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Oxyfunctionalization of Non-Natural Targets by Dioxiranes. 5. Selective Oxidation of Hydrocarbons Bearing Cyclopropyl Moieties[1]

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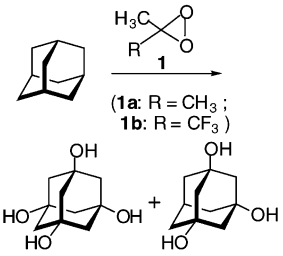
The powerful methyl(trifluoromethyl)dioxirane (**1b**) was employed to achieve the direct oxyfunctionalization of 2,4-didehydroadamantane (**5**), spiro[cyclopropane-1,2′-adamantane] (**9**), spiro[2.5]-octane (**17**), and bicyclo[6.1.0]nonane (**19**). The results are compared with those attained in the analogous oxidation of two alkylcyclopropanes, i.e., *n*-butylcyclopropane (**11**) and (3-methyl-butyl)-cyclopropane (**14**). The product distributions observed for **11** and **14** show that cyclopropyl activation of α-C−H bonds largely prevails when no tertiary C−H are present in the open chain in the tether; however, in the oxyfunctionalixation of **14** cyclopropyl activation competes only mildly with hydroxylation at the tertiary C−H. The application of dioxirane **1b** to polycyclic alkanes possessing a sufficiently rigid framework (such as **5** and **9**) demonstrates the relevance of relative orientation of the cyclopropane moiety with respect to the proximal C−H undergoing oxidation. At one extreme, as observed in the oxidation of rigid spiro compound **9**, even bridgehead tertiary C−H's become deactivated by the proximal cyclopropyl moiety laying in the unfavorable "eclipsed" (perpendicular) orientation; at the other end, a cyclopropane moiety constrained in a favorable "bisected" orientation (as for didehydroadamantane **5**) can activate an "α" methylene CH_2 to compete effectively with dioxirane O-insertion into tertiary C−H bonds. Comparison with literature reports describing similar oxidations by dimethyldioxirane (**1a**) demonstrate that methyl(trifluoromethyl)dioxirane (**1b**) presents similar selectivity and remarkably superior reactivity.

Introduction

During the past decade, the direct oxyfunctionalization of "unactivated" C−H bonds of simple and structurally complex alkanes[1,2] using dioxiranes (**1**) became a highlight of the chemistry of these powerful oxidants.[3] These reactions are characterized by high selectivity, and it is found that tertiary C−H bonds are considerably more reactive toward dioxirane O-insertion than their secondary C−H or primary complements.[1−3] Thus, high tertiary vs secondary selectivities (R_s^t from 15 to over 250) can be routinely achieved;[2b] as an example, the selective bridgehead hydroxylation of adamantane (eq 1) by methyl(trifluoromethyl)dioxirane (TFD) (**1b**) yields adamantan-1,3,5,7-tetraol along with the 1,3,5-triol, in 73% and 24% yield, respectively.[2c] In these oxidations, kinetic data have shown that **1b** is more reactive than dimethyldioxirane (DMD) (**1a**) by a factor of over 700, with no loss of selectivity.[2c,3a]



(1)

More recent data suggest that alkane C−H bonds positioned "α" to a cyclopropane ring might become "activated" toward dioxirane O-insertion.[4] In fact, in the dioxirane oxyfunctionalization of Binor S (a polycyclic

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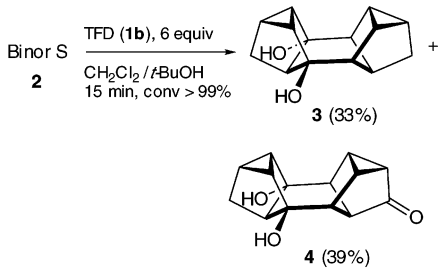
hydrocarbon of complex architecture),[1,5] we reported that applying the powerful TFD yields the valuable ketone resulting from C-9 methylene oxidation,[1] along with products expected from preferential hydroxylation at bridgehead C−H bonds.[1,3]



