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A Novel Approach to the Efficient Oxygenation of Hydrocarbons under Mild Conditions. Superior Oxo Transfer Selectivity Using Dioxiranes†

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ABSTRACT

The design of efficient and general methods for the selective oxyfunctionalization of unactivated carbon−hydrogen bonds continues to represent a major challenge for the community of chemists, despite the fact that the oxidation of alkanes is a major feature of the chemical economy. A low level of selectivity is characteristic of large-scale oxidation of hydrocarbons performed under customary industrial oxidizing conditions (e.g., the catalytic air oxidation of cycloalkanes); in these processes, selectivity is difficult to control, because they are often impacted by the usual problems associated with free-radical chain reactions. Thus, in the last decades much work has been devoted to the search for general methods of *selective* oxidation that could be applied to a variety of satured hydrocarbons. In this context, just a few leading methods appear encouraging at the present time. This Account addresses a new approach developed in our laboratory, consisting in the application of isolated dioxiranes, a class of powerful yet selective oxidants. We contend that the method shows promise to contribute resolution of a well-recognized general problem in the existing chemistry of alkanes, that is, to achieve efficient oxyfunctionalizations with high selectivity for simple as well as structurally complex targets.

Introduction

With most classical methods of hydrocarbon oxidation, the main problem does not lay much in the notoriously low reactivity of the alkane molecules themselves, but rather in the difficulty of achieving selective transformations.[1] Indeed, the efficient oxidation of nonactivated alkane C−H bonds that is also highly selective pertains to a few biological processes, which are hard to imitate. In nature, biochemical activation of alkanes is fostered by metal-containing monooxygenases, as exemplified by the cytochrome P450 group of enzymes.[1,2]

Several groups have addressed the many problems associated with the reactivity and the selective conversion of alkanes into functional compounds. Thus, major areas of research have regarded catalytic alkane oxidation by organometallic compounds,[1] alkane hydroxylation catalyzed by metalloporphyrin and related complexes,[3] superacid electrophilic alkane oxidation,[1,4] catalytic alkane functionalization by the Gif and Gif-Orsay systems[1,5] or by methyltrioxorhenium ($MeReO_3$)/H_2O_2,[6] by OsO_4,[7] oxidations by early-transition-metal polyoxometalate (PMO) complexes,[8] and other systems.[1] The mechanistic features of these systems differ drastically from industrial free-radical chain oxidations.[1] However, despite efforts, several problems have remained. For instance, for metalloporphyrin-catalyzed oxidations, making most processes truly catalytic is difficult, and the stability of the catalyst is often a problem.[3] Superacid media[4] present limitations of their own including handling and oxygenated functional group

† Dedicated to the memory of Professor Christopher S. Foote, a distinguished scientist and esteemed friend, who prematurely passed away in June 2005.

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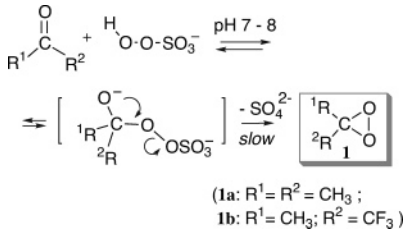
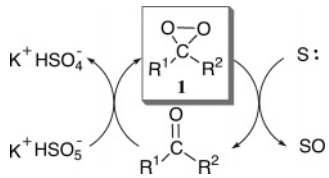
Scheme 1



Scheme 2



compatibility. As for the PMO approach, concerns were raised[9] about the rather large amounts of heavy metals involved.[9]

Parallel to catalytic methods, the search for *stoichiometric* oxidants capable of selective alkane oxygenations[10] has continued. Actually, some strong stoichiometric oxidation agents including Cr^{VI} and Mn^{VII} species[11] as well as ozone, O_3,[12] can yield alkane oxidation, albeit generally with modest yields and selectivities.

Since a joint Account in 1989,[13] our own approach to the selectivity problems associated with the oxidation of alkanes has been the application of dioxiranes, a now established powerful class of oxidants.[14] The salient developments of our work in the area are outlined below.

Background

Dioxiranes (**1**) are three-membered ring, strained peroxides that might be considered as paradigm reagents of electrophilic O-transfer reagents. The broad developments of dioxirane chemistry now witnessed was triggered by the discovery, first reported in 1979,[15] that the reaction of simple ketones with potassium caroate ($KHSO_5 = K^+ {}^-OSO_2OH$, pK_a 9.2) at a pH close to neutrality (7.5−8.0) generates dioxiranes (**1**). Stringent kinetic, stereochemical, and ^{18}O-labeling data allowed establishment of a likely mechanism for dioxirane formation (Scheme 1).[15]

The dioxirane generated in solution can bear attack by further caroate ion yielding sulfate ion and molecular oxygen; however, competitive with this, it can then be attacked by a variety of electron-rich substrates, S, yielding oxidation products SO (Scheme 2). In both reactions, the parent ketone is regenerated, so it returns to the catalytic cycle.[14,15]

