different and decrease in the order 8.0 > 7.8 > 7.5. In fact, the conversion is strikingly similar to that seen for acetone (with **5**) after 6.5 h (Table 3): pH 7.5, 22%; pH 7.8, 47%; pH 8.0, 61%. The slower rate but complete oxidation at lower pH has practical consequences for slow reacting substrates because of the slower rate of Oxone consumption at pH 7.5 (vide infra).

Substrate Generality. To illustrate the utility of the catalytic oxidation procedure, a range of olefin types was examined. The results collected in Table 7 are for preparative scale (2 mmol) oxidations using catalytic amount of **8d**$^+$OTf$^-$ and 10 equiv of Oxone under the standard conditions. Various representatives of olefin substitution were surveyed including styrenes and allylic alcohols. In all cases the alkene was oxidized efficiently (96–100% conversion) affording the epoxides in very good yield (83–96% analytically pure epoxides). The rate of oxidation increased with increasing olefin substitution: tetra > tri > di > mono and isolated olefins reacted faster than conjugated alkenes (styrenes) and allylic alcohols. For the less reactive alkenes, complete conversion required lowering of the pH to 7.5. The more reactive olefins were completely consumed at pH 8.0. Highly electron deficient olefins (ethyl cinnamate) failed to react at an appreciable rate. The absence of a pronounced hydroxyl-directing effect in 2-cyclohexenol was also noted as both syn and anti epoxy alcohols **36** were formed in nearly equal amounts.

Scheme 10



37 **38**

To evaluate the chemical selectivity of this oxidation protocol, we examined the steroid substrate **37** which contains four different double bonds. Under the standard reaction conditions at pH 7.5, the vinyl ether function was selectively oxidized to afford the corticosteroid side chain in **38** in 81% yield (Scheme 10).[41] The only other isolated product was the C-20 methyl ketone from hydrolysis of **37**.

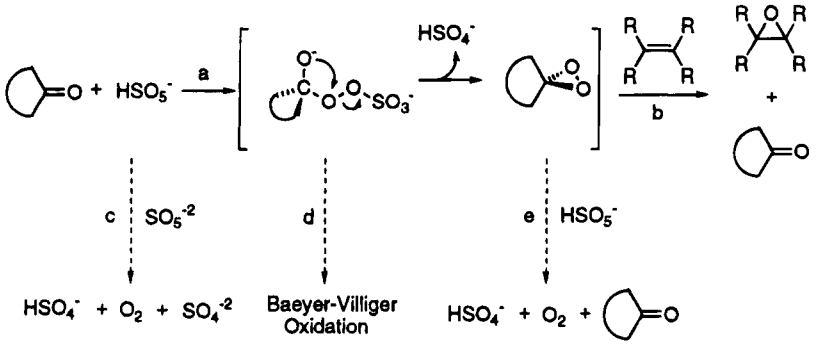
Discussion

Understanding of the role of various reaction parameters in this multicomponent system is complicated by the interdependence of many of the variables. The following discussion is organized to address the significance of the most critical variable first and analyze the implications for reactivity and opportunities for design elements for asymmetric catalysts. As stated in the introduction, our main objectives were (1) to identify and optimize key experimental variables for biphasic reaction conditions using acetone as the promoter, (2) survey ketone structure/reactivity models for potential catalysts, (3) optimize promoters that exhibit high levels of activity, and (4) demonstrate generality.

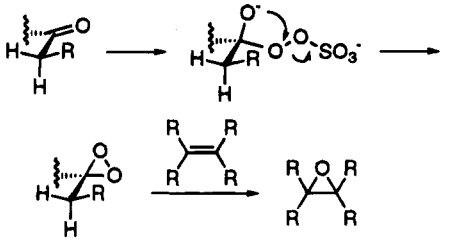
A. Optimization of Reaction Conditions. Control of the reaction pH is *critical* for all of the biphasic oxidations examined. The use of a pH-stat has enabled us to systematically evaluate each variable in our multicomponent system while maintaining pH within ±0.2 units. Outlined in Scheme 11 is a unified mechanism for the various transformations of intermediates in the conversion of Oxone to dioxiranes and related products under biphasic conditions. Maximizing substrate conversion through path b involves a delicate balance of both oxidant stoichiometry and addition rate. We and others have shown that Oxone self-decomposition (path c) predominates at high pH values (>8.0).[10,11a] Under these conditions the peroxomonosulfate species exists as the dianion increasing its nucleophilicity and thus leading to self-destruction. Mechanistic studies have shown that the catalyzed rate of decomposition is first order in both $[HSO_5^-]$ and $[OH^-]$.[10,11a] This nonproductive pathway could be suppressed by slow addition of the oxidant as well as careful pH control (path a). Variable pH values not only affect the lifetime of the oxidant but of the ketone promoter as well.[11a] The irreversible consumption of the ketone promoter by Baeyer–Villiger oxidation (path d) was minimized by strict pH regulation and by the introduction of functionality within the ketone framework to slow the migration of flanking groups. Once the dioxirane intermediate is formed, it can either be consumed by reaction with peroxomonosulfate in the aqueous phase (path e) or transfer oxygen to the substrate in the organic phase (path b). The former, unproductive

(41) For other dioxirane epoxidations of steroids see: (a) Bovicelli, P.; Lupattelli, P.; Mincione, E.; Prencipe, T.; Curci, R. *J. Org. Chem.* **1992**, *57*, 2182. (b) Sacks, C. E. U.S. Patent No. 4,613,463; 1986.

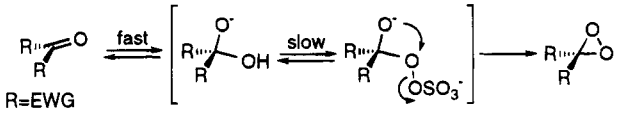
Scheme 11



Scheme 12



Scheme 13



process was minimized by slow addition of the oxidant, thereby keeping the peroxomonosulfate concentration low. The latter, productive process was facilitated by the introduction of a lipophilic residue on the ketone (see below). Thus, by consideration of the potential pitfalls, the multicomponent system can be manipulated to favor the reaction flux through paths a and b.

A. Ketone Structure. The efficiency of oxygen transfer to the test substrate was defined as the percent conversion to the epoxide after 24 h under the standard reaction conditions. By this definition, we thus evaluated the ability of each ketone promoter to carry out *both* stages of the oxidation, namely dioxirane formation and oxygen atom transfer. Since both stages are critical to the success of the epoxidation, we must evaluate how the structure of the ketone influences the two stages. Factors that need to be evaluated for each structure are (1) ease of rehybridization of the carbonyl carbon, (2) facility for nonproductive consumption of Oxone, (3) propensity for irreversible ketone consumption (Baeyer–Villiger oxidation), and (4) accessibility of the oxygen atom for transfer to the substrate. Limitations for any of these features can dramatically change the overall outcome of the oxidation in the biphasic reactions.

A. 1. Acyclic Ketones. α-Substitution of the ketone promoters resulted in a significant drop in reactivity. For example, acetone yielded 87% epoxide whereas 2-butanone and 3-pentanone resulted in 40 and 5% epoxide formation, Table 4, entries 1, 2, and 3 respectively. By increasing the steric congestion about the carbonyl carbon, any one of the reasons listed above may account for the drop in epoxidation efficiency (Scheme 12). For example, substitution at the carbon next to the carbonyl group disfavors the equilibrium formation of the tetrahedral intermediate en route to dioxirane formation. Second, the migratory aptitude of the flanking groups increases with each substitution of a hydrogen for an alkyl group leading to consumption via Baeyer–Villiger oxidation.[42] Finally, approach of the reactive center to the olefin may be retarded due to the increased steric congestion about the dioxirane. At this time we cannot distinguish which of these pitfalls dominate the change in epoxidation rate.

Employment of the electronically activated ketones such as trifluoro- and hexafluoroacetone (Table 4, entries 7 and 8) led to negligible amounts of epoxidation, 29 and 2%, respectively. The former ketone is indeed a powerful dioxirane precursor when employed in its *isolated* state[12] which suggests that the problem lies in the formation or partitioning of the dioxirane under biphasic conditions. The carbonyl groups in both substrates are highly activated toward nucleophilic attack and thus should exhibit a high propensity for addition of peroxomonosulfate. We believe that the loss of reactivity for these specific examples may result from facile hydration of the semi- and perfluorinated promoters. In aqueous medium, these ketones exists as stable hydrates and if the exchange of the groups on the central carbon (OH for OSO_4^-) is slow, an inefficient promoter will result, Scheme 13. We can rule out a competitive Baeyer–Villiger oxidation since the placement of electron-withdrawing groups should suppress this pathway by significantly reducing the migratory aptitude at the α-substituents.[42] (**Note Added in Proof**: We have recently discovered that 2-fluorocyclohexanones are extremely efficient promoters, which supports the notion that fluorine substitution can be beneficial provided the ketones are not too hydrophilic.)

Another factor related to steric bulk and electrophilicity, namely water solubility, should also be considered. This parameter could impact the overall outcome at both stages of the oxidation process. Consider both limits of water solubility of the promoter. At one extreme is the organic insoluble/water soluble promoter. According to Scheme 11, if the resulting dioxirane were also completely water soluble (as for example **8a**$^+NO_3^-$), then unproductive pathway e is expected to dominate as the dioxirane would stay in the aqueous phase with the peroxomonosulfate and not be transported to the organic phase where the substrate is located. At the other extreme would be an organic soluble/water insoluble promoter. In this example, the biphase prevents contact of the water soluble oxidant with the water insoluble dioxirane precursor and will fail to produce a dioxirane unless the PTC can serve to shuttle the oxidant into the organic phase.

(42) For a recent review of the Baeyer–Villiger oxidation see: Krow, G. R. *Org. React.* **1993**, *43*, 251.

Table 8. Survey of Cyclic Ketone Promoters[a]

entry	ketone	relative addition rates: Oxone	relative addition rates: $NaBH_4$	solubility in H_2O	yield of **6**, %
1	cyclobutanone	–	1.6	–	2
2	cyclopentanone	0.02	0.04	30%, 25 °C	3
3	cyclohexanone	1.0	1.0	8–9%, 20 °C	67

[a] All reactions done in CH_2Cl_2/H_2O (pH 7.8) with 10 mol % of n-$Bu_4N^+HSO_4^-$, 2.0 equiv of ketone, 10.0 equivalents Oxone (8 h addition time) at 0 °C for 24 h.

