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A New Protocol for *in Situ* Dioxirane Reactions: Stoichiometric in Oxone and Catalytic in Fluorinated Acetophenones

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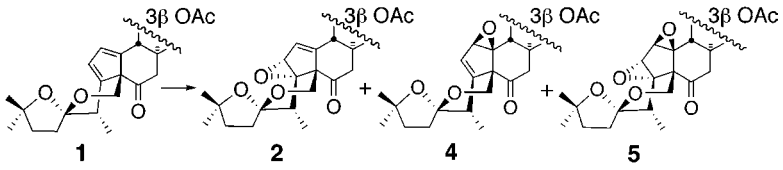
ABSTRACT



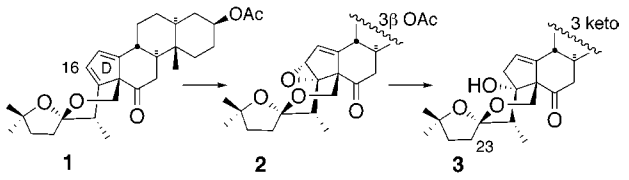
94~96% conversion, **2**:(**4** + **5**) = 6~8:1

Conditions: fluoroacetophenones (**7**, **8** or **9**, 0.2 eq), Oxone (0.6 eq), $NaHCO_3$ (2.4 eq), CH_3CN-0.05 M $Na_2B_4O_7$ in 4 X 10^{-4} M Na_2EDTA

Dioxiranes made *in situ* from the commercially available tetrafluoroacetophenones (7, 8) and pentafluoroacetophenone (9) are reported for highly efficient epoxidation of olefins for the first time. Studies showed that ketone 7, 8, or 9 can be used in catalytic amount (0.2 equiv) with only 0.6 equiv of Oxone (equal to 1.2 equiv of peroxymonosulfate) to selectively oxidize diene 1 to epoxide 2. The epoxidation reactions of dioxiranes of fluoroacetophenones are compared with the recently described complementary aliphatic acyclic fluorinated ketones.

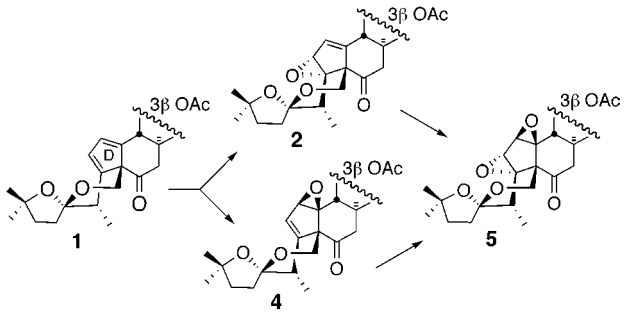
In the preceding Letter we reported a particularly demanding epoxidation of steroidal D-ring cyclopentadiene (**1**) needed to complete the synthesis of 23-deoxy,17α-hydroxy South 1 (**3**, Scheme 1). The relative rate of epoxidation of this

Scheme 1



material with *m*CPBA and dimethyldioxirane (DMDO) to give **2** was only about twice as fast as the oxidation to the unwanted epoxide **4** (Scheme 2). To further complicate the problem, both **2** and **4** suffered competitive subsequent epoxidation to give the same bis-epoxide **5**.[1]

Scheme 2



To improve the synthesis of monoepoxide **2** from diene **1**, we initially considered using enantiopure dioxiranes developed by Shi[2] and Denmark.[3] Such species would both be more sterically demanding than the parent DMDO while

(1) Cephalostatin support studies 27. Oxidations 5.[2]

(2) For the epoxidation of diene **1** using *m*CPBA and DMDO, see the preceding Letter.

(3) (a) Tu, Y.; Wang, Z.; Shi. Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806−9807. (b) Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.* **2003**, *5*, 293−296.