Many complex or environmentally friendly simple ketones (e.g., acetone) can be employed in aqueous media (or under phase-transfer conditions) and are not appreciably consumed since they merely act as catalysts.[14,15]

A variety of applications, including enantioselective oxidations using suitable chiral ketones,[16] have utilized dioxiranes generated in situ. Dioxiranes thus generated from several D-fructose-derived carbonyls, as well as from C_2 symmetric ketones by the chiral binaphthalene scaffold, have been shown to yield often remarkable enantioselectivity in the asymmetric epoxidation of prochiral alkenes.[16]

Besides the applications in synthesis of dioxiranes in situ, a major breakthrough ensued from the finding that a few representatives of this family of peroxides, chiefly dimethyldioxirane DDO (**1a**)[17] and its trifluoro analogue TFDO (**1b**),[18] could actually be isolated (in solution of the parent ketone) by a simple process amounting to codistillation from buffered ketone−caroate mixtures. The detailed experimental procedures for obtaining solutions of isolated dioxiranes **1a** and **1b**, as well as the full spectroscopic characteristics of these peroxides, are now widely available.[14,17,18] Solutions of DDO and TFDO can be stored at −20 to 0 °C for weeks with only minor loss. For the DDO nonradical decomposition in acetone,[19,20] an activation energy (E_a) of 24.9 kcal mol^{-1} was estimated by Hull[20] by extrapolation at 25 °C of rate data taken at higher temperatures; our own estimate (Arrhenius plot) from rate data at 0, 10, 25, and 35 °C in CH_2Cl_2/acetone comes fairly close, that is, $E_a = 21.3 \pm 0.5$ kcal mol^{-1}. Similarly, in the absence of conditions that promote dioxirane radical decomposition,[19] we estimate $E_a = 18.6 \pm 0.6$ kcal mol^{-1} for TFDO unimolecular rearrangement into ester in CH_2Cl_2 from rates at −10, 0, 5, and 12 °C.[21]

The availability of DDO (**1a**) and of TFDO (**1b**) in the isolated form prompted an intensive utilization of these powerful oxidants to carry out a variety of synthetically useful oxidations under mild conditions.[14−16] Several reviews have covered the general reactivity of dioxiranes comprehensively.[14] The chemo-, regio-, and stereoselective olefin epoxidation presently remains the most extensively investigated application, chiefly because of the synthetic utility of epoxides as building blocks.[22]

Among the myriad of useful dioxirane oxidations, relatively less screened remains the transformation that undoubtedly counts as the highlight of dioxirane chemistry, that is, the oxygenation of simple, "unactivated" C−H bonds of alkanes.[23]

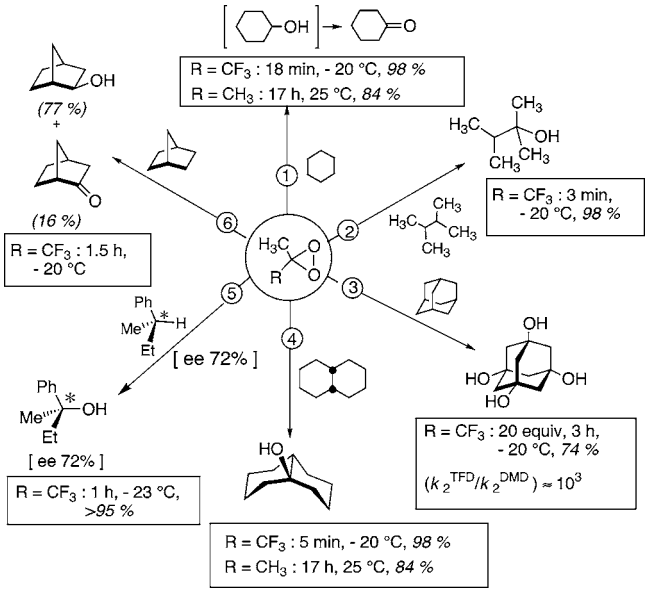
This Account will mainly focus on the chemo-, regio-, and stereoselectivities achievable in this key transformation. In addition to the preparative aspects, the key mechanistic features of the O-transfer process by these unique nonmetal oxidants will be outlined.

The Question of the Mechanism for Dioxirane O-Insertions

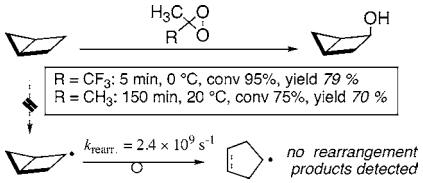
A few representative cases might serve to illustrate the key feature of dioxirane reactivity, that is, its efficiency to give selective O-atom insertions into alkane and cycloalkane C−H bonds under *extremely* mild conditions so that even simple "unactivated" hydrocarbons can be oxyfunctionalized (Scheme 3).

