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Chemospecific Chromium[VI] Catalyzed Oxidation of C−H Bonds at −40 °C[1]

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In the course of our research involving hyperactive analogues of the cephalostatin[2]/ritterazine[3] family of marine natural products, we wished to effect sequential allylic oxidation of olefin **1** to hemiacetal **2** followed by directed epoxidation to epoxide **3α**. While dioxiranes have been shown to smoothly oxidize tertiary C−H bonds of saturated spiroketals,[4] reaction of **1** with DMDO or TFDO (methyl(trifluoromethyl)dioxirane) produces complex mixtures. Furthermore, neither of the epoxy isomers of **4** undergoes additional C−H oxidation under extended reaction times with the dioxirane reagents (Scheme 1).

The search for a reagent capable of *C−H oxidation in the presence of olefins* avoided reagents that produce alkoxy radicals.[5] Instead, we employ a metallic peroxide to pursue oxidative C−H insertion akin to the dioxiranes.[6] Our study was strongly influenced by a pair of excellent reviews by Dickman and Pope,[7] and Shilov and Shul'pin[8] in conjunction with a recent theoretical paper by Rösch.[9] Calculations by the latter group indicated that the *unknown*[10] bisoxo, monoperoxo Cr[VI] species were less prone to epoxidation than similar Mo or W complexes.[9] Moreover, inclusion of additional basic ligands is calculated to further increase the activation barrier for oxidation by all three metals.[9,10] A smattering of references offers encouragement that Cr[VI] can effect certain C−H oxidations,[11] but because bis and trisperoxo complexes of Cr are known to be only weak C−H oxidizing agents,[12] we elected to initially seek preparation of a monoperoxo, bisoxo Cr[VI] species associated with weak donor ligands.[13] Therefore, our beginning studies employed acetic acid, acetonitrile, and dichloromethane as solvents. Initial oxidations were carried out with excess CrO_3, but the more soluble chromoyl diacetate is superior. Other chromium[VI] substrates including chromoyl chloride, chromoyl bistrifluoroacetate, chromoyl bistriflate, and chromoyl bis *tert*-butylester were far inferior. The premier co-oxidant is periodic acid (or tetrabutylammonium periodate), while hydrogen peroxide, *tert*-butyl hydroperoxide, TMSOOTMS, peroxydisulfate, and persulfate are poor.

Of considerable significance is that C−H oxidations occur at about −40 °C, and the reaction is *catalytic* in chromium. Reactions deficient in co-oxidant begin as brownish-orange, but rapidly turn green and cease oxidation. Addition of excess periodic acid reestablishes both the brown-orange color and the oxidative process. Both excess periodic acid and acetic anhydride are required for optimal yield of acetophenone from ethyl benzene (Table 1).

An expanded series of substrates (Table 2) reveals several generalities. The reaction is stereospecific with the retention of stereochemistry of the C−H bond oxidized (entries 6−9, 10). Where a second oxidation can give a *cis*-diol, periodate effects rapid oxidative cleavage (entries 5, 10). While substantially preferred, the oxidation is not restricted to tertiary C−H bonds. Cyclohexane and its perdeuterio analogue are oxidized to cyclohexanone ($k_H/k_D = 2.5$, similar to the TFDO oxidation of cyclohexane $k_H/k_D = 2.2$[14]).

Scheme 1

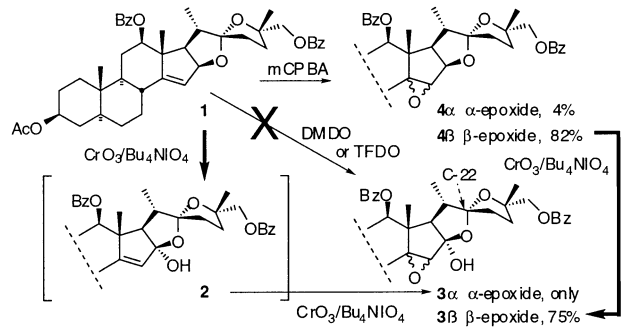
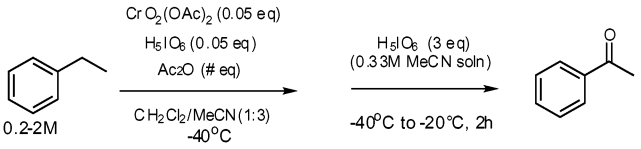


Table 1. Cr[VI] Catalyzed Oxidation of Ethylbenzene



run	1	2	3	4	5	6
Ac_2O (equiv)	0[a]	1[b]	2[b]	3[b]	5[b]	6[c]
yield (%)	85	89	96	92	79	25

[a] Light yellow mixture. [b] Light orange mixture. [c] Dark brown mixture.