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simultaneously providing the advantage of double stereoselection. Unfortunately, diene **1** was inert to the bulky dioxirane reagents. The smaller dioxirane from trifluoroacetophenone (**6**, Figure 1) previously applied several times

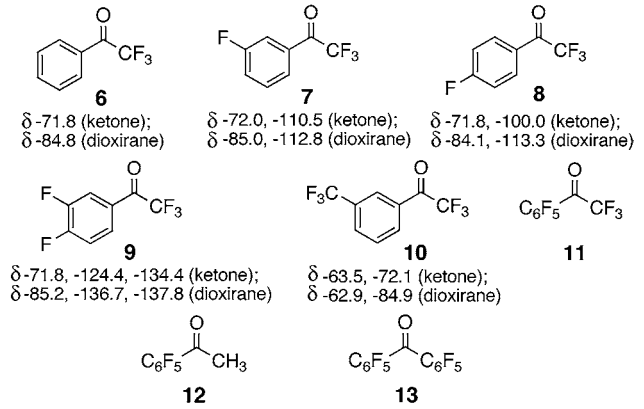


Figure 1. Fluorinated acetophenones and ^{19}F NMR data ($CDCl_3$).

for epoxidation[4] gave increased selectivity for conversion of diene **1** to epoxide **2** (Table 1).

Table 1. Epoxidation of Diene **1** with Dioxiranes Derived from Ketone **6**, **7**, and **10**

run[a]	ketone	time (h)	conversion[b]	ratio[c] **2**:(**4** + **5**)
1	**6**	24	88%	4.7:1
2	**7**	<10	100%	6.3:1
3	**10**	24	97%	5.0:1

[a] All reactions were carried out at 0 °C with diene **1** (1 equiv), ketone (2 equiv), Oxone (2 equiv), $NaHCO_3$ (8 equiv), and *n*-Bu_4NHSO_4 (5% equiv) in (1.5:1) CH_3CN−0.05 M $Na_2B_4O_7$ in 4×10^{-4} M aqueous Na_2EDTA. [b,c] Based on ^1H NMR integration.

Encouraged by this result, we envisioned that reactivity and selectivity could be further increased by introducing fluorine atoms on the phenyl ring of trifluoroacetophenone. A 1999 review by Denmark reported that inductive activation of the carbonyl carbon of acyclic ketones by proximal fluorine atoms was sensitive to both the location and number of fluorines.[4a] *Surprisingly, dioxiranes derived from more highly fluorinated trifluoroacetophenone analogs have never appeared in the literature*. Commercially available (Aldrich) fluorinated ketones used in this study are shown in Figure 1.

We first investigated epoxidation of diene **1** following Shi's procedure[5] using ketones **7** and **10** instead of the fructose-derived ketone. The results are shown in Table 1. Ketone **7** gave the best reaction rate and good selectivity with 100% conversion within 10 h at 0 °C (run 2).

(4) For recent reviews on enantioselective epoxidation of alkenes using chiral, nonracemic dioxiranes, see: (a) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847−859. (b) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979−2000.

Before examining other fluorinated acetophenones, we optimized the reaction conditions using ketone **7**. The results are summarized in Table 2. Increasing the concentration to

Table 2. Optimization of Epoxidation of Diene **1** Using Ketone **7**

run[a]	**7**/Oxone (equiv)	concn[b] (M)	temp/time (°C)/(h)	conversion[c]	ratio[d] **2**:(**4** + **5**)
1	0.5/2	0.024	0/34.5	86%	6.8:1
2	0.5/2	0.1	0/34.5	45%	5.3:1
3	1.5/2	0.024	0/44	100%	6.3:1
4	1.5/2	0.024	0/1.5, 25/9	100%	1:1.3[e]
5	0.1/0.6	0.024	0/1.5, 25/1.5	92%	7.4:1

[a] All reactions employed diene **1** (1 equiv), ketone **7**, Oxone, $NaHCO_3$ (4 times of Oxone), and *n*-Bu_4NHSO_4 (5% equiv) in (1.5:1) CH_3CN−0.05 M $Na_2B_4O_7$ in 4×10^{-4} M aqueous Na_2EDTA. [b] The concentration of diene **1** in CH_3CN. [c,d] Based on ^1H NMR integration. [e] Large amount of bisepoxide **5** formed.