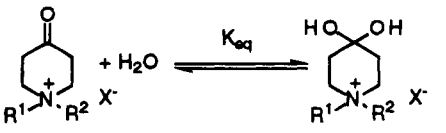
A. 2. Cyclic Series. Epoxidation efficiency displayed a dramatic dependence on ring size in the series of alicyclic ketones, cyclobutanone, cyclopentanone, and cyclohexanone. This trend may be understood by considering the facility of rehybridization of the carbonyl carbon and the eclipsing interactions with the α-methylenes Table 8. Edwards has previously noted a parallel in the rate of ketone-catalyzed decomposition of Oxone with the rates of the $NaBH_4$ reductions of those ketones.[10] The key feature here is rehybridization of the carbonyl carbon from sp^2 to sp^3 which relieves ring strain and alleviates (or engenders) unfavorable eclipsing interactions at the α-methylenes of the ketone. Accordingly, cyclobutanone should be the best promoter within this series. However, under the oxidation conditions, ring expansion via Baeyer–Villiger oxidation creates a secondary pathway that shunts the rehybridized intermediate to an irreversible destruction. The failure of cyclopentanone to serve as an effective promoter is most likely due to the strain associated with formation of a sp^3 center by increasing the eclipsing interactions with the neighboring methylenes.

The ability of cyclohexanone to serve as an effective promoter is clearly understood by the comparisons in Table 8. Cyclohexanone is between 9 and 50 times more efficient that cyclopentanone at Oxone decomposition.[10,24] Moreover, classical studies by Brown reveal that the rate of $NaBH_4$ reduction of cyclohexanone is approximately 13 times faster than that for cyclopentanone.[43] Finally, destruction of the promoter by Baeyer–Villiger oxidation of cyclohexanone at the working pH of 7.8–8.0 is minimal.[11a]

B. 4-Oxopiperidinium Structure. The amalgamation of the carbonyl precursor of the dioxirane with the ammonium function of the phase transfer catalyst had a profound effect on the efficiency of epoxidation. This was observed both with Oxone decomposition studies as well as epoxidation studies. Our consideration of 4-oxopiperidinium salts was stimulated by Montgomery's observation that **8a**$^+NO_3^-$ promoted the homogeneous decomposition of Oxone 1400 times faster than acetone and 150 times faster than cyclohexanone. Furthermore, Montgomery found that the *homogeneous* oxidation of chloride ion by Oxone is promoted by **8a**$^+NO_3^-$ at a rate 1300 times that of acetone and 213 times that of cyclohexanone.[24] The spectacular ability of **8a**$^+NO_3^-$ to promote these reactions can be understood by considering the influence of the ammonium group on the various stages in Scheme 11. First, for maximum throughput to the dioxirane, the addition equilibrium to the Criegee intermediate must be rapid and favorable. As a mimic of this process we can consider the hydration equilibrium of the ketone. The tendency for hydration of ketones increases with increasing electronegativity of the substituents

(43) Brown, H. C.; Ichikawa, I. *Tetrahedron* **1957**, *1*, 221.

Table 9. Hydration Equilibria for 4-Oxopiperidinium Salts[a]



entry	R^1	R^2	X^-	K_{eq}
1	H	–	–	1.1
2	H	H	Cl	5
3	CH_3	–	–	0.30
4	CH_3	H	Cl	7.1
5[b]	CH_3	CH_3	I	>100

[a] Data taken from ref 45. [b] **8a**$^+I^-$.

bonded to the carbonyl group.[44] More specifically, the hydration equilibrium for a series of 4-oxopiperidines and piperidinium salts has been determined by NMR spectroscopy at various pH's.[45] The data summarized in Table 9 clearly shows that the inductive effect of the ammonium group has a dramatic influence on the hydration equilibrium; less than 1% of **8a**$^+I^-$ exists in the keto form in neutral water. Second, given a high formation constant for the Criegee intermediate, the partitioning to dioxirane formation or Baeyer–Villiger oxidation is also effected by the ammonium group. The inductive effect of the ammonium group should suppress the migratory aptitude of the methylenes[42] even though cyclohexanone itself suffered little oxidation at pH 7.8. Thus the efficient formation of dioxirane under homogeneous conditions led to the rapid consumption of Oxone via path e or oxidation of chloride ion via path b. The failure of **8a**$^+NO_3^-$ then to promote the epoxidation of (*E*)-**4** must be related to the fate or reactivity of the dioxirane. This matter was clarified by changing the solubility properties of the salts.

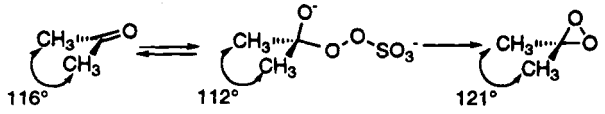
The efficiency of epoxidation of olefins was found to be dramatically dependent on the length of alkyl substituent on the ammonium ion. Increasing the lipophilicity of the salt lead to extremely efficient promoters which could be used in catalytic quantities to effect complete conversion of the test olefin. While stoichiometric amounts of the promoters lead to complete conversion of (*E*)-**4** to epoxide **6** within a few hours, the catalytic process, albeit slower, was optimized for future investigations with chiral ketones. Under these conditions, slow introduction of oxidant was necessary for complete conversion, presumbly because of nonproductive Oxone consumption. Titration experiments revealed that the effective concentration of Oxone at the 8 h data point (after complete addition) was 0.075 M. Nonetheless, the reaction profile in Figure 2 shows that the epoxidation continues, highlighting the efficiency of dioxirane formation.

The diverse behavior of the salts with various chain lengths can be understood in terms of their phase partitioning properties. At catalytic loadings, both the highly hydrophilic, (**8a**$^+NO_3^-$ and **8b**$^+OTf^-$) and the highly lipophilic (**8f**$^+OTf^-$) salts failed to promote the epoxidation at a rate greater than the background. For the hydrophilic promoters, this likely results from their inability to partition into the organic phase with suf-

(44) Bell, R. P. In *Advances in Physical Organic Chemistry*; Gold, V., Ed.; Academic Press: New York, 1966; Vol. 4; pp 1–29.

(45) Van Luppen, J. J.; Lepoivre, J. A.; Dommisse, R. A.; Alderweireldt, F. C. *Org. Mag. Reson.* **1979**, *12*, 399.

Scheme 14



ficient concentration, and consequently the oxidant is destroyed in the aqueous phase. The lipophilic promoter simply cannot form the dioxirane since it has no solubility in water (no additional PTC is added). The methyl, *n*-nonyl (**8c**$^+$OTf$^-$) and *n*-hexyl, *n*-hexyl (**8g**$^+$OTf$^-$) promoters both showed catalytic behavior, but the rate leveled off after 8 h (end of the addition). This suggests that both are slightly too hydrophilic and even with slow addition rates the consumption of Oxone in the aqueous layer is competitive. Of the salts examined, the methyl, *n*-dodecyl (**8d**$^+$OTf$^-$) was the most efficient, while complete conversion of the olefin was also observed for the for methyl, *n*-pentadecyl (**8e**$^+$OTf$^-$) but at a slower rate. This is presumably due to the lower efficiency of conversion to the dioxirane since **8e**$^+$OTf$^-$ should be less water soluble than **8d**$^+$OTf$^-$. The reaction still goes to completion for the same reason; the dioxirane spends little time in the aqueous phase. We are uncertain about the origin of the superiority of the methyl, *n*-dodecyl (**8d**$^+$OTf$^-$) catalyst. It is certainly possible that micelles are involved (the biphasic reaction mixtures are emulsified by **8d**$^+$OTf$^-$), and work in this area is currently under investigation.

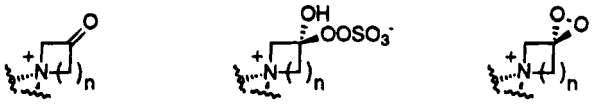
C. Other Oxo Ammonium Structures. No other oxo-ammonium salt exhibited the same catalytic properties as the piperidinium salts. With either of the smaller ring heteroycles, azetidinium and pyrrolidinium, no epoxidation was observed even at stoichiometric loadings. Even though the corresponding alicyclic ketones were also poor promoters we felt that the influence of the ammonium center to (1) inductively activate the carbonyl moiety, (2) provide phase transfer ability, and (3) suppresses the migratory aptitudes of the α-sites, would lead to active promoters. However, another structural factor not yet considered is ring strain.

To evaluate the impact of this feature, we must consider the geometrical changes that take place upon dioxirane formation, Scheme 14. As a model reaction the formation of dimethyldioxirane itself is considered to identify the bond angle changes that take place at the carbonyl carbon. This will in turn provide an estimate of the deformation that will occur in the formation of a spiro bicyclic peroxide from a cyclic ketone. The angles provided in Scheme 14 are obtained from the gas phase structures of acetone[46a] and dimethoxypropane[46b] (as a model of the Criegee intermediate). No experimental structure for dimethyldioxirane is available, but the C−C−C angle has been calculated to be 121° at the MP2/6-31G* level.[7d] The gas phase structure of dioxirane (CH_2O_2) reveals a 117° H−C−H angle. As expected, the initial formation of the tetrahedral intermediate is associated with a narrowing of the C−C−C angle. However, the formation of the dioxirane causes a widening of this angle again.

To understand the consequences of these changes in the different ring systems, the idealized C−C−C bond angles (from Scheme 14) and the "actual" angles for that heterocycle are compared, Table 10. The actual data is

(46) (a) Iijima, T. *Bull. Chem. Soc. Japan* **1972**, *45*, 3526. (b) Astrup, E. E.; Aomar, A. M. *Acta Chem. Scand.* **1975**, *A29*, 794.

Table 10. Representative Internal Angles for 8$^+$, 12$^+$, 13$^+$, and 14$^+$



entry	cyclic promoter	internal angle, deg ideal-ized	internal angle, deg actual (Δ)	internal angle, deg ideal-ized	internal angle, deg actual (Δ)	internal angle, deg ideal-ized	internal angle, deg actual (Δ)
1	**12**$^+$ (n = 1)	116	91 (−25)	112	88 (−24)	121	88 (−33)
2	**13**$^+$ (n = 2)	116	108 (−12)	112	106 (−6)	121	106 (−15)
3	**14**$^+$ (n = 3)	116	116 (0)	112	110 (−2)	121	110 (−11)
4	**8**$^+$	116	115 (+1)	112	111 (−1)	121	111 (−10)

collected from X-ray analyses of azetidinium, pyrrolidinium, and 3- and 4-piperidinium salts; data for sp^3 type carbons were available for all ring sizes. However, data for sp^2 type carbons were available only for 4-piperidinones. In the other cases the "actual" values were obtained from calculation of the parent *N,N*-dimethyl-3-oxoazetidinium and *N,N*-dimethyl-3-oxopyrrolidium salts (MNDO, AM1). In each column, the term Δ is defined as the difference between the idealized angle for that species (as reflected from the data in Scheme 14) and the angle found for that particular ring structure. The magnitude of Δ is a reflection of the deformation of ring and is related to the increase or relief of strain.

Analysis of Table 10 reveals some interesting trends. In the azetidinium case (**12**$^+$), the strain of accommodating a carbonyl carbon is weakly relieved by the formation of the Criegee intermediate. However, the formation of the cyclic peroxide requires an expansion of the C−C−C angle and thus causes a reintroduction of strain. The energetic cost of the second stage of dioxirane formation translates to negligible rates of Oxone decomposition as well as no epoxidation which is observed experimentally. In the pyrrolidinium series, the same argument of strain release and reintroduction can made, with the caveat that eclipsing interactions will offset the energy gain on formation of the intermediate. In fact, by ^{13}C NMR in CD_3OD, the salt **13**$^+$OTf$^-$ exists predominantly (75%) in the keto form. The experimental results with **13**$^+$OTf$^-$ also parallel the azetidinium series.

