Catalytic Epoxidation of Alkenes with Oxone. 2. Fluoro Ketones

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Over the past 20 years, dioxiranes have evolved from structural curiosities to extremely useful reagents for epoxidation of alkenes under neutral conditions.[1] Dioxiranes are easily generated by the action of potassium monoperoxysulfate (Oxone) on a ketone (usually acetone) either in a biphasic mixture or in a homogeneous aqueous organic solution.[2] Initially, distilled solutions of dimethyldioxirane (**1a**, Chart 1) were used, but in recent years, as less volatile ketones have been employed, the in situ methods have become more practical.

Since the oxygen atom transfer to the substrate regenerates the initial ketone, the epoxidations can in principle be catalytic. This feature is particularly important for asymmetric epoxidations using chiral ketones. Indeed, high enantioselectivities have been reported in recent years for the epoxidation of unfunctionalized olefins with various ketonic promoters.[3] However, the development of a truly general and efficient catalyst remains an important challenge. Recently, we developed a novel class of catalysts (4-oxopiperidinium salts) for epoxidation with Oxone under biphasic conditions.[4] In continuation of our structure/reactivity survey, we report herein the efficient catalysis of epoxidation with simple fluoro ketones.

The use of fluorine substitution was first introduced into dioxirane chemistry in 1988 by Mello and Curci, who isolated methyl(trifluoromethyl)dioxirane (**1b**), Chart 1.[5,6] Compared to **1a**, **1b** can perform virtually the same oxidations faster and can be applied to some previously unreactive substrates. The strong electron-withdrawing effect of fluorine substituents dramatically increases the electrophilicity of the carbonyl carbon.[7] This interesting phenomenon prompted us to introduce fluorine to both acyclic and cyclic ketones that would be featured in the structure of future asymmetric catalysts.[8]

We previously reported that, despite the superiorityof **1b**, both 1,1,1-trifluoroacetone and hexafluoroacetone were poor epoxidation promoters under biphasic conditions.[4] A delicate balance between lipophilicity and hydrophilicity of the ketone promoter is essential for effective catalysis under these conditions.[4] Thus, we examined the more lipophilic ketones **3a** and **4a** and their trifluoromethyl analogues **3b** and **4b**[9] in the epoxidation of our standard substrate (*E*)-**5** under the reaction conditions previously developed, Table 1. As expected, the longer chain ketones **3a** and **4a** were much poorer promoters than **2a**. However, the corresponding fluoro ketones **3b** and **4b** were far superior to **2b**. In addition, the more lipophilic **4b** affected complete conversion of (*E*)-**5** to **6** after 9 h. Unfortunately, these reagents were not effective as catalysts.[10]

We next turned our attention to mono- and difluorinated ketones and, in particular, the stereoelectronic effects of fluorine substitution in a conformationally defined structure. Five different ketones bearing one (**7**, **8**) or two (**9**−**11**) α-fluorine substituents were examined, Chart 2.[9] Our initial studies were performed with substrate (*E*)-**5** under the standard biphasic conditions described above. Unfortunately, the results were irreproducible due to the unpredictable formation of emulsions.

To better clarify the differing effects of the fluorine substituents, we opted to carry out these reactions under monophasic conditions (1.5/1 acetonitrile/water) with catalytic amounts (10 mol %) of the ketones.[11] The reaction progress was monitored by GC and the product **6** was also isolated after 24 h reaction time. The results of these epoxidations are plotted in Figure 1 along with the results for 4-*tert*-butylcyclohexanone as a reference.

Chart 1

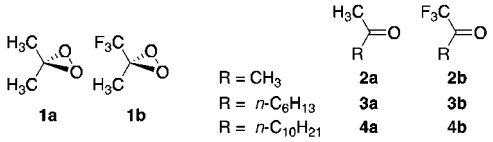
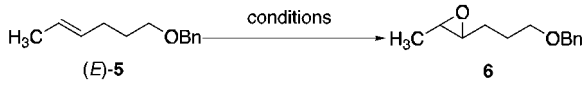


Table 1. Biphasic Epoxidation of (*E*)-5 with Acyclic Ketones[a]



entry	ketone	epoxide/olefin[b]	recovery,[c] %
1	**2a**	87/13	92
2	**3a**	12/88	92
3	**4a**	6/94	87
4	**2b**	29/71	95
5	**3b**	76/24	90
6[d]	**4b**	97/3	90

[a] Conditions: ketone (2.0 equiv), Oxone (10 equiv, 8 h addition), n-$Bu_4N^+HSO_4$ (0.1 equiv), CH_2Cl_2/H_2O (pH 7.8), 0 °C, 24 h. [b] GC ratio. [c] (*E*)-**5** and **6**. [d] Reaction complete after 9 h.