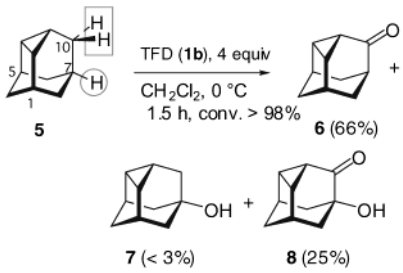
(2)

The results were rationalized on ground of a FMO model, suggesting that the mentioned methylene C−H bonds might become activated by the neighboring cyclopropyl group.[1] In **2**, the rich-in-*p* character cyclopropane ring orbitals are constrained by the rigid framework to lay in the favorable "bisected" orientation[1] with respect to the *p* component of the "α" methylene C−H bonds; the latter *p* orbitals interact with the dioxirane empty σ^*_{O-O} orbital during the "oxenoid" O-insertion.[1] To test this hypothesis, we undertook to examine the reactivity of dioxiranes toward a few hydrocarbons of choice, aiming to establish the effect of the cyclopropyl moiety on selectivity. Our findings are reported below.

Results and Discussion

That the cyclopropyl moiety can exercise a marked activating effect on dioxirane oxidation at "α" C−H bonds is illustrated by the case of 2,4-didehydroadamantane (**5**). For this substrate, Murray et al. have reported [7] that reaction with 2.2 equiv of DMD (**1a**) proceeds at room temperature with 82% conversion, yielding 2,4-didehydroadamantan-10-one (**6**) and 2,4-didehydroadamantan-7-ol (**7**) in 29% and 21% yield, respectively, during 12 h. We verified that the comparable selectivity is attained in the oxyfunctionalization of **5** on going from DMD (**1a**) to the more powerful TFD (**1b**). In the presence of 2 equiv of TFD, hydrocarbon **5** is converted to ketone **6** and alcohol **7** in 40 and 60% yield, respectively. The oxidation with TFD is notably faster, achieving 80% conversion in 1.5 h at 0 °C.

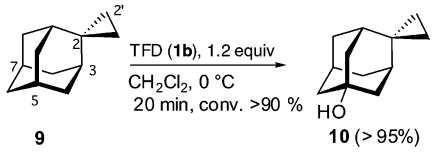
Then, treatment of **5** with TFD excess (4 equiv) at the conditions in eq 3 results in the practically complete substrate conversion into ketone **6** and the valuable 7-hydroxy-2,4-didehydroadamantan-10-one (**8**) as the main products. GC monitoring of the reaction showed that ketol **8** is generated by the consecutive oxidation of the alcohol **7**. In fact, in control experiments we verified that authentic samples of 2,4-didehydroadamantan-7-ol



(3)

(**7**)[8] could be cleanly transformed into **8** (>95% GC yield, 93% conv, 2 h) using TFD (2 equiv). The novel ketol (**8**) presents a strong IR C=O absorption at 1689 cm^{-1}, as well as inter- and intramolecular bonded OH stretching bands; it was fully characterized by HRMS and by NMR. The ^1H NMR spectra of **8** (akin to that of ketone **6**) display inter alia one doublet and one complex multiplet, respectively, at δ 2.64 and 2.19 (ratio 2:1) due to the C-*H* resonances of the constrained cyclopropane ring. In the ^{13}C NMR spectrum, well-resolved methine carbon signals at δ 34.2, and 35.7 are attributed to the cyclopropane carbons (reflecting the C_s symmetry of **8**), while the *C*=O and the *C*−OH signals are positioned, respectively, at δ 211.3 and 72.8.