The 3- and 4-oxopiperidinium species represent a different scenario. While there is little change in the angles for the formation of the intermediate, the closure to the dioxirane is associated with less angle deformation. In addition, this strain energy can be distributed over six ring atoms. Thus the energetic cost of dioxirane formation is less in these systems. Indeed, NMR analysis in methanol showed clearly that both 3- and 4-oxopiperidinium salts exist completely in the hemiacetal form. Moreover, both 3- and 4-oxopiperidinium salts are qualitatively similar at the early stage of reaction in decomposition of Oxone, Figure 3. Why then, do they behave so differently? The answer lies in the observations that with **14**$^+$OTf$^-$ both the decomposition of Oxone and the epoxidation reactions begin rapidly and stall. This is indicative of an irreversible destruction of the promoter, presumably by Baeyer−Villiger oxidation. This hypothesis was supported by the observation of a lactone resonance the ^{13}C NMR spectrum of the recovered promoter. This was disappointing since it was expected that placement of the ammonium center closer to the carbonyl should enhance the tendency for dioxirane formation and at worst suffer Baeyer−Villiger oxidation

at the same rate as cyclohexanone. Conceivably, the strain in the tetrahedral intermediate due to 1,3-diaxial interactions with the ammonium substituents finds escape in the ring expansion.

With the cyclohexanone derivative **24**$^+$OTf$^-$, the activation provided by the ammonium center is attenuated because of its distance from the carbonyl group, though it was still considerably more effective than cyclohexanone itself. Interestingly, Montogomery found that the trimethylammonium analog of **24**$^+$OTf$^-$ is nearly as effective as **8a**$^+$NO$_3^-$ in chloride ion oxidation. In the biphasic oxidation, **24**$^+$OTf$^-$ was the second best of all the other types of salts examined, though still inferior to **8a**$^+$OTf$^-$. The complete consumption of (*E*)-**4** with a full equivalent of **24**$^+$OTf$^-$ suggests that Baeyer–Villiger oxidation is not a competitive process and the incomplete conversion at catalytic loadings is due to less efficient production of the dioxirane.

The bicyclic oxo-ammonium derivative **25**$^+$BF$_4^-$ was designed to evaluate the effects of attaching the ammonium group at the α-carbon in such an orientation to reinforce the dipole of the carbonyl group. While the manifestation of this phenomenon in the increased electrophilicity of the carbonyl group abounds in the literature,[47] the congestion of the bicyclic system combined with the cyclopentanoid nature of the structure eliminated any electronic advantage and rendered the salt inactive.

Counterion Dependence. The reactivity trends for the epoxidations catalyzed by **8d**$^+$X$^-$ was greatly influenced by choice of counterion. Of the four counterions surveyed, either tetrafluoroborate or trifluoromethanesulfonate provided the best results. Both overall activity as well as rates of reaction were comparable. However, if the counterion was replaced by either a nitrate or perchlorate ion, the efficiency of biphasic oxidation dropped.

This behavior can be qualitatively understood in terms of the hydrotropic properties (ability to increase the mutual solubility between water and nonionic amphiphiles) of electrolytes containing these anions.[48] Unfortunately, data is only available for sulfate, nitrate, and perchlorate and their hydrotropicity decreases (lyotropicity increases) in that order. Given the parallel of hydrotropicity and epoxidation efficiency, we are currently examining still more lipophilic salts (alkyl sulfonates) for their epoxidation efficiency.

Substrate Generality. The reactivity trends for the epoxidations catalyzed by **8d**$^+$OTf$^-$ are qualitatively similar to those observed for epoxidation of olefins with **1**. The oxygen atom transfer appears to be a stereospecific, electrophilic process.[14b,49] The rate increases with increasing alkyl substitution and decreases with conjugating or electron-withdrawing substituents. In our initial survey of substrates we found that the less reactive olefins, e.g. 1-octene and the styrenes gave incomplete conversion under standard conditions. This problem could be solved by increasing the catalyst loading to 15% or better by lowering the pH to 7.5. We recognized that incomplete conversion was due to competitive Oxone consumption (not catalyst destruction) which is slower at pH 7.5. For electron-rich olefins, the epoxidation is fast enough to compete with Oxone consumption even at pH 8.0.

Interestingly, the absence of a pronounced hydroxyl-directing effect was also found. In the epoxidation of allylic alcohols with **1**, the regio- and stereodirecting effect of the hydroxyl group was found to be variable and substrate dependent.[11b] The ability to carry out selective epoxidations of electron rich olefins in the presence of simple olefins was also demonstrated in the substrate **37** and highlights the potential for applications in synthesis.

Conclusions. A practical, general, and efficient protocol for the catalytic epoxidation of alkenes with Oxone has been developed. The best catalysts under biphasic reaction conditions were found to be 4-oxopiperidinium salts. Primary factors responsible for the success of the oxidation are ketone structure, lipophilicity and counterion. Secondary factors include pH, reagent stoichiometry, and addition rate. The generality of the procedure was demonstrated with a variety of alkene substitution patterns and functionality. We are currently investigating (1) the origin of catalysis by oxo-ammonium salts and (2) the design of chiral ketones for asymmetric catalytic epoxidation.

Experimental Section

General. See supplementary material.

Ethyl (*E*)-4-Hexenoate (2). Triethyl orthoacetate (37.1 g, 229 mmol, 1.10 equiv) was placed in a 100 mL, three-necked, round-bottomed flask equipped with thermometer, glass stopper, magnetic stirrer, and a reflux condenser on which was mounted a Claisen head equipped with a 10 mL dropping funnel and a short path condenser with thermometer. With the reflux condenser off, the 1-buten-3-ol (18.0 mL, 208 mmol) was added dropwise over 1 h. After an additional 1 h, no additional ethanol was being produced. The reflux condenser was turned on, and the solution was refluxed for 3 h (135 °C internal temperature). After cooling to room temperature, the solution was poured into 100 mL diethyl ether and washed with 1 N NaOH (1 × 60 mL), H$_2$O (2 × 60 mL), and brine (1 × 60 mL). The organic layer was dried (MgSO$_4$), filtered, and concentrated in vacuo. The resulting residue was taken up in THF (20 mL) and stirred with 10% aqueous HCl (20 mL) for 20 min to hydrolyzed the remaining triethyl orthoacetate. The organic layer was drawn off, washed with H$_2$O (2×), and brine (1×), and dried (MgSO$_4$). (Occasionally Et$_2$O and brine are added to aid the separation of phases.) The organic phase was filtered, concentrated, and fractionally distilled in vacuo to afford 16.7 g (59%) of **2** as a colorless oil with an *E*/*Z* ratio of 98/2: ^{1}H NMR (300 MHz) 5.52–5.38 (m, 2 H), 4.12 (q, J = 7.1, 2 H), 2.37–2.26 (m, 4 H), 1.63 (d, J = 5.3, 3 H), 1.24 (t, J = 7.1, 3 H); TLC R_f 0.46 (hexane/EtOAc, 8/1); GC t_R (*E*)-**2**, 9.00 min (98%); t_R (*Z*)-**2**, 9.15 min (2%) (HP-U2; 130 °C (5 min), 10 °C/min, 200 °C (10 min)).

(*E*)-4-Hexen-1-ol (3). A solution of ethyl 4-hexenoate (**2**) (16.0 g, 113 mmol) in diethyl ether (45 mL) was added to an ice-cold suspension of lithium aluminum hydride (4.27 g, 113 mmol, 1.00 equiv) in diethyl ether (200 mL) over 45 min. After stirring for 2 h at 0 °C, the reaction was quenched by careful addition of ethyl acetate (10.2 mL). The lithium salts were precipitated out by sequential addition of H$_2$O (4.3 mL), NaOH (6 N, 4.3 mL), and H$_2$O (12.8 mL). The white salts were filtered out, and the resulting solution was dried (MgSO$_4$) and concentrated in vacuo. The resulting slightly yellow oil was fractionally distilled in vacuo to afford 9.38 g (83%) of **3** as a colorless oil: ^{1}H NMR (300 MHz) 5.50–5.39 (m, 2 H), 3.63 (t, J = 6.5, 2 H), 2.09–2.03 (m, 2 H), 1.69–1.55 (m, 6 H); IR (CHCl$_3$) 3600 (m, sh), 3400 (w), 2900 (s). TLC R_f 0.48 (hexane/EtOAc, 1/1).

(47) See for example Hanack, M. *Conformation Theory*; Academic Press: New York, 1965; pp 152–157.

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(*E*)-6-(Phenylmethoxy)-2-hexene ((*E*)-4). In a flame-dried, three-necked, 250 mL, round-bottomed flask fitted with a N_2 inlet, rubber septum, and magnetic stir bar was placed 1.1 g (47.2 mmol, 1.1 equiv) of oil-free sodium hydride. The sodium hydride was suspended in 50 mL of dry THF and then a solution of (*E*)-4-hexene-1-ol (4.3 g, 42.9 mmol) in 10 mL of THF was added. The mixture was stirred at rt for 7 h, at which time the white, foamy suspension was treated with tetrabutylammonium iodide (887 mg, 2.4 mmol, 0.05 equiv) and benzyl bromide (5.1 mL, 42.9 mmol, 1.0 equiv). After stirring for an additional 2.2 h, the mixture was partitioned between EtOAc (150 mL) and saturated aqueous NH_4Cl solution (150 mL). The organic layer was drawn off, and the aqueous layer was washed with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (1 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by silica gel column chromatography (hexane/EtOAc, 30/1) and bulb-to-bulb distillation to yield 7.6 g (93%) of (*E*)-**4** as a clear colorless oil: bp 91–92 °C (0.2 Torr/air bath); ^{1}H NMR (300 MHz) 7.37–7.28 (m, 5 H), 5.57–5.43 (m, 2 H), 4.52 (s, 2 H), 3.49 (t, J = 6.6, 2 H), 2.13–2.06 (m, 2 H), 1.74–1.65 (m, 5 H); ^{13}C NMR (75.5 MHz) 138.61, 130.67, 128.28, 127.58, 127.42, 125.18, 72.81, 69.77, 29.55, 29.11, 17.90; IR (neat) 3088 (w), 3063 (w), 3029 (m), 2936 (s), 2855 (s); MS (10 eV) 190 (M^+, 24), 99 (100); TLC R_f 0.27 (hexane/EtOAc, 12/1). Anal. Calcd for $C_{13}H_{18}O$ (190.28): C, 82.06; H, 9.53. Found: C, 82.08; H, 9.52.