Inspection of Scheme 3 suggests that these oxidations generally require reaction times of hours and excess oxidant employing DDO.[14,23] Also, over long reaction times or abnormal reaction conditions (depletion of dissolved air O_2, nitroxide initiators, etc.), DDO free radical reactivity

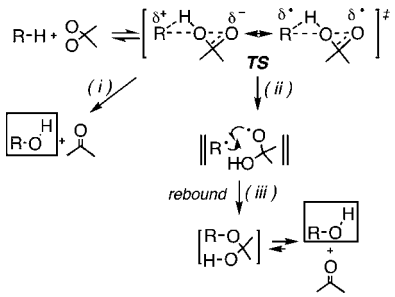
Scheme 3



Scheme 4



Scheme 5



might become triggered.[20,24]By of way contrast, the more powerful TFDO is capable of carrying out these transformations often in a matter of minutes and with unchanged selectivity.[23a] In this respect, quite telling is the practically complete conversion of cyclohexane into cyclohexanone by TFDO (transformation 1) in over 95% yield at −20 °C during ca. 20 min. Kinetic data for this representative oxyfunctionalization at 0 °C in CH_2Cl_2 are $k_2 = 2.9 \times 10^{-2}$ M^{-1} s^{-1}, $E_a = 14.3$ kcal mol^{-1}, $\Delta S^{\ddagger} = -15$ cal K^{-1} mol^{-1}, and $k_H/k_D = 2.2$.[23a] In general, when, as in this case, secondary alcohols are the initial oxidation products, these are further oxidized to the corresponding ketones. Actually, it is found that both DDO and TFDO are reagents useful also in the transformation of alcohols into carbonyl compounds.[25]

With the notable exception of norbornane (transformation 6, Scheme 3), in general TFDO oxygenations of alkanes are earmarked by high tertiary vs secondary selectivities (R_s^t from 15 to over 250). Indicative is the selective bridgehead hydroxylation of adamantane by TFDO to yield tetrahydroxy adamantane (transformation 3), accompanied only by its trihydroxy analogue. In this reaction, kinetic data show that TFDO is more reactive than DDO by a factor of ca. 10^3. However, taming the reactivity−selectivity principle (RSP),[14a] the sharp selectivity for tertiary bridgehead C−H hydroxylation remains unchanged despite the much higher TFDO reactivity.

As exemplified by the stereospecific bridgehead hydroxylation of *cis*-decalin (transformation 4), the high regio- and stereoselectivities recorded with DDO are maintained (and even enhanced) using TFDO. Also, optically active (−)-2-phenylbutane can be cleanly converted by TFDO into 2-phenyl-2-butanol in over 90% yield and with *complete retention of configuration* (transformation 5).

It is well established that oxygen atom transfer from dioxiranes to nucleophilic two-electron σ- or π-donors (e.g., S = sulfide, phosphine, alkene) involve an S_N2-like displacement at the peroxide O−O with concerted bond breaking of the and formation of a S−O bond.[13,14] Clearly, dioxirane O-insertion into a C−H bond cannot proceed via such an S_N2 pathway since it involves C−H bond cleavage in the hydrocarbon fragment in addition to the breaking of the peroxide O−O bond. A series of careful mechanistic studies have discounted that these reactions proceed via a free-radical pathway. For instance, the kinetic isotope effect (KIE) for oxygen insertion into a tertiary C−H bond (k_H/k_D ca. 2.2 with TFDO and ca. 5 with DDO) and the mentioned selective hydroxylation of (−)-2-phenylbutane with complete retention of configuration strongly militate against a radical pathway and support a mechanism involving concerted electrophilic O-insertion.[14a] Furthermore, the claim of a mechanism involving freely diffusing alkyl radicals could be conclusively set aside by the application of fast radical-clock probes such as 2-cyclopropyl propane,[26] and bicyclo[2.1.0]-pentane (BCP).[27] For instance, in the oxidation of BCP (Scheme 4) the *endo*-C-2 alcohol is accompanied by the corresponding C-2,C-3 diol only, and no rearrangement products could be detected; instead, the latter would be expected if bicyclo[2.1.0]pent-2-yl radicals were involved. Thus, the application of sensitive probes unequivocally excluded diffusively free radicals as intermediates in the hydroxylation.[26−28] Then, the mechanistic issue remains to revolve around whether the dioxirane hydroxylation of alkane C−H bonds occurs by a somewhat concerted oxenoid insertion (path i) or by initial singlet radical pair formation and subsequent collapse (paths ii and iii)-(Scheme 5). The latter would resemble the pathway advanced for cythochrome P450 oxygenations.[2]

It is worth noting that the "rebound" mechanisms (ii and iii) should be characterized by a different time scale with respect to a direct insertion path (i). Indeed, in the latter the direct collapse to products should occur during the time of a bond vibration, a subpicosecond lifetime. On the other hand, in a mechanism proceeding via the formation of a caged radical pair, in-cage reorganization and atomic translations would claim at least a few