0.1 M greatly decreased the conversion (runs 1 and 2). Reaction temperature has a major effect on the reaction rates, as shown in runs 3 and 4. Using excess of ketone **7** gave 100% conversion. However, run 4 produced a large amount of bis epoxide **5** as a result of the high reactivity of the dioxirane at room temperature. Ketone **7** and its dioxirane peaks were seen in the ^{19}F NMR after workup; however, only the peaks from ketone **7** appeared after 12 h at room temperature. No Baeyer−Villiger product from ketone **7** was formed, in comparison with methyl(trifluoromethyl) dioxirane, which decomposes to methyl trifluoroacetate,[6] the Baeyer−Villiger product.

^{19}F NMR of an initial 1:1 mixture of ketone **7** and its dioxirane revealed only ketone **7** remaining after 12 h. These observations indicated that (1) the reaction rate is fast at room temperature; (2) decomposition of the dioxirane only gave the ketone; and (3) ketone **7** could serve as a catalyst with near stoichiometric amounts of Oxone. Indeed, epoxidation of **1** using 0.1 equiv of ketone **7** and 0.6 equiv of Oxone (equal to 1.2 equiv of oxidant) within 3 h gave 92% conversion with 7.4:1 ratio between the desired monoepoxide **2** and the other two unwanted epoxides (run 5).

The Denmark research group demonstrated that strict control of pH was critical for the *in situ* generated biphasic dioxirane epoxidations.[7] They reported that the best pH range was 7.8−8.0. Reactions conducted outside of this region resulted in either Oxone decomposition to give oxygen at high pH (>8) or dioxirane destruction by the peroxymonosulfate at lower pH (<7.5). However, Shi reported that highest conversion of *trans*-*β*-methylstyrene was achieved at pH 10−12 (0 °C, homogeneous) using the fructose

(5) (a) Grocock, E. L.; Marples, B. A.; Toon, R. C. *Tetrahedron* **2000**, *56*, 989−992. (b) Harburn, J. J.; Loftus, G. C.; Marples. B. A. *Tetrahedron* **1998**, *54*, 11907−11924.

(6) (a) Wu, X. Y.; She, X.; Shi. Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792−8793. (b) Wang, Z. X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328−2329.

(7) Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1988**, *53*, 3891−3893.

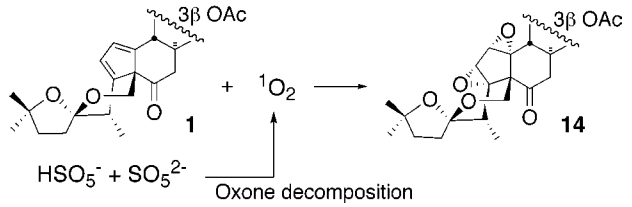
Table 3. Comparison of Epoxidations of **1** with Fluorinated Acetophenones[a]

ketone	conversion	ratio **2**:**4**:**5**	ratio **2**:(**4** + **5**)
6	85%	40:5.5:1	4.9:1
7	96%	39:5.1:1	6.4:1
8	96%	59:7.5:1	6.9:1
9	94%	308:37:1	8.1:1
10	88%	23:3.4:1	5.2:1
11	40%	no **5**	2.6:1
12	20%	no **5**	2.0:1
13	33%	no **5**	1.9:1

[a] All reactions were carried out at 0 °C (60 min) and rt (80 min) with diene **1** (1 equiv), ketone (0.2 equiv), Oxone (0.6 equiv, equal to 1.2 equiv oxidant), $NaHCO_3$ (2.4 equiv), and *n*-Bu_4NHSO_4 (0.1 equiv) in (1.5:1) CH_3CN−0.05 M $Na_2B_4O_7$ in 4×10^{-4} M aqueous Na_2EDTA. Data were based on ^1H NMR integration.