2,6-Dimethyl-6-(phenylmethoxy)-2-heptene (5). Following the procedure for (*E*)-**4**: from 8.9 g (63.1 mmol) of 1,1,5-trimethyl-4-hexen-1-ol, 2.8 g (117.0 mmol) of sodium hydride, 8.3 mL (69.8 mmol) of benzyl bromide, and 1.32 g (3.57 mmol) of tetrabutylammonium iodide was obtained 10.0 g (68%) of **5** after distillation as a clear colorless oil: bp 180–200 °C (0.7 Torr/air bath); ^{1}H NMR (300 MHz) 7.43–7.30 (m, 5 H), 5.20 (tt, J = 7.1, J = 1.1, 1 H), 4.48 (s, 2 H), 2.19–2.11 (m, 2 H), 1.75 (br s, 3 H), 1.68 (br s, 3 H), 1.67–1.62 (m, 2 H), 1.32 (s, 6 H); ^{13}C NMR (75.5 MHz) 139.92, 131.30, 128.31, 127.34, 127.10, 124.74, 75.09, 63.65, 40.32, 25.81, 22.73, 17.67; IR (neat) 3065 (m), 3031 (m), 2971 (s), 2919 (s); MS (70 eV) 149 (1), 91 (100); TLC R_f 0.53 (hexane/EtOAc, 16/1). Anal. Calcd for $C_{16}H_{24}O$ (232.37): C, 82.70; H, 10.41. Found: C, 82.38; H, 10.25.

***rel*-(1*R*,2*R*)-1-Methyl-2-(3-phenylmethoxypropyl)-oxirane (6).** A reference sample of this epoxide was prepared by both catalytic Oxone oxidation (see General Procedure below) or MCPBA oxidation (98% yield). The following data was obtained from a sample of **6** from catalytic oxidation after purification by silica gel chromatography and distillation: **6** is a clear colorless oil, by 135 °C (0.2 Torr/air bath); ^{1}H NMR (300 MHz) 7.37–7.25 (m, 5 H), 4.51 (s, 2 H), 3.57–3.45 (m, 2 H), 2.78–2.72 (dq, J_q = 5.2, J_d = 2.2, 1 H), 2.68–2.63 (m, 1 H), 1.85–1.31 (m, 4 H), 1.28 (d, J = 5.2, 3 H); ^{13}C NMR (75.5 MHz) 138.50, 128.37, 127.63, 127.56, 72.90, 69.77, 59.44, 54.59, 28.84, 26.25, 17.68; IR (neat) 3031 (w), 2928 (m), 2859 (s); MS (10 eV) 188 (20), 187 (36), 71 (100); TLC R_f 0.40 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{13}H_{18}O_2$ (206.28): C, 75.69; H, 8.79. Found: C, 75.61; H, 8.83.

2,2-Dimethyl-1-[3-(phenylmethoxy)-3-methylbutyl]-oxirane (7). A reference sample of this epoxide was obtained by MCPBA oxidation of **5**. Olefin **5** (2.0 g, 8.60 mmol) was added neat to a 0 °C solution of *m*-chloroperoxybenzoic acid (1.94 g, 11.3 mmol) in 25 mL of CH_2Cl_2. The ice bath was removed after 10 min, and the mixture was allowed to stir for 6 h. The solution was then partitioned between 100 mL each of 10% $Na_2S_2O_3$ and CH_2Cl_2. The aqueous phase was separated and washed with 100 mL of CH_2Cl_2. The organic extracts were combined and washed with 1 M aqueous Na_2CO_3 solution followed by brine and then dried over $MgSO_4$ and concentrated. Distillation of the residue afforded 1.85 g (87%) of **7** as a colorless oil: bp 200 °C (0.7 Torr/air bath); ^{1}H NMR (300 MHz) 7.36–7.25 (m, 5 H), 4.43 (s, 2 H), 2.75 (t, J = 5.9, 1 H), 1.79–1.62 (m, 4 H), 1.31 (s, 3 H), 1.28 (s, 9 H); ^{13}C NMR (75.5 MHz) 139.66, 128.28, 127.27, 127.14, 74.71, 64.62, 63.68, 58.47, 37.00, 25.75, 25.51, 24.93, 23.64, 18.69; IR (neat) 3031 (m), 2973 (s), 1453 (s); MS (70 eV) 163 (1), 91 (100); TLC R_f 0.23 (hexane/EtOAc, 8/1). Anal. Calcd for $C_{16}H_{24}O_2$ (248.37): C, 77.38; H, 9.74. Found: C, 77.10; H, 9.63.

Preparation of 4-Piperidinones. Representative Procedure I. *N*-Dodecyl-*N*,*N*-bis[2-(methoxycarbonyl)ethyl]-amine (9d). The general procedure of McElvain and Rorig was followed for the preparation of **9b** through **9f**.[34] The preparation of **9d** is representative. To a stirred, cold (0 °C) solution of dodecylamine (9.27 g, 50.0 mmol) in methanol (7 mL) in a 50 mL round bottom flask (under a N_2 atmosphere) was added methyl acrylate (9.91 mL, 110 mmol, 2.20 equiv) in one portion. The reaction mixture was allowed to warm to room temperature and was stirred for 24 h. The methanol and excess methyl acrylate were removed on a rotary evaporator, and the residue was passed through a pad of silica (hexanes/EtOAc, 2/1) to afford 17.5 g (98%) of **9d** as a clear, colorless oil: bp 250 °C (0.2 Torr/air bath); ^{1}H NMR (400 MHz) 3.66 (s, 6 H), 2.75 (t, J = 7.0, 4 H), 2.43 (t, J = 7.1, 4 H), 2.38 (t, J = 7.2, 2 H), 1.41–1.36 (m, 2 H), 1.25 (m, 18 H), 0.87 (t, J = 6.7, 3 H); ^{13}C NMR (100.6 MHz) 172.92, 53.62, 51.34, 49.05, 32.33, 31.75, 29.51, 29.48, 29.41, 29.19, 27.18, 26.93, 25.53, 13.95; IR (neat) 2924 (s), 2853 (s), 1740 (s); TLC R_f 0.30 (hexane/EtOAc, 1/1).

Representative Procedure II. 3-Carbomethoxy-1-dodecyl-4-piperidinone (10d). The general procedure of McElvain and Rorig[34] was followed for the preparation of **10b** through **10f**. The preparation of **10d** is representative. In a flame-dried, three-necked, round-bottomed flask fitted with a reflux condenser topped with a N_2-inlet and septa containing a suspension of oil-free NaH (2.6 g, 107.0 mmol, 2.2 equiv) in benzene (75 mL) was added the diester **9d** (17.0 g, 47.5 mmol). The reaction was initiated with 200 μL of MeOH and warmed to reflux. After 4 h the reaction mixture was quenched by the addition of glacial acetic acid (6.1 mL) and then H_2O (5.9 mL). The resulting mixture was passed through a pad of Celite, dried over K_2CO_3, and concentrated under reduced pressure. The resulting residue was divided into two equal portions and passed through a pad of silica gel (hexane/EtOAc) to afford a slightly yellow oil. This was further purified by silica gel column chromatography (hexane/EtOAc 3/1) to yield 12.9 g (83%) of keto ester **10d** as a clear, colorless oil which solidified in the freezer: ^{1}H NMR (400 MHz) enol form; 11.92 (s, 1 H), 3.75 (s, 3 H), 3.14 (s, 2 H), 2.62–2.56 (m, 2 H), 2.45–2.44 (m, 4 H), 1.53–1.50 (m, 2 H), 1.28–1.25 (m, 18 H), 0.87 (dd, J = 7.1, J = 6.6, 3 H), keto form; 3.77 (s, 3 H), 3.51–3.45 (m, 1 H); ^{13}C NMR (100.6 MHz) enol form; 170.20, 169.15, 96.50, 54.96, 53.28, 52.08, 29.49, 27.20, keto form; 204.00, 171.20, 57.90, 56.94, 56.20, 51.20, 49.63, 49.21, 40.57, 31.76, 29.51, 29.47, 29.44, 29.35, 29.62, 29.20, 27.37, 27.13, 22.53, 13.98; IR (neat) 2915 (s), 2855 (s), 2811 (s), 1750 (m), 1725 (m), 1667 (s), 1626 (s); MS (70 eV) 325 (M^+, 2), 170 (100); TLC R_f 0.30 (hexane/EtOAc, 1/1). Anal. Calcd for $C_{19}H_{35}NO_3$ (325.50): C, 70.11; H, 10.84; N, 4.30. Found: C, 70.06; H, 10.86; N, 4.32.

Representative Procedure III. 1-Dodecyl-4-piperidinone (11d). The general procedure of McElvain and Rorig[34] was followed for the preparation of **11b** through **11f**. The preparation of piperidinone **11d** is representative. A 250-mL, round-bottomed flask was equipped with a magnetic stir bar, N_2 gas inlet adapter and a reflux condenser and charged with 50 mL of 2.4 N aqueous HCl. The β-keto ester **10d** (12.0 g, 36.87 mmol) was added, whereupon a white solid formed. Upon heating to near reflux, the white solid dissolved to give a cloudy solution. The reaction was refluxed for 15 h. The solution was adjusted to pH 8 by addition of saturated aqueous $NaHCO_3$ solution which caused a white solid to precipitate out of solution. The aqueous layer was extracted with *tert*-butyl methyl ether (3 × 150 mL), and the combined organic layers were dried (K_2CO_3), filtered through a pad of Celite, and concentrated in vacuo. The residue was passed through a pad of silica using ethyl acetate as an elutant and kugelrohr distilled to afford 8.04 g (82%) of **11d** as a colorless oil which solidified upon cooling: bp 155 °C (0.2 Torr/air bath); ^{1}H NMR (300 MHz) 2.74 (m, 4 H), 2.46 (m, 6 H), 1.52 (m, 2 H), 1.29–1.19 (m, 18 H), 0.88 (t, J = 6.6, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) 209.23, 57.48, 53.01, 41.10, 31.77, 29.51, 29.49, 29.47, 29.44, 29.40, 29.21, 27.37, 27.33, 22.54, 13.99; IR (neat) 2926 (s), 2853 (s), 2807 (m), 1723 (s); MS (70 eV) 267 (M^+, 1), 112

(100), 91 (11); TLC R_f 0.38 (EtOAc/hexane, 3/1). Anal. Calcd for $C_{17}H_{33}NO$ (267.46): C, 76.34; H, 12.44; N, 5.24. Found: C, 76.35; H, 12.49; N, 5.19.