Similar to the Binor S case mentioned above, the finding that dioxirane O-insertion at C-10 methylene in **5** can compete effectively with the normally favored insertion at tertiary bridgehead C−H may be ascribed to the favorable bisected orientation of the methylene C−H bonds relative to the cyclopropyl ring. This view is reinforced by the observation that no hydroxylation occurs at C-1 and C-5 tertiary C−H; indeed, these bridgehead bonds would become deactivated toward O-insertion since their *p* orbital component nearly lays in the unfavorable "eclipsed" ("perpendicular") orientation with respect to the C2′−C3′ bond of the cyclopropyl moiety.[1,6]



(4)

The peculiar arrangement of the spirofused cyclopropyl moiety in the framework of **9** makes this substrate another attractive probe. We find that hydroxylation of spiro adamantanecyclopropane **9** occurs at bridgehead C-5 exclusively, yielding the bridgehead alcohol **10**[9] (eq 4). In a parallel with the cyclopropylcarbinyl cation case,[6] it is likely that the constrained perpendicular conformation of the transition state for dioxirane O-insertion results in sizable destabilization. Indeed, the proximal C−H's at C-3 and C-1 become deactivated because their *p* orbital component is forced to lay in the unfavorable "eclipsed" arrangement with respect to the cyclopropane ring. It is instructive to compare the data above with those collected for representative open-chain alkylcyclopropanes such as **11** and **14** (Chart 1). Here, in the absence of serious steric constrains, the cyclopropane moiety is relatively free to adopt orientations with almost continuous angles between the extremes of 0° and 90°

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CHART 1

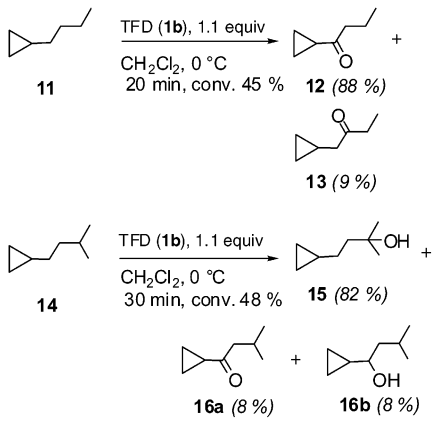
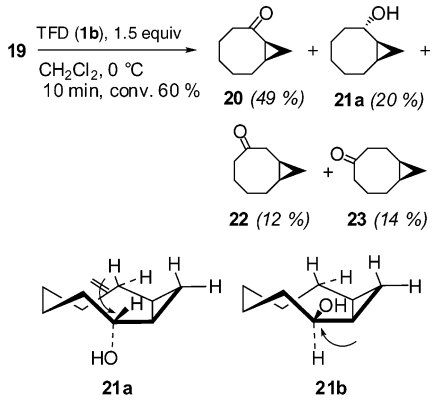
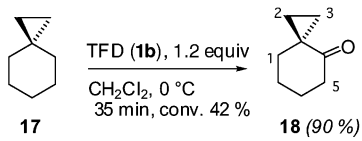


CHART 2



with respect to the *p* orbital component of the proximal C−H bonds.

The product distributions observed for **11** indicate that cyclopropyl activation of α-C−H bonds largely prevails when no tertiary C−H is present. However, the products formed in the oxidation of **14** (Chart 1) clearly demonstrate that normally cyclopropyl activation can compete only mildly with oxidation at tertiary C−H. Cyclopropyl activation might again be invoked in order to rationalize the preferential oxyfunctionalization at α-CH_2 observed for spirooctane **17** (eq 5) and for bicyclononane **19** (Chart 2). Indeed, in the oxidation of **17**, the spiro[2.5]octan-4-one (**18**)[10] produced was accompanied by just small amounts of the isomeric 5-one and 6-one (3% and 4%, respectively).



(5)

The reaction of *cis*-bicyclononane (**19**) with DMD (**1a**) has been previously explored; ketones **20**, **22**, and **23** were all produced (with **20** in highest proportion, ca. 65%), but with a combined yield of a mere 9%.[11] The advantage of using the powerful TFD (**1b**) in these oxidation is further demonstrated by the results reported in Chart 2.