ketone.[4b] Oxone decomposition was significant at room temperature but very slow at 0 °C under our reaction conditions (homogeneous, pH ~10). Slow epoxidation reactions therefore require additional amounts of Oxone because the reaction must be run at room temperature. This was the case using 2 mol % of ketone **7**. The reaction was very slow and diene **1** reacted with oxygen derived from Oxone decomposition to give significant amount of singlet oxygen product **14** (Scheme 3).[2]

Scheme 3



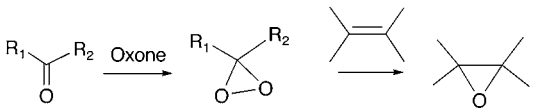
A systematic study of the general class of commercially available fluorinated acetophenones (Aldrich, Figure 1) was next conducted. Tetrafluoroacetophenones (**7**, **8**) and pentafluoroacetophenone **9** gave best combination of reaction rate and selectivity (Table 3).

A recent seminal study by a CNRS group has provided the definitive architecture of dioxirane precursors from synthetic fluorinated acyclic *aliphatic* ketones (Table 4).[8] Table 5 compares a series of epoxidations using the dioxirane from tetrafluoroacetophenone **7** with the olefin testing set employed by the CNRS group. As previously observed, smaller amounts of Oxone were required when the reaction pH decreased from 10 (Method A) to 8−9 (Method B). The reaction rate was faster when the addition period of the Oxone/$NaHCO_3$ extended (runs 8 and 9). In all cases ketone **7** was unchanged on the basis of GC analysis, so the epoxidations could be completed simply by adding more Oxone/$NaHCO_3$ if the reaction was incomplete (runs 6, 9, and 10). As low as 5 mol % of ketone **7** and 1.0 equiv of Oxone (equals 2.0 equiv of oxidant) can be used for reactive cyclooctene (run 3). Although 1-dodecene is far less reactive, 10 mol % of ketone **7** and 1.5 equiv of Oxone still gave 97% conversion (run 10). However, the rate of epoxidation of diene **1** was slow using method B. Only 92% conversion was observed after 3 h at room temperature when 0.2 equiv of ketone **7** and 0.6 equiv of Oxone were used. The rate of Oxone decomposition was increased by using hexafluoro-2-propanol (HFIP) as cosolvent (run 12, Method C), requiring additional oxidant when using the CNRS protocol.

It has been reported that *hydrogen peroxide can be used as the terminal oxidant in dioxirane epoxidations* of olefins.[9] The conversion and pH relationship has been studied by Shi's group who determined the best condition is pH 11.[10(b)] With our protocol, hydrogen peroxide was found to smoothly epoxidize cyclooctene. The reaction gave 100% conversion within 1 h by using H_2O_2 (30%, 6 equiv, added in 1 h) and ketone **7** (0.1 equiv) in 1:1 acetonitrile (0.5 M) and 1.5 M K_2CO_3 in 4×10^{-4} M EDTA solution. For the less reactive 1-dodecene, the same conditions only gave 10% conversion because the H_2O_2 was more rapidly undergoing decomposition than epoxidation at the high reaction pH.

In summary, dioxiranes derived from commercially available tetrafluoroacetophenones (**7**, **8**) and pentafluoro-

Table 4. Key Experiments from CNRS Group Using 1 Equiv of Synthetic Aliphatic Fluoroketones