1,1-Dimethyl-4-oxopiperidinium Nitrate Monohydrate ($8a^+NO_3^-$). A solution of silver nitrate (6.62 g, 39.0 mmol) in 50 mL of H_2O was cooled to 5 °C, and then 9.54 g (37.4 mmol) of 4-oxo-1,1-dimethylpiperidinium iodide[50] was added portionwise over 5 min. The precipitation of silver iodide was seen immediately. After warming to 20 °C over 1 h, the solution was filtered through a plug of Celite and evaporated at low temperature until the product began to crystallize. The precipitate was collected by filtration and was then washed with a small portion of cold methanol to afford 5.75 g (81%) of $8a^+NO_3^-$ in analytically pure form. Further recrystallization from methanol resulted in extensive decomposition: mp 200 °C dec; ^{1}H NMR (D_2O, 300 MHz) 3.39 (t, J = 5.7, 4 H); 3.07 (s, 6 H); 2.02 (br t, J = 5.0, 4 H); ^{13}C NMR (D_2O, 75.5 MHz) 89.8, 60.5, 32.3; IR (KBr) 3347 (s), 3139 (s), 1750 (w); MS (70 eV) 127 (6), 82 (5), 58 (100). Anal. Calcd for $C_7H_{16}N_2O_5$ (208.22): C, 40.38; H, 7.75; N, 13.45. Found: C, 40.41; H, 7.83; N, 13.21.

Preparation of 4-Oxopiperidinium Triflates. Representative Procedure IV. 1-Dodecyl-1-methyl-4-oxopiperidinium Trifluoromethanesulfonate ($8d^+OTf^-$). The following procedure for the preparation of $8d^+OTf^-$ is representative. A 100-mL, round bottom flask equipped with stir bar and septum was charged with 1-dodecyl-4-piperidone **11d** (4.00 g, 15.0 mmol) and placed under a nitrogen atmosphere. Methylene chloride (65 mL) was added via syringe, the solution was cooled to 0 °C, and then MeOTf (2.39 mL, 21.1 mmol, 1.41 equiv) was added neat in one portion via syringe. After 10 min, a white precipitate appeared which dissolved upon warming to room temperature. The reaction mixture was stirred at room temperature for 4 h. Volatiles were removed in vacuo to afford a white solid which was recrystallized (EtOAc/hexane, 2/1) to afford 6.22 g (96%) of $8d^+OTf^-$ as white plates: mp 168–169 °C; ^{1}H NMR (acetone-d_6, 400 MHz) 4.05 (t, J = 6.6, 4 H), 3.80 (m, 2 H), 3.51 (s, 3 H), 2.95–2.84 (m, 4 H), 2.01 (m, 2 H), 1.49–1.38 (m, 4 H), 1.28 (br s, 14 H), 0.87 (t, J = 6.8, 3 H); ^{13}C NMR (100.6 MHz, acetone-d_6) 199.81, 121.13 (q, J = 322), 63.17, 58.93, 47.46, 47.43, 34.78, 31.61, 29.34, 29.24, 29.12, 29.06, 28.83, 25.93, 22.31, 21.95, 13.37; IR (KBr) 2921 (s), 2851 (s), 1730 (s); MS (FAB) 282 (M^+, 57). Anal. Calcd for $C_{19}H_{36}F_3NO_4S$ (431.56): C, 52.88; H, 8.41; N, 3.25. Found: C, 52.92; H, 8.40; N, 3.28.

1-Hexyl-1-methyl-4-oxopiperidinium Trifluoromethanesulfonate ($8b^+OTf^-$). Following representative procedure IV, from 1.87 g (10.2 mmol) of **11b** and 2.37 g (14.4 mmol) of methyl trifluoromethanesulfonate was obtained 2.83 g (80% yield) of $8b^+OTf^-$ as white plates after recrystallization: mp 115–116 °C (hexane/EtOAc, 2/1); ^{1}H NMR (400 MHz) 3.90–3.80 (m, 4 H), 3.54–3.49 (m, 2 H), 3.30 (s, 3 H), 2.94–2.71 (m, 4 H), 1.83–1.75 (m, 2 H), 1.44–1.30 (m, 6 H), 0.90 (dd, J = 7.3, J = 6.8, 3 H); ^{13}C NMR (CD_3CN, 100.6 MHz) 200.15, 120.66 (q, J = 282.3), 63.05, 58.77, 47.73, 34.60, 30.73, 25.30, 21.93, 21.66, 13.10; IR (Nujol) 2967 (s), 2934 (s), 2896 (s), 2886 (s), 2841 (s), 1730 (m), 1458 (s); MS (FAB) 199 (M^+ + 1, 4), 198 (M^+, 24). Anal. Calcd for $C_{13}F_3H_{24}NO_4S$ (347.39): C, 44.95; H, 6.96; N, 4.03. Found: C, 44.89; H, 6.94; N, 4.03.

1-Methyl-1-nonyl-4-oxopiperidinium Trifluoromethanesulfonate ($8c^+OTf^-$). Following representative procedure IV, from 0.455 g (2.02 mmol) of **11c** and 0.479 g (2.92 mmol) of methyl trifluoromethanesulfonate was obtained 0.379 g (48% yield) of $8c^+OTf^-$ as white plates after recrystallization: mp 148–150 °C (hexane/EtOAc, 2/1); ^{1}H NMR (300 MHz) 3.93–3.80 (m, 4 H), 3.55–3.45 (m, 2 H), 3.31 (s, 3 H), 2.97–2.70 (m, 4 H), 1.93–1.85 (m, 2 H), 1.50–1.20 (m, 12 H), 0.88 (t, J = 6.6, 3 H); ^{13}C NMR (100.6 MHz) 200.34, 120.40 (q, J = 320), 64.15, 58.82, 47.2, 34.83, 31.64, 29.17, 28.98, 28.96, 25.95, 22.50, 22.25, 19.35; IR (CCl_4) 2959 (s), 1736 (s), 1616 (m); MS (FAB) 242 (M^+ + 2, 13), 241 (M^+ + 1, 8), 240 (M^+, 100). Anal. Calcd for $C_{16}H_{30}F_3NO_4S$ (389.47): C, 49.34; H, 7.76; N, 3.60. Found: C, 49.43; H, 8.01; N, 3.56.

1-Methyl-4-oxo-1-pentadecylpiperidinium Trifluoromethanesulfonate ($11e^+OTf^-$). Following representative procedure IV, from 0.197 g (0.636 mmol) of **11e** and 0.146 g (0.891 mmol) of methyl trifluoromethanesulfonate was obtained 0.205 g (68% yield) of $8e^+OTf^-$ as white plates after recrystallization: mp 163–166 °C (hexane/EtOAc, 2/1); ^{1}H NMR (300 MHz) 3.96–3.80 (m, 4 H), 3.57–3.44 (m, 2 H), 3.33 (s, 3 H), 2.98–2.70 (m, 4 H), 1.88–1.74 (m, 2 H), 1.42–1.20 (br m, 24 H), 0.88 (t, J = 6.7, 3 H); ^{13}C NMR (100.6 MHz) 199.97, 120.46 (q, J = 320), 64.31, 58.99, 47.49, 34.82, 31.72, 29.49, 29.47, 29.45, 29.41, 29.29, 29.18, 29.14, 28.91, 26.00, 22.46, 22.28, 13.83; IR (CCl_4) 2920 (s), 2851 (s), 1722 (m); MS (FAB) 327 (M^+ + 3, 10), 326 (M^+ + 2, 44), 325 (M^+ + 1, 27), 324 (M^+, 65). Anal. Calcd for $C_{22}H_{42}F_3NO_4S$ (473.63): C, 55.79; H, 8.94; N, 2.96. Found: C, 55.83; H, 8.96; N, 2.90.

1-Methyl-1-octadecyl-4-oxopiperidinium Trifluoromethanesulfonate ($8f^+OTf^-$). Following representative procedure IV, from 1.05 g (2.99 mmol) of **11f** and 0.78 g (4.78 mmol) of methyl trifluoromethanesulfonate was obtained 1.05 g (68% yield) of $8f^+OTf^-$ as a microcrystalline white solid after recrystallization: mp 179–181 °C (CH_2Cl_2); ^{1}H NMR (DMSO-d_6, 400 MHz) 3.70 (dd, J = 5.8, J = 5.6, 4 H), 3.47–3.43 (m, 2 H), 3.16 (s, 3 H), 2.73–2.62 (m, 4 H), 1.70 (m, 2 H), 1.29–1.22 (m, 30 H), 0.83 (dd, J = 6.8, J = 5.4, 3 H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) 202.06, 62.44, 58.41, 47.52, 35.16, 31.68, 29.45, 29.22, 29.12, 28.91, 26.10, 22.46, 21.83, 14.22; IR (Nujol) 2944 (s), 2930 (m), 2882 (s), 2843 (s), 1726 (w); MS (FAB) 368 (M^+ + 2, 14), 366 (M^+, 24). Anal. Calcd for $C_{25}H_{48}F_3NO_4S$ (515.71): C, 58.22; H, 9.38; N, 2.72. Found: C, 58.08; H, 9.33; N, 2.65.

1-Dodecyl-1-methyl-4-oxopiperidinium Iodide ($8d^+I^-$). Following representative procedure IV, from 2.0 g (7.48 mmol) of **11d** and 0.65 mL (10.5 mmol) of methyl iodide was obtained 2.8 g (92% yield) of $8d^+I^-$ as a colorless, flaky plate-like solid after recrystallization: mp 176–177 °C (CH_3CN/EtOAc); ^{1}H NMR (DMSO-d_6, 400 MHz) 3.71 (t, J = 6.3, 4 H), 3.50–3.45 (m, 2 H), 3.18 (s, 3 H), 2.73–2.63 (m, 4 H), 1.71–1.68 (m, 2 H), 1.29–1.23 (m, 18 H), 0.83 (dd, J = 7.1, J = 6.6, 3 H); ^{13}C NMR (DMSO-d_6, 125.8 MHz) 202.33, 62.63, 58.68, 48.01, 35.58, 31.88, 29.61, 29.54, 29.41, 29.31, 29.12, 26.31, 22.68, 22.13, 14.56; IR (Nujol) 2965 (s), 2940 (s), 2919 (s), 2841 (s), 1723 (m); MS (FAB) 282 (M^+, 27). Anal. Calcd for $C_{18}H_{36}INO$ (409.39): C, 52.81; H, 8.86; N, 3.42. Found: C, 52.88; H. 9.03; N, 3.32.

1,1-Dihexyl-4-oxopiperidinium Trifluoromethanesulfonate ($8g^+OTf^-$). An oven-dried, 25-mL, round bottom flask equipped with a magnetic stir bar and septum was charged with 1-hexyl-4-piperidinone (**11b**) (141 mg, 0.77 mmol), placed under an nitrogen atmosphere, and then methylene chloride (2.5 mL) was added via syringe. The flask was cooled to 0 °C, and then a solution of n-hexyl triflate[35] (250 mg, 1.12 mmol) in methylene chloride (2.5 mL) was added via syringe. After 1.25 h the ice bath was removed, and the mixture was stirred for an additional 6 h. Volatiles were removed in vacuo, and the resultant off-white solid was recrystallized (EtOAc/hexane, 1/1) to afford 0.213 g (66%) of $8g^+OTf^-$ as white plates: mp 152–155 °C; ^{1}H NMR (300 MHz) 3.85 (t, J = 6.4, 4 H), 3.55–3.40 (m, 4 H), 2.82 (t, J = 6.3, 4 H), 1.80–1.62 (m, 4H), 1.52–1.26 (m, 12 H), 0.90 (t, J = 6.8, 6 H); ^{13}C NMR (100.6 MHz) 200.37, 120.64 (J = 321), 58.87, 57.31, 34.75, 31.08, 25.75, 22.29, 21.98, 13.74; IR (CCl_4) 2961 (m), 2928 (m), 1732 (s); MS (FAB) 270 (M^+ + 2, 26), 269 (M^+ + 1, 16), 268 (M^+, 83). Anal. Calcd for $C_{18}H_{34}F_3NO_4S$ (417.53): C, 51.78; H, 8.21; N, 3.35. Found: C, 51.70; H, 8.23; N, 3.35.