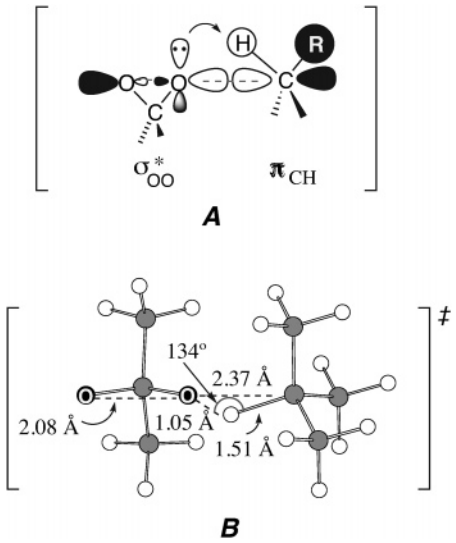


FIGURE 1. (A) General FMO model for dioxirane O-insertion into C−H bonds and (B) optimized (B3LYP/6-31-G*) TS for DDO oxygenation at *tert*-CH of isobutane.

picoseconds. The finding that no rearrangement products are found in BCP oxygenation and that the dioxirane oxidation of (−)-2-phenylbutane takes place with complete retention (see above) allows one to set a limiting lifetime for the caged radicals of ca. 1 ps, probably too short to be reconciled with a radical-pair pathway. Actually, the application of the ultrafast radical clock (*trans*-2-phenyl-cyclopropyl)ethane to DDO oxidation has allowed Newcomb to estimate an even shorter maximum lifetime of 0.2 ps for the putative "radical-pair" intermediate.[28] This is comparable to the lifetime of a TS computed from transition state theory, that is, 0.17 ps. The whole of the evidence above is definitely not consistent with the intermediacy of a radical pair, but rather argues for an "oxenoid" mechanism of concerted O-insertion into hydrocarbon C−H bonds.

Based on careful ab initio calculations, Bach proposed[29] a frontier molecular orbital (FMO) model for dioxirane O-insertion into hydrocarbon C−H bonds (panel A in Figure 1). In this FMO analysis, the electrophilic attack is directed along the peroxide O−O bond axis toward the relevant carbon atom of the hydrocarbon, so that the dioxirane electrophilic oxygen approaches a filled C−H fragment orbital, either π-CHR or σ-CHR, containing both a carbon 2p orbital and a hydrogen atom. The latter is then favorably oriented to be shifted to the approaching oxygen atom, which employs an electron pair to serve as migration terminus while the O−O bond is being broken.

In line with Bach's suggestions,[29] we find that this FMO model provides a unique rationale for both the stereospecificity and the stereoselectivity of dioxirane O-insertion into C−H bonds.

A number of high-level computations have provided insight concerning the detailed TS geometries for the process. The insertion of oxygen into the tertiary C−H in isobutane by DDO is reported[29] to proceed with a barrier of 22.4 kcal mol^{-1} in the gas phase at the CCSD(T)/6-31G*//B3LYP/6-31G* level; a correction for solvation ($CHCl_3$) reduces the barrier to 15.6 kcal mol^{-1}, in reasonable agreement with experimental data. The TS for the hydroxylation of isobutane by DDO (panel B in Figure 1) exhibits extensive C−H bond elongation (1.51 Å), which is consistent with the measured kinetic isotope effect for DDO oxygen insertion into a tertiary C−H bond (k_H/k_D ca. 5). However, the TS does exhibit some biradicaloid character. In fact, migration of the hydrogen is largely advanced (due to its lower mass), while the dioxirane electrophilic oxygen moves toward the tertiary carbon center *after* the O−H bond is nearly completely formed. On the whole, such a TS represents an *asynchronous*, albeit substantially *concerted*, "oxenoid" process of direct insertion.[29,30] In fact, it appears that ground-state singlet DDO can trigger molecule-induced homolysis of just very weak alkane σ bonds that already present some biradical character per se, such as the C−C bond in highly strained 1,3-didehydroadamantane.[30c]

Besides, intrinsic reaction coordinate (IRC) calculations and a restricted bond distance geometry optimization of the radical pair applied by Rauk[31] led to a alternative rendering of the oxidation mechanism in terms of a bifurcation of the reaction path (Scheme 5), which involves either a direct collapse to products (path i) or a radical pair (path ii) *via a common transition structure*. This mechanistic scenario had been earlier suggested by us.[25] We also envisaged[23a,25] that the TS for the dioxirane O-insertion could develop, along with some biradical character, certain polar nature with a partially charged cationic carbon (Scheme 5). This feature might become manifest in peculiar cases and occasionally bring about a reversal of the customary tert- over sec-CH selectivities of dioxirane oxygenations. Indeed not surprising in view of the outstanding stability of norbornyl cations, this is observed in the case of oxidation of norbornane (transformation 6, Scheme 3).