Concerning products of oxyfunctionalization at the CH_2 that are activated by the contiguous cyclopropane ring in **19**, it is worth of note that just some of the *anti* alcohol **21a** (and none of the *syn* **21b**) is left behind as intermediate during the transformation into carbonyl. This might be ascribed to stereochemical effects that govern the O-insertion at the *syn* vs the *anti* alcohol leading to the *gem*-diol precursor of carbonyl. Specifically, in a preferred quasi chair-boat conformation, the *anti* alcohol **21a** would experience a greater steric hindrance (Chart 2) to the optimal stereoalignment required for dioxirane O-insertion,[12] hence its slowest conversion into carbonyl with respect to the its *syn* counterpart **21b**.[13]

In conclusion, data reported herein confirm that the cyclopropane moiety can have a marked influence in activating proximal α-C−H bonds toward dioxirane oxyfunctionalization; normally, this directing effect is distinctly minor compared to that exercised by a tertiary C−H. However, the application of dioxiranes to polycyclic alkanes possessing a sufficiently rigid framework demonstrates the relevance of relative orientation of the cyclopropane moiety with respect to the C−H bonds undergoing oxyfunctionalization. For acyclic substrates, the directing effect is significantly weaker than the activating influence of a tertiary C−H. At one extreme, even bridgehead tertiary C−H's are deactivated by a perpendicular orientation relative to the plane of a proximal cyclopropane. At the other extreme, secondary C−H bonds constrained to a "bisected" orientation relative to the neighboring cyclopropane are sufficiently activated to a point that their oxyfunctionalization effectively competes with the otherwise preferred O-insertion into tertiary C−H bonds at bridgeheads. Thus, stringent stereoalignment factors seem to dictate transitions in regioselectivity. In fact, even bridgehead *tertiary* C−H's might become deactivated by a proximal cyclopropyl moiety laying perpendicularly, as observed in the oxidation of rigid spiro compound **9** (hence the selective hydroxylation at the distal (γ) bridgehead C5−H).

It should be mentioned that in none of the cases examined does oxidative scission of the cyclopropyl moiety take place. This behavior is in contrast with the application of ozone (a bona fide ground-state singlet biradical)[14] to analogous systems, for instance, 2,4-didehydroadamantane (**5**).[7] Thus, it seems that dioxiranes are capable of giving oxyfunctionalization exclusively at C−H's neighboring the cyclopropane moiety,

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(13) This was confirmed through competition experiments wherein authentic samples of the stereomeric alcohols were made to react with TFD in CH_2Cl_2 at 0 °C. With 3.8×10^{-2} M **21a** and 3.1×10^{-2} M **21b**, both in excess over dioxirane (the limiting reagent, 1.4×10^{-2} M), GC monitoring and peak integration (Freon A112 internal standard) allowed us to estimate that the calibrated (A_{syn}/A_{anti}) area ratio changes from 0.95 to 0.46 upon dioxirane complete consumption (10 s, iodometry). Thus, the transformation of *syn* alcohol **21b** into ketone **20** is over twice faster than that of its *anti* counterpart **21a**.
(14) For instance, see: Harding, L. B.; Goddard, W. A. *J. Am. Chem. Soc.* **1978**, *100*, 7180.

leaving cyclopropane C−C bonds intact.[15] This is similar to hydroxylations of several hydrocarbons containing annealated or spirofused cyclopropane moieties by cytochrome P450 enzymes.[16] There are significant differences, however. For bicyclo[2.1.0]pentane (BCP), a fast radical "clock",[17] P450 oxidation gives a 7:1 relative yield of unrearranged to ring-opening products,[16a] whereas none of the latter result from the application of DMD (**1a**).[4a] Altough the reaction of the bacterial enzyme $P450_{cam}$ with spiro[2.5]octane (**17**) yields no products derived from ring-opening of a cyclopropyl carbinyl radical, the product distribution from this oxidation varies significantly from dioxirane oxidation (eq 5) since the 6-hydroxy, 5-hydroxy, and 4-hydroxy derivatives are all produced, with the latter (amounting to hydroxylation at CH_2 β to the cyclopropane ring) as the major product (63%).[16b] It is likely that the direct, highly regio- and stereospecific dioxirane oxidation of target non-natural molecules herein and of strained "cage" compounds[18] will find convenient applications in the facile access to new compounds and useful building blocks.