***n*-Dodecyl Trifluoromethanesulfonate.** A 100-mL, round bottom flask equipped with a magnetic stir bar and septum was charged with silver triflate (2.10 g 8.17 mmol) and placed under a nitrogen atmosphere. Benzene (50 mL) was added via syringe and the solution was stirred until the silver triflate had dissolved, whereupon neat dodecyl iodide (1.50 mL, 6.08 mmol) was added via syringe. The flask was covered with aluminum foil, and then the reaction mixture was stirred at room temperature for 23 h. The resultant mixture was filtered to remove a pale yellow precipitate, washed with water (2 × 25 mL), and dried over Na_2SO_4, and volatiles were removed on a vacuum line to afford 1.58 g (82%) of n-dodecyl triflate which had the following spectral properties: ^{1}H NMR (300

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MHz) 4.54 (t, J = 6.5, 2 H, $H_2C(1)$), 1.82 (tt, J = 7.6, 7.4, 2 H), 1.44–1.35 (m, 2 H), 1.26 (bs, 16 H), 0.88 (t, J = 6.4, 3 H).

1-Dodecyl-1-methyl-4-oxopiperidinium Trifluoromethanesulfonate (8d$^+$OTf$^-$). An oven-dried, 25-mL, round bottom flask equipped with a magnetic stir bar and septum was charged with 1-methyl-4-piperidinone (0.226, 2.0 mmol) and then placed under a nitrogen atmosphere. Methylene chloride (10.0 mL) was added via syringe and the flask was cooled to 0 °C, and then neat *n*-dodecyl triflate (0.866 g, 2.70 mmol) was added via syringe. After 2 h the ice bath was removed and the reaction was stirred for an additional 3.5 h. Volatiles were removed in vacuo, and the resultant off-white solid was recrystallized (EtOAc/hexane, 1/1) to afford 0.493 g (57%) of 8d$^+$OTf$^-$ as white plates: ^{1}H NMR (300 MHz) 3.83 (m, 4 H), 3.47 (m, 2 H), 3.28 (s, 3 H), 2.93–2.66 (m, 4 H), 1.76 (m, 2 H), 1.33 (m, 4 H), 1.25 (br s, 14 H), 0.87 (t, J = 6.6, 3 H). Anal. Calcd for $C_{19}H_{36}NO_4SF_3$ (431.56): C, 52.88; H, 8.41; N, 3.25. Found: C, 52.78; H, 8.39; N, 3.25.

1-Dodecyl-1-methyl-4-oxopiperidinium Tetrafluoroborate Monohydrate (8d$^+$BF$_4^-$·H$_2$O). All three salts were obtained from 8d$^+$I$^-$ by silver salt precipitation. The preparation of 8d$^+$BF$_4^-$ is representative. To an oven-dried, two-necked, round-bottomed flask fitted with a N_2-inlet and septum was placed a solution of 8d$^+$I$^-$ (0.35 g, 0.87 mmol) in 8 mL of CH_3CN/H_2O (1/1). Silver tetrafluoroborate (0.17 g, 0.88 mmol) was added at room temperature portionwise over 2 min. The precipitation of silver iodide was observed immediately. After 3 h the resulting yellow/green slurry was filtered through a plug of Celite and concentrated under reduced pressure until the crystalline product began to precipitate. The solid was collected by filtration, washed with a small portion of cold water, and then recrystallized to afford 0.25 g (79%) of 8d$^+$BF$_4^-$ as a flaky white solid: mp 162–163 °C (CH_3CN/EtOAc); ^{1}H NMR (DMSO-d_6, 500 MHz) keto form 3.67 (m, 4 H), 3.42–3.41 (m, 2 H), 2.96 (s, 3 H), 2.66–2.64 (m, 4 H), 1.83–1.82 (m, 2 H), 1.21 (m, 18 H), 1.05–0.82 (m, 3 H); hydrate 5.97 (s, 1 H), 5.92 (s, 1 H), 3.31–3.28 (m, 4 H), 3.19–3.14 (m, 4 H), 1.68–1.61 (m, 2 H); ^{13}C NMR (DMSO-d_6, 125.8 MHz) keto form 202.29, 62.72, 58.79, 47.80, 35.38, 31.88, 29.60, 29.52, 29.40, 29.30, 29.09, 26.33, 22.67, 22.04, 14.49; hydrate 89.66, 58.67, 33.21, 21.85; IR (Nujol) 3366 (br), 2944 (s), 2926 (s), 2842 (s), 1728 (w), 1458 (s); MS (FAB) 284 (M$^+$ + 2, 10), 282 (M$^+$, 23). Anal. Calcd for $C_{18}H_{38}BF_4NO_2$ (387.30): C, 55.82; H, 9.89; N, 3.62. Found: C, 55.94; H, 9.99; N, 3.53.

1-Dodecyl-1-methyl-4-oxopiperidinium Nitrate Monohydrate (8d$^+$NO$_3^-$). Following the procedure for 8d$^+$BF$_4^-$, from 0.24 g (0.58 mmol) of 8d$^+$I$^-$ and 0.98 g (0.58 mmol) of silver nitrate was obtained 0.15 g (73% yield) of 8d$^+$NO$_3^-$ as a white solid after recrystallization: mp 124–125 °C (CH_3CN/EtOAc); ^{1}H NMR (DMSO-d_6, 500 MHz) keto form 3.68 (m, 4 H), 3.44–3.39 (m, 2 H), 2.97 (s, 3 H), 2.66–2.65 (m, 4 H), 1.83 (m, 2 H), 1.21 (m, 18 H), 0.82 (m, 3 H); hydrate 5.97 (s, 1 H,), 5.93 (s, 1 H), 3.36–3.22 (m, 4 H), 3.18–3.15 (m, 4 H), 1.68–1.60 (m, 2 H); ^{13}C NMR (DMSO-d_6, 125.8 MHz) keto form 202.39, 62.67, 58.78, 47.80, 35.42, 31.87, 29.59, 29.51, 29.40, 29.32, 29.13, 29.10, 26.36, 22.67, 14.52; hydrate 89.67, 58.67, 33.22, 29.29, 29.25, 21.86; IR (Nujol) 2915 (s), 1715 (s), 1468 (s); MS (FAB) 283 (M$^+$ + 1, 10), 282 (M$^+$, 41). Anal. Calcd for $C_{18}H_{38}N_2O_5$ (362.50): C, 59.64; H, 10.57; N, 7.73. Found: C, 59.81; H, 10.34; N, 7.78.

1-Dodecyl-1-methyl-4-oxopiperidinium Perchlorate (8d$^+$ClO$_4^-$). Following the procedure for 8d$^+$BF$_4^-$, from 0.10 g (0.25 mmol) of 8d$^+$I$^-$ and 0.51 g (0.25 mmol) of silver perchlorate was obtained 0.66 g (70% yield) of 8d$^+$ClO$_4^-$ as a microcrystalline white solid after recrystallization: mp 138–139 °C (CH_3CN/EtOAc); ^{1}H NMR (DMSO-d_6, 500 MHz) 3.69 (dd, J = 6.6, J = 6.3, 4 H), 3.46–3.42 (m, 2 H), 3.16 (s, 3 H), 2.70–2.65 (m, 4 H), 1.71–1.68 (m, 2 H), 1.29–1.23 (m, 18 H), 0.84 (dd, J = 6.8, J = 6.6, 3 H); ^{13}C NMR (DMSO-d_6, 125.8 MHz) 202.41, 62.65, 58.66, 47.88, 35.43, 31.86, 29.58, 29.50, 29.37, 29.28, 29.09, 26.33, 22.67, 22.04, 14.54; IR (Nujol) 2955 (s), 2940 (s), 2888 (s), 2844 (s), 1723 (w), 1460 (s); MS (FAB) 282 (M$^+$, 20). Anal. Calcd for $C_{18}H_{36}ClNO_5$ (381.94): C, 56.60; H, 9.50; N, 3.67. Found: C, 56.45; H, 9.61; N, 3.53.

1-(Diphenylmethyl)-1-methyl-3-oxoazetidinium Trifluoromethanesulfonate (12$^+$OTf$^-$). A solution of azetidinone **16** (0.98 g, 4.14 mmol) in 5 mL of CH_2Cl_2 was cooled to 0 °C, and methyl trifluoromethanesulfonate (1.00 mL, 8.84 mmol) was added slowly *via* syringe. Upon slow warming to 20 °C and stirring overnight, a white precipitate formed, which was collected by filtration and recrystallized from ethyl acetate to give 1.63 g (98%) of pure salt 12$^+$OTf$^-$: mp 154–156 °C (EtOAc); ^{1}H NMR (acetone-d_6, 300 MHz) 7.91–7.88 (m, 4 H), 7.57–7.50 (m, 6 H), 6.67 (s, 1 H), 6.05 (d, J = 19.0 Hz, 2 H), 5.63 (d, J = 19.0 Hz, 2 H), 3.80 (s, 3 H); ^{13}C NMR (acetone-d_6, 75.5 MHz) 186.7, 132.6, 130.4, 130.3, 129.7, 86.4, 78.9, 50.8; IR (KBr) 3017, 1838; MS (70 eV) 335 (2), 334 (5), 333 (3), 167 (100), 165 (45). Anal. Calcd for $C_{18}H_{18}F_3NO_4S$ (401.40): C, 53.86; H, 4.52; N, 3.49; F, 14.20; S, 7.99. Found: C, 53.82; H, 4.63; N, 3.46; F, 14.13; S, 7.95.