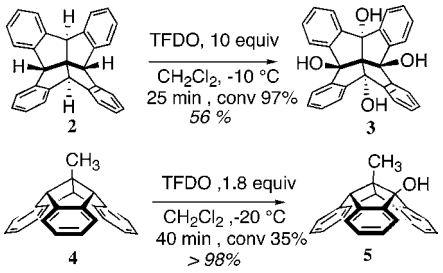
Altogether, the mechanistic scenario for dioxirane O-insertion into hydrocarbon carbon−hydrogen bonds somewhat resembles the mechanistic dilemma envisaged for certain cytochrome P450-catalyzed C−H oxygenations,[32,33] wherein a main insertion process competes with a pathway involving the production of cationic species.[32]

Selectivity in the Oxyfunctionalization of Target Compounds

During the last decade, we showed that the powerful TFDO is the reagent of choice to carry out the direct oxyfunctionalization even of structurally complex alkanes leading to higher yields, much faster conversions, and no loss of selectivity with respect to DDO.[14]

The regioselective functionalization of compounds presenting a complex molecular framework is an important goal in organic synthesis. In particular, the bridgehead functionalization of polycyclic compounds can provide an access to derivatives bearing quaternary carbon centers or even strained bridgehead double bonds. In this context, the controlled functionalization of centropolyindans[34] at

Scheme 6



their benzylic or benzhydrylic bridgehead positions or both is of particular interest since it allows the synthesis of complex three-dimensionally fused polyquinane skeletons.[34]

We found that representative centropolyindanes undergo selective oxygen atom insertion into their bridgehead C−H bonds by dioxiranes.[35] For instance, by variation of the excess of the TFDO reagent, tetrabenzo[5.5.5.5]-fenestrane (fenestrindane, **2**) could be converted either into the corresponding monoalcohol or into the corresponding all-bridgehead tetraalcohol **3** (Scheme 6).[35]

As for centrotriindans, paradigmatic is the oxygenation of 10-methyltribenzotriquinacene (**4**)[35] at variance with the sluggish reaction using DDO, the selective bridgehead oxyfunctionalization of this substrate was easy employing TFDO, affording the monoalcohol **5** as the only reaction product (Scheme 6).

Akin to "dry ozonation",[36] dioxirane oxidation of simple hydrocarbons bearing cyclopropyl moieties suggests that alkane C−H bonds positioned "α" to a cyclopropane ring might become "activated" toward dioxirane O-insertion.[37] Product distributions indicate that usually cyclopropyl activation of α-C−H bonds largely prevails when no tertiary C−H is present. It turns out that the cyclopropyl moieties, if suitably oriented, have a significant activating influence even on methylene C−H bonds α to the cyclopropyl group. Indeed, these are the positions where a developing carbocation would be conspicuously stabilized by a cyclopropyl group anchored in a favorable "bisected" orientation because of the prominent p character of the orbital generated at the cyclopropylcarbinyl carbon (Scheme 7).[38] The preference for a bisected cyclopropylcarbinyl radical is significantly smaller.

On basis of the general FMO model presented above, it is apparent that methylene C−H bonds could become cyclopropyl-activated also in an "oxenoid" O-insertion by dioxiranes, for instance, as sketched in panel C (Scheme 7). Such cyclopropyl activation can be invoked to rationalize the preferential oxyfunctionalization at the α-CH_2 for spirooctane **6** (Scheme 8).[37]

However, with the cyclopropane moiety relatively free to adopt orientations with almost a continuum of angles between the extremes of 0° and 90° with respect to the p orbital component of the proximal C−H bonds, cyclopropyl activation can compete only mildly with oxidation at tertiary C−H.[37] Thus, in the absence of serious steric constrains preventing the cyclopropane moiety from reaching a favorable orientation, the normal order of dioxirane reactivity toward alkane C−H bonds is tertiary C−H ≈ benzhydrylic C−H > α-cyclopropyl C−H > benzylic C−H ≈ secondary C−H > primary C−H.

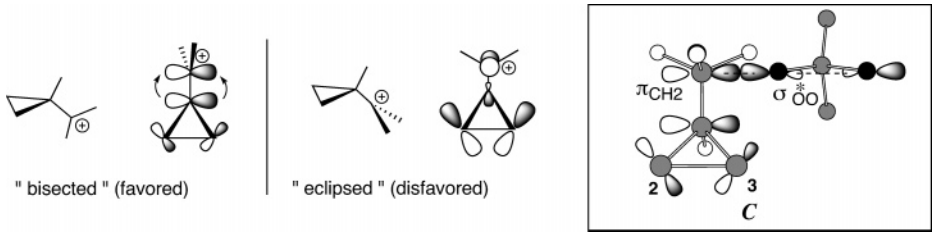
That a suitably oriented cyclopropyl moiety can exercise a marked activating effect on dioxirane oxidation at "α" C−H bonds is further illustrated by the 2,4-didehydroadamantane (**8**) case (Scheme 9).[37,39]