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(6) Hexafluoroacetone has been used to catalyze the epoxidation of alkenes: Heggs, R. P.; Ganem, B. *J. Am. Chem. Soc.* **1979**, *101*, 2484.

(7) For general reviews of organofluorine chemistry see: (a) Hudlicky, M., Pavlath, A. E., Eds. *The Chemistry of Organic Fluorine Compounds II: A Critical Review*; ACS Monograph No. 187; American Chemical Society: Washington, DC, 1995. (b) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*, John Wiley: New York, 1979.

(8) The application of this concept to more structurally complex ketones failed due to the choice of ring size and steric congestion surrounding the carbonyl group. (a) Brown, D. S.; Marples, B. A.; Smith, P.; Walton, L. *Tetrahedron* **1995**, *51*, 3587. (b) Curci, R.; D'Accolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett.* **1995**, *36*, 5831.

(9) The preparation and full characterization of all new fluoro ketones are provided as Supporting Information.

(10) (a) 10 mol % of ketone **4b** gave only 6.3% conversion of (*E*)-**5** to **6** after 24 h. (b) Yang has also shown that in monophasic systems 1,1,1-trifluoromethyl ketones are not catalytically active. Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887.

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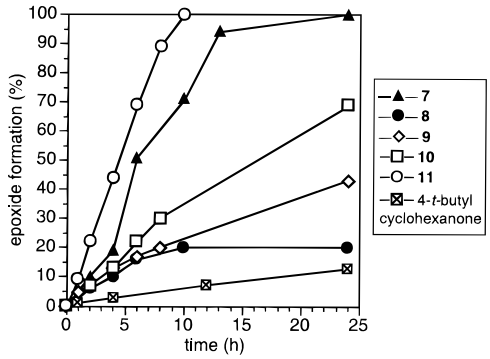
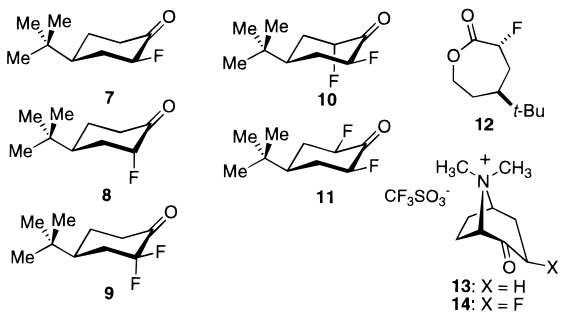


Figure 1. Epoxidation of (*E*)-**5** with fluoro ketones **7**−**11**.

Chart 2



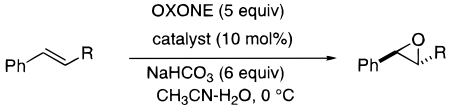
Both monofluoro ketones **7** and **8** were superior to 4-*tert*-butylcyclohexanone in the epoxidation of (*E*)-**5**. Interestingly, the epoxidation efficiency was highly dependent on the orientation of the fluorine substituent. Compound **7**, which has an equatorial fluorine atom, was a much better epoxidation catalyst than **8**, which has an axial fluorine atom. Indeed, complete consumption of (*E*)-**5** was promoted by a catalytic quantity of **7** in 24 h. Whereas **8** was an effective catalyst at early stages of reaction, it was completely inactive after 10 h.

The difluorinated ketones also displayed disparate activities depending the orientation of the fluorine substituents. As in the monofluoro series, all three difluoro ketones were more efficient catalysts than 4-*tert*-butylcyclohexanone. To appreciate the influence of the additional fluorine substituents, it is instructive to compare the results from ketones **9**−**11** with that from the epoxidation using monofluoro ketone **7**. For example, if we consider the effect of placing the second α-fluorine in an axial position either geminally (**9**) or *trans*-2,6 (**10**), it is clear that this axial fluorine substituent decreased the epoxidation activities compared to **7**. Furthermore, if the second α-fluorine is placed in an equatorial position, i.e., *cis*-2,6 (**11**), then the ketone catalyst is even more reactive than **7** and gave complete epoxidation of (*E*)-**5** in 10 h. Thus, it is clear that equatorial fluorine substituents enhance the activity of ketones as epoxidation catalysts, while axial fluorine substituents attenuate the activity.