1-Dodecyl-1-methyl-3-oxopyrrolidinium Trifluoromethanesulfonate (13$^+$OTf$^-$). Following representative procedure IV, from 0.21 g (0.84 mmol of **20** and 0.10 mL (0.9 mmol) of methyl trifluoromethanesulfonate was obtained 0.28 g (80%) of 13$^+$OTf$^-$ as a white solid after recrystallization: mp 172–174 °C (EtOAc/hexane); ^{1}H NMR (500 MHz) 4.18–4.02 (m, 4 H), 3.58–3.47 (m, 2 H), 3.26 (s, 3 H), 3.06–2.98 (m, 1 H), 2.94–2.87 (m, 1 H), 1.84–1.69 (m, 2 H), 1.40–1.30 (m, 2 H), 1.28–1.21 (m, 16 H), 0.88 (t, J = 6.8, 3 H); ^{13}C NMR (125.8 MHz) 203.44, 120.54 (q, J = 320.0), 68.15, 66.28, 61.69, 50.06, 34.15, 32.04, 29.73, 29.59, 29.48, 29.18, 26.21, 23.53, 22.82, 14.27; IR ($CHCl_3$) 2953 (s), 2929 (s), 1775 (m); MS (FAB) 271 (M$^+$ + 3, 20), 270 (M$^+$ + 2, 46), 269 (M$^+$ + 1, 35), 268 (M$^+$, 71). Anal. Calcd for $C_{18}H_{34}F_3NO_4S$ (417.53): C, 51.78; H, 8.21; N, 3.35. Found: C, 51.48; H, 8.27; N, 3.56.

1-Dodecyl-1-methyl-3-oxopiperidinium Trifluoromethanesulfonate (14$^+$OTf$^-$). Following representative procedure IV, from 0.50 g (12.9 mmol) of **23** and 0.32 mL (2.8 mmol) of methyl trifluoromethanesulfonate was obtained 0.62 g (77%) of 14$^+$OTf$^-$ as a white plate-like solid after recrystallization: mp 156–158 °C (EtOAc/hexane); ^{1}H NMR (500 MHz) 4.17 (d, J = 14.5, 1 H), 4.03 (d, J = 14.5, 1 H), 3.97–3.90 (m, 2 H), 3.38–3.34 (m, 2 H), 3.19 (s, 3 H), 2.80–2.76 (m, 2 H), 2.34–2.32 (m, 1 H), 2.26–2.25 (m, 1 H), 1.75–1.70 (m, 2 H), 1.35–1.28 (m, 2 H), 1.26 (s, 16 H), 0.88 (t, J = 6.8, 3 H); ^{13}C NMR (125.8 MHz) 198.82, 120.61 (q, J = 320), 68.59, 64.93, 58.52, 49.43, 36.38, 31.99, 29.69, 29.54, 29.43, 29.13, 26.11, 22.77, 22.15, 18.70, 14.21; IR ($CHCl_3$) 2928 (m), 1774 (s), 1469 (s); MS (FAB) 284 (M$^+$ + 2, 15), 283 (M$^+$ + 1, 21), 282 (M$^+$, 80). Anal. Calcd for $C_{19}H_{36}F_3NO_4S$ (431.56): C, 52.88; H, 8.41; N, 3.25. Found: C, 53.02; H, 8.50; N, 3.19.

***N,N*-Dimethyl-*N*-dodecyl-*N*-(4-oxocyclohexyl)ammonium Trifluoromethanesulfonate (24$^+$OTf).** To a solution of 4-(dimethylamino)cyclohexanone (120 mg, 0.85 mmol) in 20 mL of Et_2O at −20 °C was added a solution of dodecyl triflate (380 mg, 1.19 mmol) dissolved in 1 mL of Et_2O. The resulting solution was allowed to slowly warm to room temperature. Volatile materials were removed in vacuo, and the resulting paste was triturated with hexane (6 × 40 mL). The residue was dried in vacuo to afford 216 mg (55%) of 24$^+$OTf$^-$ as a white, waxy solid: ^{1}H NMR (300 MHz) 4.23 (m, 1 H), 3.35 (m, 2 H), 3.17 (s, 6 H), 2.67 (m, 2 H)), 2.50 (m, 4 H), 2.06 (m, 2 H), 1.81 (m, 2 H), 1.36 (s, 2 H), 1.25 (s, 16 H), 0.88 (t, J = 6.7, 3 H); ^{13}C NMR (125.8 MHz) 206.71, 120.48 (q, J = 319.6), 69.00, 63.48, 48.53, 37.92, 31.73, 29.43, 29.29, 29.24, 29.16, 28.88, 26.12, 24.59, 22.52, 22.31, 13.96; IR ($CDCl_3$) 2956 (s), 2928 (vs), 2856 (s), 1723 (s), 1486 (m); MS (FAB) 312 (M$^+$ + 2, 24), 311 (M$^+$ + 1, 25), 310 (M$^+$, 100), 214 (35), 212 (15). Anal. Calcd for $C_{21}H_{40}F_3NO_4S$ (459.61): C, 54.88; H, 8.77; N, 3.05. Found: C, 54.41; H, 8.94; N, 3.21.

(1*S*)-*N,N*-Dimethyl-*N*-dodecyl-*N*-(7,7-dimethyl-2-oxobicyclo[2.2.1]heptyl)ammonium Tetrafluoroborate (25$^+$BF$_4^-$). A flame-dried, 25-mL, round-bottomed flask equipped with a magnetic stir bar and septum was charged with trimethyloxonium tetrafluoroborate (0.28 g, 1.9 mmol, 2.4 equiv) and placed under a nitrogen atmosphere, and then methylene chloride (2.0 mL) was added via syringe. The flask was cooled to 0 °C, and then a solution of amino ketone **29** (0.25 g, 0.78 mmol, 1.0 equiv) in methylene chloride (1.0 mL) was added via syringe. To the resulting off-white slurry was added 2,6-di-*tert*-butylpyridine (0.18 mL, 0.82 mmol, 1.05 equiv) via syringe, and the mixture was allowed to warm to

room temperature and was stirred for 13 h. The volatiles were removed in vacuo and the resultant off-white solid was taken up in MeOH (10.0 mL) and water (10.0 mL) which contained Na_2CO_3 (0.30 g, 2.8 mmol). The solution was stirred at room temperature for 15 min at which point the layers were extracted with hexane (20 mL). The aqueous layer was concentrated in vacuo and subsequently triturated with methylene chloride (200 mL). The organic layer was filtered through a pad of acid-washed Celite and concentrated in vacuo. The resulting white solid was purified via recrystallization (EtOAc/hexane, 2/1) to afford 0.90 g (26%) of **25**$^+BF_4^-$ as white plates: mp 119–120 °C; ^{1}H NMR (500 MHz) 3.70–3.65 (m, 1 H), 3.41–3.40 (m, 1 H), 3.27 (s, 3 H), 3.26 (s, 3 H), 2.94–2.89 (m, 1 H), 2.72–2.66 (m, 1 H), 2.33–2.27 (m, 1 H), 2.18 (d, J = 19.3, 1 H), 2.08 (t, J = 4.7, 1 H), 2.05–1.99 (m, 1 H), 1.84–1.78 (m, 2 H), 1.60–1.54 (m, 1 H), 1.5 (s, 3 H), 1.39 (s, 3 H), 1.35–1.28 (m, 2 H), 1.26 (s, 16 H), 0.88 (t, J = 6.8, 3 H); ^{13}C NMR (125.8 MHz) 208.21, 89.23, 63.16, 49.76, 48.27, 48.09, 44.82, 42.57, 32.02, 29.74, 29.64, 29.56, 29.46, 29.33, 26.30, 25.37, 24.42, 23.72, 23.43, 22.80, 22.64, 14.26; IR ($CHCl_3$) 2959 (m), 2928 (s), 1753 (m); MS (FAB) 352 (M^+ + 2, 14), 351 (M^+ + 1, 39), 350 (M^+, 100). Anal. Calcd for $C_{23}H_{44}BF_4NO$ (437.41): C, 63.16; H, 10.14; N, 3.20. Found: C, 62.93; H, 10.14; N, 3.30.

General Procedure for Oxone Epoxidations. Apparatus. A three neck, 250-mL, round bottom flask is fitted with a Brinkman Heidolph overhead stirrer (Model No. 2050) with a glass stirring shaft. The stir shaft is fitted with a Teflon stir paddle (dimensions 40 mm length × 18 mm height × 3 mm width, elliptical shaped). A glass pH probe/electrode (Broadley-James Model No. C1207A-121-A03BC), connected to a Brinkman pH stat (Brinkman Models: E512 pH meter, Impulsomat No. 473, and Dosimat No. E412) is inserted into the flask through one of the side necks of the flask and clamped such that the bottom of the probe is approximately 0.5–1.0 cm from the bottom/side of the flask. The third neck of the flask is equipped with two separate Teflon tubes; one delivers potassium hydroxide solution (2 N) as required and is controlled by the pH stat. The other Teflon tube delivers an Oxone water solution which is controlled via a syringe pump (Sage Instruments Model 355). Metal needles or ferrules cannot be used with Oxone, hence a teflon ferrule, which is equipped with teflon tubing, is attached directly to the glass syringe which delivers the Oxone solution.

Preparation of Oxone Solutions. The Oxone stock solution was prepared as a ca. 0.45 M, 1 L aqueous solution stabilized by 0.43 mM EDTA·2Na and titrated by the standard iodometric method. The concentration of a 0.45 M Oxone solution drops ca. 11% over 9 weeks when stored at ambient temperature.

Procedure. The following represents the general method used for Oxone related epoxidations. Into a 250-mL, three-neck, round bottom flask were placed phosphate buffer (23 mL, pH 7.8), methylene chloride (20 mL), olefin (2.00 mmol), and catalyst **8d**$^+$OTf$^-$ (0.20 mmol, 0.1 equiv). The reaction flask was then attached to the Brinkman overhead stirrer and connected to the pH stat. The solution was then cooled to 0 °C via ice bath and addition of an aqueous (0.472 M) Oxone solution (42.5 mL, 20.0 mmol, 10.0 equiv) was achieved via syringe pump over an 8 h period. The pH of the reaction was maintained at 8.0 (±0.1) by automatic addition of 2 N aqueous KOH. The solution was stirred at approximately 800–1000 rpm via the overhead stirrer, and the solution was kept at 0 °C for 24 h. The progress of the reaction was monitored at ca. 2–4 h intervals by shutting off the stirrer and removing approximately 0.1 mL of the organic layer and analyzing the aliquots by GC. After 24 h the organic layer was drawn off. The aqueous layer was treated with 60 mL of brine and then it was extracted with methylene chloride (4 × 75 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting product mixture was purified by silica gel column chromatography and/or distillation.

***rel*-(1*R*,2*R*)-1-Methyl-2-[3-(phenylmethoxy)propyl]-oxirane (5).** From 0.381 g (2.0 mmol) of (*E*)-**4**, 0.086 g (0.20 mmol) of catalyst **8d**$^+$OTf$^-$, and 42.9 mL (20.0 mmol) of Oxone was obtained 0.374 g (91% yield) of **5** as a colorless oil after silica gel chromatography (hexane/EtOAc, 8/1): ^{1}H NMR (300 MHz) 7.37–7.25 (m, 5 H), 4.51 (s, 2 H), 3.55-3.45 (m, 2 H), 2.78–2.72 (dq, J_d = 5.2, J_q = 2.2, 1 H), 2.68–2.63 (m, 1 H), 1.82–1.31 (m, 4 H), 1.28 (d, J = 5.2, 3 H); GC: t_R (**5**), 6.87 min (column HP/U2, 250 °C isothermal). Anal. Calcd for $C_{13}H_{18}O_2$ (206.30): C, 75.69; H, 8.80. Found: C, 75.59; H, 8.78.