Attempts at trapping secondary alcohol intermediates using excess trifluoroacetic anhydride[15] were not successful. Reaction of substrates bearing tertiary amide or lactam functionality revealed that amides prevented the oxidation, possibly due to their serving as nondissociable ligands. Trichloroacetonitrile and benzonitrile do not facilitate the reaction, but this may be a result of their inability to dissolve the periodic acid. All of the yields reported herein are based upon 1 equiv of C−H substrate.

While much remains to be done to define the mechanism, scope, and limitations of this amazing reaction, we have returned to the oxidation of the spiroketals shown in Scheme 1. It is very rewarding that stoichiometric oxidation of **1** produces the desired epoxyalcohol **3α** in 66% yield along with 26% of the C-22 spiroketal isomer, due to acid-catalyzed isomerization. Monitoring the reaction by NMR provides no evidence of intermediates **2** or **4α** (see Scheme 1). Evidence in support of C−H oxidation preceding epoxidation is seen in the Cr oxidation of ***4β*** which requires more forcing conditions (−10 °C, 1 h) to stereospecifically generate lactol epoxide ***3β***. Related noteworthy reactions are the unprecedented chemospecific oxidations of **5** to hemiacetal **6** and allylic oxidations of enol ethers **7** and **9** (Scheme 2).[16]

We postulate intermediacy of chromoylperiodate[17] $\mathbf{A}_1$ (or analogue $\mathbf{A}_2$) formed from reaction of CrO_3 $\mathbf{SM}_1$ (or chromoyl diacetate $\mathbf{SM}_2$) via addition of "anhydrous" HIO_4. Formation of the putative peroxy intermediates $\mathbf{R}_{1,2}$ (IR shows a Cr peroxy stretch

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Table 2. Cr[VI] Mediated C−H Oxidation

Entry	Substrate (X=H)	Product (% yield) [a] Stoichiometric [b]		catalytic [c]	
1		X=OH	68		
2		X=O	57 [d]	X=O	41
3		X=O	23 [d]		
4				X=OH	65 [e]
5			43		48
6				X=OH	54
7				X=OH	73
8				X=OH	65
9		X=OH	69	X=OH	51
10		X=OH	84		56
11		X=OH,Y=H	55	X=OH, Y=H X,Y=OH	86 [h] <2 [h]
12		X=OH	92	X=OH	64 [f]
13				X=OH	89 [g]
14				X=O	91
15	Ph_3CX	X=OH	97	X=OH	95
16		NR		NR	

[a] Isolated yield. [b] CrO_3 (3 equiv), Bu_4NIO_4 (3 equiv), −40 °C, 10 min. [c] $CrO_2(OAc)_2$ (5 mol %), H_5IO_6 (3 equiv), −40 to 0 °C, 2 h. [d] −20 °C, 1 h. [e] Prolonged reaction 12 h gave tertiary acetamide (82%, X = NHAc). [f] Amide (19%, X = NHAc) and acetophenone (10%) isolated. [g] Amide (4%, X = NHAc) and acetophenone (3%) formed. [h] H_5IO_6 (10 equiv), 2 h.

(O−O); 945 cm^{-1}), followed by insertion to the hydrocarbon C−H bond, may afford Cr[VI] compounds $\mathbf{C}_1$ and $\mathbf{C}_2$ which decompose to $\mathbf{SM}_1$ and $\mathbf{SM}_2$, the precatalysts (Scheme 3). The major decrease in yield with 6 equiv of acetic anhydride (Table 1) seems to indicate a role for water in the oxidative process.

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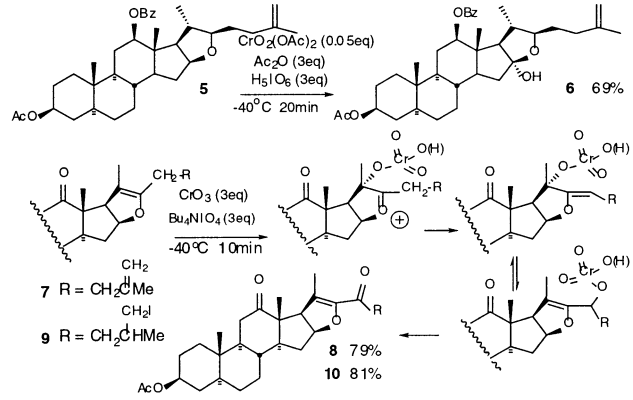
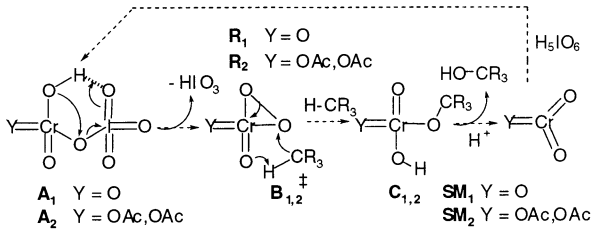
Supporting Information Available: Representative experimental procedures, and ^1H, ^{13}C NMR of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

Scheme 2



Scheme 3



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