R_1/R_2	olefin	Oxone (equiv); solvent; add'n time + rx time	olefin:epoxide (GC yield)
CH_3/C_7F_{15}	cyclooctene	5; $MeCN/H_2O$; 2 h + 3 h	0:100 (96%)
CH_3/C_7F_{15}	cyclooctene	2.5; HFIP/H_2O 3:1; 1 h + 1 h	0:100 (78%)
CF_3/C_8F_{17}	1-dodecene	2.5; HFIP/H_2O 3:1; 2 h + 1 h	30:70
CF_3/C_8F_{17}	1-dodecene	4; HFIP/H_2O 3:1; 2 h + 0 h	0:100 (90%)
$CF_3/CH_2CH_2C_6F_{13}$	1-dodecene	2.5; HFIP/H_2O 3:1; 2 h + 1 h	0:100[a] (95%)
$C_3F_7/CH_2CH_2C_6F_{13}$	1-dodecene	2.5; HFIP/H_2O 3:1; 2 h + 1 h	45:55[a]
$C_7F_{15}/CH_2CH_2C_6F_{13}$	1-dodecene	2.5; HFIP/H_2O 3:1; 2 h + 1 h	100:0[a]

[a] R_1COR_2 was found unchanged (>98% by GC analysis). HFIP = hexafuoro-2-propanol.

Table 5. Oxidation of Common Olefins with Ketone **7**

run[a]	olefin	**7** (equiv);[b] method	Oxone (equiv);[c] addn time + rx time	conversion[d] (yield)[e]
1	cyclooctene	0.2; A	1.5; 7h + 2h	100% (92%)
2	cyclooctene	0.1; B	1.0; 2h + 10h	>99% (90%)
3	cyclooctene	0.05; B	1.0; 2 h + 22 h	98%
4	styrene	0.2; A	1.5; 10 h + 1.5 h	100%
5	styrene	0.2; B	1.0; 2h + 13h	100% (83%)
6	styrene	0.1; B	1.0; 2h + 21h	86%
			0.5; 0 h + 7 h	100%
7	1-dodecene	0.2; A	3.0; 30 h + 6 h	97%
8	1-dodecene	0.2; B	1.5; 12 h + 2 h	>99%
9	1-dodecene	0.2; B	1.5; 2 h + 27 h	91%
			0.5; 0 h + 1 h	100%
10	1-dodecene	0.1; B	1.0; 2 h + 22 h	70%
			0.5; 0 h + 12h	97% (86%)
11	1-dodecene	0.2; B	1.5; 2 h + 9 h	62%
12	1-dodecene	0.2; C	1.5;[f] 2 h + 9 h	74%

[a] All reactions were carried at room temperature with olefin, ketone **7**, Oxone, and $NaHCO_3$ (4 × Oxone) in (1.5:1) acetonitrile−0.05 M $Na_2B_4O_7$ in 4 × 10^{-4} M aqueous Na_2EDTA (Method A, reaction pH is about 10), or in (1.5:1) acetonitrile−4 × 10^{-4} M aqueous Na_2EDTA (Method B, reaction pH is 8−9), or in (1.5:1) HFIP−4 × 10^{-4} M aqueous Na_2EDTA (Method C). [b] Ketone **7** was shown to be unchanged by GC analysis. [c] Oxone remaining when method B was used as assayed by potassium iodide−starch paper. [d] Based on GC. [e] Isolated yield. [f] No Oxone remained.

acetophenone **9** are demonstrated for the first time to have very good reactivity for epoxidation of olefins. The fluorinated acetophenones do not suffer from Baeyer−Villiger oxidations. Thus catalytic amounts of ketones can be used, and less reactive olefins can be driven to completion by adding excess of Oxone and extending the reaction time. Although many epoxidation reagents have been developed, *the dioxiranes reported here provide excellent alternatives for the catalytic epoxidation of olefins using a minimum of terminal oxidant.*

Acknowledgment. We thank the National Institute of Health (CA 60548) for support of this project.

Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391−1407.
(9) Legros, J.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J. *Tetrahedron* **2002**, *58*, 3993−3998.
(10) (a) Shu, L.; Shi, Y. *Tetrahedron Lett.* **1999**, *40*, 8721−8724. (b) Shu, L.; Shi, Y. *J. Org. Chem.* **2000**, *65*, 8807−8810.