Experimental Section

Materials and Methods. Boiling points and melting points were not corrected. The GC analyses were run using a SPB-5 column (30 m × 0.25 μm id); in most cases, 1,1,1,2-tetrachloro-2,2-difluoroethane (Freon A112) was employed as inert internal standard. Column chromatography was performed using silicagel (230−400 mesh), *n*-pentane to *n*-pentane/Et_2O 9:1 gradient eluent. The MS analyses were performed in EI mode (70 eV). The ^{1}H NMR spectra were recorded on a 500 MHz and/or 200 MHz spectrometer; resonances are referenced to residual isotopic impurity $CHCl_3$ (7.26 ppm) of solvent $CDCl_3$ and/or to TMS. The ^{13}C NMR spectra (125.759 MHz) are referenced to the middle peak of $CDCl_3$ solvent (77.0 ppm). FTIR spectra are relative to KBr pellets or films (deposited on KBr plates). High-resolution MS spectra were run in EI^+ mode (source temperature 200 °C, trap current 150 μA, EE 30 eV, DIP). Commercial 1,1,1-trifluoro-2-propanone (TFP) (bp 22 °C) was purified by fractional distillation over granular P_2O_5, stored over 5 Å molecular sieves, and routinely redistilled prior to use. Commercial starting materials, methylene chloride, and other solvents were purified by standard methods. Curox triple salt $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$ (a gift from Peroxid-Chemie GmbH, Münich, Germany) was our source of potassium peroxymonosulfate employed in the synthesis of dioxirane. Solutions of 0.8−1.0 M methyl(trifluoromethyl)dioxirane (**1b**) in TFP and solutions of 0.08−0.16 M dimethyldioxirane (**1**) in acetone were obtained by adopting procedures, equipment, and precautions already reported in detail.[2b,19] 2,4-Didehydroadamantane (**5**) [mp 201−203 °C; lit.[20a] mp 201−204 °C] was prepared upon pyrolysis of the lithium salt of adamant-2-one-*p*-tosylhydrazone,[20b] and purified by column chromatography (silicagel, pentane). 2-Methyleneadamantane was obtained upon dehydration (H_3PO_4) of commercial 2-methyl-2-adamantanol and purified (99%+, GC) by sublimation (mp 136−137 °C).[21] Starting with the corresponding alkenes, spiro[cyclopropane-1,2′-adamantane] (**9**),[9] *n*-butylcyclopropane (**11**),[22a,23] (3-methyl-butyl)-cyclopropane (**14**) (HRMS calcd for C_8H_{16} 112.1252, found 112.1251; ^{1}H and ^{13}C NMR cf. Supporting Information), spiro[2.5]octane (**17**),[24] and bicyclo[6.1.0]-nonane (**19**),[24d,25] were obtained upon Simmons−Smith cyclopropanation with CH_2I_2/Zn/CuCl.[22] Authentic samples of oxidation products 1-cyclopropyl butan-1-one (**12**),[26,27] 1-cyclopropylbutan-2-one (**13**),[27b] 4-cyclopropyl-2-methyl-butan-2-ol (**15**), 1-cyclopropyl-3-methyl-butan-1-one (**16a**),[28] 1-cyclopropyl-3-methyl-butan-1-ol (**16b**),[28] *cis*-bicyclo[6.1.0]nonan-2-one (**20**),[29,30] and *anti*- and *syn*-bicyclo[6.1.0]nonan-2-ol (**21a** and **21b**, respectively)[29] were obtained following the literature procedures.[22,31]