For this compound, Murray et al. reported that reaction with DDO (2.2 equiv) proceeds at room temperature with 82% conversion in 12 h, yielding 2,4-didehydroadamantan-10-one and 2,4-didehydroadamantan-7-ol in 29% and 21% yield, respectively.[39] We found that a comparable selectivity is attained with the more powerful TFDO, despite the oxidation being considerably faster, achieving 80% conversion in just 1.5 h only at 0 °C. Then, treatment with TFDO excess (4 equiv) at the conditions in Scheme 9 results in the practically complete substrate conversion into ketone and the valuable 7-hydroxy-2,4-didehydroadamantan-10-one (Scheme 9). Control experiments showed that the latter is generated by the consecutive oxidation of the alcohol 7-hydroxy-2,4-didehydroadamantane initially formed.[37]

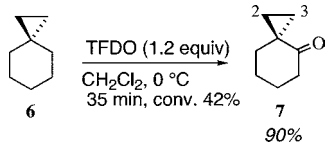
In this, and in all of the cases examined, oxidative scission of the cyclopropyl moiety by dioxiranes does not take place. This behavior contrasts with the application of ozone (a bona fide ground-state singlet biradical) to 2,4-didehydroadamantane (Scheme 9).[39] Thus, dioxiranes are capable of giving oxyfunctionalization at C−H's neighbors of the cyclopropane moiety, leaving cyclopropane C−C bonds intact. Again, this is reminiscent of hydroxylations of several hydrocarbons containing annealated or spirofused cyclopropane moieties by cytochrome P450 enzymes.[40]

Akin to the 2,4-didehydroadamantane case, in the TFDO oxyfunctionalization of Binor S (a polycyclic hydrocarbon of complex architecture), the valuable ketone **9** resulting from oxidation methylene CH_2 "α" to the cyclopropyl moiety is obtained,[41] along with the diol **10**, expected from hydroxylation at tertiary bridgehead C−H bonds (Scheme 10). In addition, the 1,2,8-triol could also be isolated, albeit in low yield.[41]

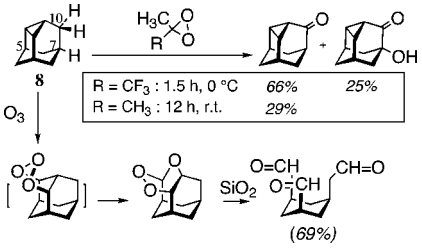
Scheme 7



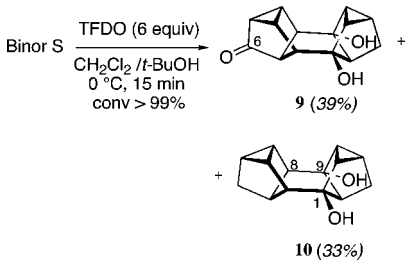
Scheme 8



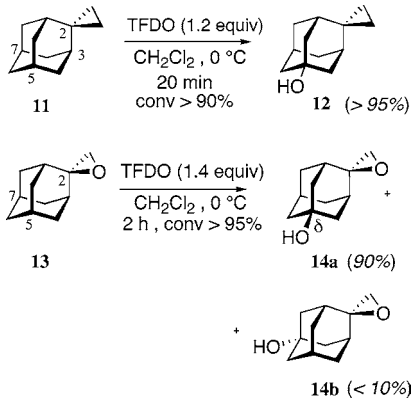
Scheme 9



Scheme 10



Scheme 11



Control experiments using the diol **10** (first isolated by Eaton et al. using DDO in situ)[42] showed that oxyfunctionalization at the C-6 methylene takes place in the facing nortricyclane subunit after hydroxylation at the bridgehead C(1)−H and C(9)−H.[41]

The arrangement of the cyclopropyl moiety in the spiro adamantylcyclopropane **11** in Scheme 11 makes this substrate another informative probe; here, TFDO hydroxylation of occurs at bridgehead C-5 exclusively, yielding the bridgehead alcohol **12** shown (Scheme 11).[37] In this case, the proximal tertiary C−H's at C-3 and C-1 become *deactivated* since their p orbital component is forced to lay in the unfavorable "eclipsed" arrangement with respect to the cyclopropane ring.