In addition to the wide range of activity as epoxidation catalysts, the ketones showed different stability under the reaction conditions. Thus, 4-*tert*-butylcyclohexanones **7** and **9**−**11** were stable under the reaction conditions, but ketone **8** with one axial fluorine atom was converted via Baeyer−Villiger (B−V) reaction to **12** in 10 h.[12]

How can we understand the dramatic stereochemical dependence of reactivity? Under monophasic conditions, the epoxidation efficiency of a ketone promoter depends on the following: (1) susceptibility of the carbonyl carbon toward nucleophilic attack to form the dioxirane, (2) ease of oxygen atom transfer to the olefin substrate, and (3) propensity for irreversible ketone consumption (B−V reaction). Thus, whereas the overall enhancement by fluorine substitution is due to all of these factors, the dramatic differences among the fluoro ketones most likely arises from significant stereoelectronic contributions these factors.[13] The effect of fluorine substituents, which is of primary relevance here, is the increased electrophilic reactivity of the carbonyl.[14] Accordingly, we measured the relative susceptibility of the five ketones to carbonyl addition (the first step in dioxirane formation)[1] by determining the solvation equilibria by NMR (^{1}H, ^{19}F) in methanol-d_4.[15] All three ketones bearing axial fluorine substituents (**8**−**10**, which exist as stable hydrates) were quantitatively converted to their methanol adducts while, despite their much larger net dipole,[16] ketones **7** and **11** bearing only equatorial fluorines contained 65−95% of the hemiketal form, respectively. Interestingly, the incorporation of methanol into the hydrates of **8**−**10** was slow (13−27 h for complete exchange). Thus, while these substrates appear to be more susceptible to carbonyl addition, the rate of formation of the Criegee intermediate may in fact be inhibited by the competitive addition of water and also be retarded by the stability (i.e., slow exchange) of the tetrahedral adducts.

As a final illustration of the influence of an equatorially oriented fluorine substitutent, we examined the chiral tropinium triflate **13**$^+$OTf$^-$ [9] (Chart 2). This compound was intended to be an asymmetric analogue of the oxopiperidinium salts we reported previously.[4] Homogeneous epoxidation of *trans*-2-methylstyrene under the conditions described above gave a disappointing conversion. However, the fluoro analogue **14**$^+$OTf$^-$ [17] displayed enhanced reactivity and afforded the epoxide in high yield (85%) but modest ee for *trans*-2-methylstyrene (58% ee for *trans*-stilbene, R = Ph).



R = Me, cat = **13**, 5h, 21% conv
R = Me, cat = **14**, 5h, 100% conv, 35% ee (*R,R*)

In summary, we have demonstrated the ability of fluorocyclohexanones to serve as efficient epoxidation catalysts with Oxone and have documented a remarkable stereochemical dependence of both epoxidation and Baeyer−Villiger reaction. We are further investigating the incorporation of fluorine atoms into chiral ketones for catalytic asymmetric epoxidation.

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Supporting Information Available: The preparation and characterization of **3b**, **4b**, and **7**−**14** along with epoxidation procedures are provided (22 pages).

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(11) Conditions: ketone (0.1 equiv), $NaHCO_3$ (10.4 equiv), Oxone (4 equiv, 8 h addition), CH_3CN/H_2O (1.5/1), 0 °C, 24 h.

(12) Determined by GC. The lactone **12** produced under biphasic epoxidation conditions employing 1 equiv of **8** was isolated and fully characterized.

(13) For a discussion of the chemistry of 2-halocyclohexanones see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; pp 731−733.

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(16) Allinger, N. L.; Blatter, H. M. *J. Org. Chem.* **1962**, *27*, 1523.

(17) The stereostructure of **14**$^+$OTf$^-$ was assured by single crystallographic analysis of the bromocamphorsulfonic acid salt of the methylation precursor.