2,2-Dimethyl-1-[3-(phenylmethoxy)-3-methylbutyl]-oxirane (7). From 0.464 g (2.0 mmol) of **5**, 0.086 g (0.20 mmol) of catalyst **8d**$^+$OTf$^-$, and 42.9 mL (20.0 mmol) of Oxone solution was obtained 0.448 g (90% yield) of **7** as a colorless oil after silica gel chromatography (hexane/EtOAc, 5/1): ^{1}H NMR (300 MHz) 7.33–7.24 (m, 5 H), 4.43 (s, 2 H), 2.74 (t, J = 5.9, 1 H), 1.79–1.62 (m, 4 H), 1.30 (s, 3 H), 1.28 (s, 9 H); GC: t_R (**7**), 8.05 min (column HP/U2, 250 °C isothermal).

1,2-Epoxyoctane (30).[51] From 0.224 g (2.0 mmol) of 1-octene, 0.086 g (0.20 mmol) of catalyst **8d**$^+$OTf$^-$, and 42.5 mL (20.0 mmol) of Oxone solution was obtained 0.233 g (91% yield) of **24** as a colorless oil after chromatography (SiO_2, *t*-BuOMe/CH_2Cl_2, 6/1): ^{1}H NMR (300 MHz) 2.90 (m, 1 H), 2.75 (t, J = 5.5, 1 H), 2.46 (m, 1 H), 1.57–1.23 (m, 10 H), 0.88 (t, J = 6.1, 3 H); GC: t_R **30**, 9.56 min (column HP/U2, 110 °C isothermal). Anal. Calcd for $C_8H_{16}O$ (128.22): C, 74.94; H, 12.58. Found: C, 74.93; H, 12.59.

1,2-Epoxycyclohexane (31).[6] From 0.164 g (2.0 mmol) of cyclohexene, 0.086 g (0.20 mmol) of catalyst **8d**$^+$OTf$^-$, and 42.9 mL (20.0 mmol) of Oxone solution was obtained 0.181 g (92% yield) of **31** as a colorless oil after silica gel chromatography (pentane/CH_2Cl_2, 1/1): ^{1}H NMR (300 MHz) 3.12 (bs, 2 H), 1.92 (m, 2 H), 1.83 (m, 2 H), 1.41 (m, 2 H), 1.24 (m, 2 H); GC: t_R **31**, 10.78 min (column HP/U2, 70 °C (8 min)/10 °C/min/110 °C).

$\Delta^{9,10}$-Octalin Epoxide (32). From 0.272 g (2.0 mmol) of 1,2,3,4,5,6,7,8-octahydronaphthalene, 0.086 g (0.20 mmol) of catalyst **8d**$^+$OTf$^-$, and 42.5 mL (20.0 mmol) of Oxone solution was obtained 0.263 g (87% yield) of **32** as a colorless oil after silica gel chromatography (*t*-BuOMe/CH_2Cl_2, 10/1): ^{1}H NMR (300 MHz) 1.91–1.82 (m, 4 H), 1.67–1.56 (m, 4 H), 1.53–1.38 (m, 4 H), 1.32–1.19 (m, 4 H); ^{13}C NMR (75.5 MHz) 62.06, 30.91, 20.44; IR (neat) 2934 (s), 2857 (s), 1447 (m); MS (70 eV) 152 (13), 134 (30), 124 (10), 111 (100); TLC R_f 0.76 (*t*-BuOMe/CH_2Cl_2, 6/1); GC: t_R **32**, 8.29 min (column HP/U2, 160 °C isothermal). Anal. Calcd for $C_{10}H_{16}O$ (152.24): C, 78.90; H, 10.59. Found: C, 78.80; H, 10.64.

***rel*-(1*R*,2*R*)-1-Phenyl-1,2-epoxypropane (33).**[52] From 0.236 g (2.0 mmol) of (*E*)-1-phenylpropene, 0.086 g (0.20 mmol) of catalyst **8d**$^+$OTf$^-$, and 42.5 mL (20.0 mmol) of Oxone solution was obtained 0.257 g (96% yield) of **33** as a colorless oil after silica gel chromatography (pentane/CH_2Cl_2, 2/1): ^{1}H NMR (300 MHz) 7.35 (m, 5 H), 3.58 (d, J = 1.9, 1 H,), 3.04 (qd, J_q = 5.1, J_d = 1.9, 1 H), 1.46 (d, J = 5.1, 3 H); GC: t_R **33**, 6.85 min (column HP/U2, 160 °C isothermal). Anal. Calcd for $C_9H_{10}O$ (134.18): C, 80.56; H, 7.51. Found: C, 80.54; H, 7.49.

***rel*-(1*R*,2*S*)-1-Phenyl-1,2-epoxypropane (34).**[7] From 0.236 g (2.0 mmol) of (*Z*)-1-phenylpropene, 0.086 g (0.20 mmol) of catalyst **8d**$^+$OTf$^-$, and 42.9 mL (20.0 mmol) of Oxone solution was obtained 0.249 g (93% yield) of **34** as a colorless oil after silica gel chromatography (pentane/CH_2Cl_2, 2/1): ^{1}H NMR (300 MHz) 7.31 (m, 5 H), 4.06 (d, J = 4.1, 1 H), 3.34 (qd, J_q = 5.5, J_d = 4.1, 1 H), 1.09 (d, J = 5.5, 3 H); GC: t_R **34**, 6.60 min (column HP/U2, 160 °C isothermal). Anal. Calcd for $C_9H_{10}O$ (134.18): C, 80.56; H, 7.51. Found: C, 80.52; H, 7.49.

***rel*-(2*R*,3*R*)-3-Phenyloxiranemethanol (35).**[53] From 0.268 g (2.0 mmol) of *trans*-cinnamyl alcohol, 0.086 g (0.20 mmol) of catalyst **8d**$^+$OTf$^-$, and 42.5 mL (20.0 mmol) of Oxone solution was obtained 0.249 g (83% yield) of **35** as a colorless oil after silica gel chromatography (hexane/EtOAc, 6/1) and distillation: bp 75–90 °C (1 Torr/air bath); ^{1}H NMR (300 MHz) 7.44–

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7.22 (m, 5 H), 4.05 (m, 1 H), 3.93 (d, J = 1.0, 1 H), 3.81 (m, 1 H), 3.23 (m, 1 H), 1.75 (bs, 1 HO); GC: t_R **35**, 10.59 min (column HP/U2, 170 °C isothermal). Anal. Calcd for $C_9H_{10}O_2$ (150.18): C, 71.98; H, 6.71. Found: C, 71.70; H, 6.63.

2,3-Epoxycyclohexanol (36).[54] From 0.196 g (2.0 mmol) of 2-cyclohexen-1-ol, 0.086 g (0.20 mmol) of catalyst **8d**$^+$OTf$^-$, and 42.5 mL (20.0 mmol) of Oxone solution was obtained 0.189 g (83% yield) of **36** as a clear, colorless oil after silica gel chromatography (EtOAc/hexane, 1/1): ^{1}H NMR (300 MHz) 4.07–3.97 (m), 3.36–3.30 (m), 3.23 (m), 3.08 (d, J = 3.6), 2.05–1.14 (m); GC: t_R syn-**36**, 8.94 min (52.3%); t_R anti-**36**, 10.09 min (47.7%) (column HP/U2, 120 °C isothermal). A small portion was then separated into the individual diastereomers with the following properties. *syn*-**36**: ^{1}H NMR (400 MHz) 3.99 (m, 1 H), 3.33 (m, 1 H), 3.29 (m, 1 H), 1.91–1.88 (m, 1 H), 1.86–1.82 (m, 1 H), 1.80–1.74 (m, 1 H), 1.57–1.49 (m, 2 H), 1.47–1.41 (m, 1 H), 1.28–1.21 (m, 1 H); GC: t_R *syn*-**36**, 8.46 min (column HP/U2, 120 °C isothermal). Data for *anti*-**36**: ^{1}H NMR (400 MHz) 4.03 (m, 1 H), 3.22 (m, 1 H), 3.06 (d, J = 3.7, 1 H), 2.15–1.96 (m, 1 H), 1.88–1.82 (m, 1 H), 1.80–1.71 (m, 1 H), 1.69–1.67 (m, 1 H), 1.48–1.40 (m, 1 H), 1.30–1.14 (m, 2 H); GC: t_R *anti*-**36**, 9.59 min (column HP/U2, 120 °C isothermal).

17α-Hydroxy-21-hydroxypregna-4,9(11)-diene-3,20-dione (38). From 0.075 g (0.21 mmol) of steroid **37**, 0.009 g (0.021 mmol) of catalyst **8d**$^+$OTf$^-$, and 4.6 mL (1.98 mmol) of Oxone solution was obtained 0.061 g (81% yield) of **38** as a colorless solid after silica gel chromatography (EtOAc/hexane, 1/1). An analytical sample was obtained by crystallization from CH_2Cl_2/hexane: mp 208–209 °C; ^{1}H NMR (400 MHz) 7.17 (d, J = 10.4, 1 H), 6.21 (dd, J = 10.4, 1.7, 1 H), 5.98 (s, 1 H), 5.47 (d, J = 5.6, 1 H), 4.49 (dd, J = 20.4, 4.0, 1 H), 4.30 (dd, J = 20.4, 4.0, 1 H), 3.26 (t, J = 4.0, 1 H), 3.17 (s, 1 H), 2.64–2.57 (m, 1 H), 2.58–2.48 (m, 1 H), 2.38–2.34 (m, 1 H), 2.28–2.23 (m, 1 H), 2.20–2.10 (m, 4 H), 1.69–1.59 (m, 1 H), 1.56–1.50 (m, 1 H), 1.36 (s, 3 H), 1.20–1.09 (m, 2 H), 1.06 (d, J = 6.4, 3 H), 0.77 (s, 3 H); ^{13}C NMR (125.8 MHz) 212.35, 186.62, 167.73, 155.40, 141.81, 126.90, 123.40, 120.73, 88.83, 68.41, 48.83, 48.64, 46.98, 46.00, 36.23, 36.04, 34.98, 33.14, 32.15, 26.40, 19.56, 14.65; IR ($CDCl_3$) 3616 (w), 3609 (m), 2936 (s), 2875 (m), 1712 (s), 1663 (vs); TLC R_f 0.33 (EtOAc/hexane, 3/1). Anal. Calcd for $C_{22}H_{28}O_4$ (356.47): C, 74.13; H, 7.92. Found: C, 73.77; H, 7.86.

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Supplementary Material Available: General experimental methods along with the preparation and characterization of **9b**, **9c**, **9e**, **9f**, **10b**, **10c**, **10e**, **10f**, **11b**, **11c**, **11e**, **11f**, **15–23**, **and 26–29** and complete ^{1}H and ^{13}C NMR assignments, IR, and MS data for all characterized compounds (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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