A similar regioselectivity is observed[43,44] for the analogous methyleneadamentane oxide **13** bearing a spiro fused oxiranyl ring.[43a] Here, hydroxylation at the remaining bridgeheads (C-5−H and C-7−H) occurs with astounding *Z*/*E* diastereoselectivity (Scheme 11). This parallels the stereo discrimination observed for the TFDO oxidation of adamantanes carrying electron-withdrawing substituents at C2.[43b]

Site-Selective Remote Hydroxylations

The selective oxyfunctionalization of *remote* C−H bonds, that is, which are several carbon atoms away from an existing functional group, constitutes a challenging goal for the synthetic chemists.[44] Indeed, in the oxidation simple or complex functionalized molecules, regio- and site selectivity is commonly ruled by the competitive reaction of the oxidant with rather indiscriminate sections of the substrate. Instead, high regio- and site-selectivities are frequently observed in microbiological hydroxylation of C−H bonds, since enzymes can anchor one or more existing functional group and *geometrically* select a specific site of the substrate. Chemical methods that imitate enzyme geometric control in achieving site selectivities have been termed *biomimetic*. An exemplary case has been recently reported by Breslow and co-workers.[45] In their elegant work, these authors employed PhIO and manganese-perfluoroporphyrin catalysts carrying cyclodextrin binding groups to perform the selective C9 hydroxylation at a cyclodextrin-anchored triester of 5α-androstane-3β,6α,-17β-triol. Of course, the selective hydroxylation at the steroid C-9 position are of much practical interest.[45]

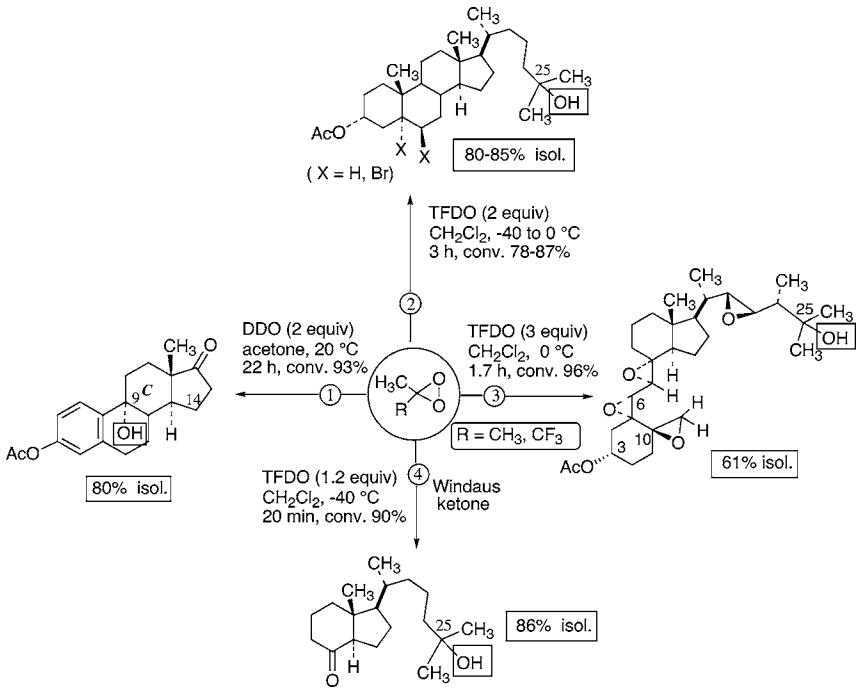
A major highlight of dioxirane chemistry consists precisely in their ability to yield site selective hydroxylations of target substrates without the need for a catalyst and for elaborate procedures. The great potential of these reagents is illustrated by a number of impressive oxyfunctionalizations on steroid substrates; selected examples are presented in Scheme 12.

For instance, valuable in synthesis is the oxidation of estrone acetate by DDO or TFDO, allowing the hydroxylation to occur selectively at C-9 (transformation 1).

Other examples in Scheme 12 illustrate the fact that in steroid oxidations the dioxirane preference for tertiary C−H oxidation is accompanied by remarkable regio- and site selectivity. As an example, dioxirane oxidation of the cholestane derivatives in Scheme 12 (transformation 2) yields the selective C-25 side-chain hydroxylation without detectable reaction at the other tertiary carbons.[46] This biomimetic site selectivity was found to apply to vitamin D derivatives as well. Indeed, upon reaction with TFDO the tetraepoxide of 3β-acetyl vitamin D_2 affords its 25-hydroxy derivative in good isolated yield (transformation 3).[47] This C-25−H site-selectivity parallels that recorded for the analogous triepoxide of vitamin D_3.[47] The feat of the *direct* C-25 side-chain hydroxylation of vitamin D derivatives is remarkable in view of the biological significance and uses of 25-hydroxy-vitamin D_3 and D_2 and their metabolites.

Using dioxiranes, one can also easily accomplish the conversion of Windaus−Grundmann ketones into their precious C25 hydroxy derivatives (transformation 4); the latter are valuable synthons in the Lythgoe-type conver-

Scheme 12



gent approach to 1,25-dihydroxy vitamin D_3. A longer reaction time (48 h) is required to achieve transformation 4 employing DDO.[46b]

The origin of the high site selectivities displayed by dioxiranes might be traced to the mentioned stringent steric and stereoelectronic alignment demands, for instance, as sketched in panel D (Figure 2) . Here, the site selectivity might derive from a distinct preference displayed by dioxiranes in attacking tertiary C−H centers bearing *geminal* methyl groups; in fact, these offer less steric opposition to optimal stereoalignment as compared to the other crowded tertiary C−H positions.

The oxyfunctionalization of unactivated methine C−H's with dioxiranes is also feasible for various substituted steroids related to the 5β-cholane and 5α-cholestane series to give novel mono- and dihydroxylated steroids.[48] This nonenzymatic procedure may be advantageously applied to selective and short-course syntheses of other bioactive molecules.[49]

The feasibility of dioxirane remote oxyfunctionalization is not limited to steroidal compounds. Indeed, we recently

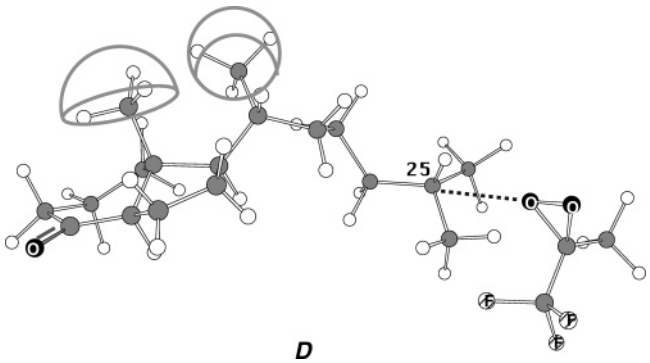
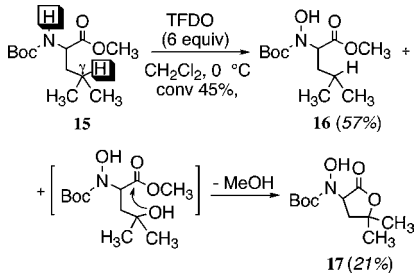


FIGURE 2. Molecular model for the selective O-insertion into the C-25−H of Grundmann ketone by methyl(trifluoromethyl)dioxirane.

Scheme 13



reported[50] that certain valuable epoxy ketones can also be obtained by the *direct* oxidation of representative bicyclic epoxides using TFDO; with respect to the epoxide ring, the oxyfunctionalization usually occurs at the remote γ or δ C−H bonds or both. The carbonyl is formed via the corresponding *gem*-diol.

Other interesting cases of remote oxyfunctionalization regarding the TFDO oxidation of ammonium salts,[51] of open-chain carbonyls,[43c] and of certain cyclic and bicyclic esters have been reported.[43]

Conspicuous site selectivity is often noted in the DDO hydroxylation of N-protected derivatives of α-amino acid esters bearing an alkyl side chain; this results in different products depending on the structure.[52] Although these reactions are rather sluggish with DDO, requiring long reaction times for sizable substrate conversion, they offer a novel entry to side-chain modified α-amino acids and peptides that avoids multistep synthetic approaches. High regioselectivity for the O-insertion into the γ-CH bond of leucine residues with respect to the weaker α-CH bonds has been found.[52]

These reactions occur more readily using the powerful TFDO instead of DDO. Thus, reaction of Boc-Leu-OMe (**15**) at the conditions given in Scheme 13 yields during 6

h (91% conv) the *N*-hydroxy derivative of the butanolide **17** in 21% yield as the major product, along with the uncyclized *N*-hydroxy derivative **16** of the starting Boc-Leu-OMe.[53]

Closing Remarks

The summary given in this Account points out that dioxiranes DDO and TFDO in the isolated form are nearly ideal *stoichiometric* O-atom insertion agents into unactivated C−H bonds. The applications in organic synthesis of these powerful oxidant reagents are proliferating since they are quite reactive under unusually mild conditions yet highly selective (chemo-, regio-, and stereo-) and easily obtained from readily available starting materials (i.e., their parent ketones and caroate). Examples herein suggest that, because of its superior reactivity and high selectivity, the powerful TFDO should be the reagent of choice to carry out alkane oxygenations. Concerns about the cost of the parent reagent, that is, 1,1,1-trifluoropropanone (TFP), subside when one considers that the expensive TFP (bp 22 °C) is easily recovered from spent reaction mixtures by fractional distillation.

The application of stereochemical and radical probes, as well as kinetics and high-level computations, all support the view of a substantially nonradical, concerted mechanism of dioxirane electrophilic insertion into C−H bonds. The gathering of unambiguous evidence concerning the propensity of dioxiranes to give concerted O-insertions appears to have been hindered by the dichotomy existing between them and bis(oxyl) diradicals, that is, $^{\bullet}O-C(R)-CH_3-O^{\bullet}$, as the actual reactive species.[13,14,19,24,30] However, the latter represent a class of ephemeral entities that, whenever formed, would quickly rearrange to ester with practically no barrier.[54]

Be the mechanistic details as they may, we trust this Account demonstrates that dioxirane oxygenation of C−H bonds is a procedure of practical value in organic synthesis because of its efficiency and simplicity.

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