Oxidation of Spiro[cyclopropane-1,2′-adamantane] (9) with Methyl(trifluoromethyl)dioxirane (1b). The following procedure is representative of hydrocarbon oxidations using TFD. To a stirred solution of **9** (220 mg, 1.36 mmol) dissolved in 10 mL of CH_2Cl_2 (also containing the Freon A112 internal standard) and kept at 0 °C was added methyl(trifluoromethyl)dioxirane (2.5 mL of 0.65 M **1b** in TFP, 1.6 mmol) in one portion. The reaction was monitored by GC. After 20 min, removal of the volatile solvents in vacuo and column chromatography afforded pure (99%+, GC) 5-hydroxy-spiro[cyclopropane-1,2′-adamantane] (**10**)[9] (225 mg, 1.26 mmol, isolated yield 93%): white solid, uncorrected mp 138−140 °C [lit.[9] mp 139−140 °C]; spectral characteristics were in agreement with literature data.[9]

Oxidation of 2,4-Didehydroadamantane (5) with Methyl(trifluoromethyl)dioxirane. According to the above procedure, hydrocarbon **5** (116 mg, 0.86 mmol) dissolved in CH_2Cl_2 (15 mL) was made to react at 0 °C with excess methyl(trifluoromethyl)dioxirane (**1b**) (5 mL, 0.74 M in TFP, 3.70 mmol), and the reaction was monitored by GC. After 1.5 h, removal of the solvents in vacuo and column chromatography afforded 8,9-didehydroadamantan-2-one **6** (86 mg, 0.58 mmol, yield 66%; uncorrected mp 206−207 °C;[32] spectral data were in agreement with literature[7,32]) and ketol **8** (38 mg, 0.23 mmol, yield 25%). 3-Hydroxy-8,9-didehydroadamantan-2-one (**8**): white solid, uncorrected mp 196−197 °C (98%+, GC); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.98 (s, 1H), 2.64 (d, 2H, J = 2), 2.45 (tt, 2H, J = 8, J = 2), 2.20 (complex m, 1H, J = 10), 2.10 (td, 1H,

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$J = 9$, $J = 2$), 1.90 (m, 4H), 1.62 (dd, 1H, $J = 9$, $J = 2$); $\{^1H\}^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 211.3 (*C*=O), 72.8 (C−OH), 50.5, 45.4, 39.7, 35.7, 34.2; IR (CH_2Cl_2) 3590, 3473, 3054, 2926, 1689, 1458, 1142, 1044 cm^{-1}; GC/MS (70 eV) *m*/*z* (rel intensity) 164 (M^+, 9), 136 (12), 79 (52), 58 (100), 43 (15); HRMS calcd for $C_{10}H_{12}O_2$ 164.0839, found 164.0837.

7-Hydroxy-didehydro-2,4-adamantane (7) was prepared upon oxidation of 2,4-didehydroadamantane (**5**) with 1 equiv of methyl(trifluoro-methyl)dioxirane (**1b**) in CH_2Cl_2 (10 mL) on a 1 mmol scale. Solvent removal in vacuo and column chromatography afforded alcohol **7**: uncorrected mp 200−201 °C (98%+, GC); ^1H and ^{13}C NMR data in agreement with literature.[7,8] Oxidation of spiro[2.5]octane (**17**) (1.8 mmol) in CH_2Cl_2 (10 mL) with 2.2 equiv of TFD (**1b**), after solvent removal and distillation. provided pure spiro[2.5]octan-4-one (**18**): uncorrected bp 85−86 °C/26 mmHg [lit.[10] bp 82−84 °C/24 mmHg] (98%+, GC); GC/MS, ^1H and ^{13}C NMR characteristics consistent with the given structure and with reported literature data.[10,33] Conversion of **18** into the corresponding 2,4-dinitrophenylhydrazone provided a light-orange crystalline derivative: mp 158−159 °C.[34]

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Supporting Information Available: Characterization data for compounds **14**, **15**, **16a**, and **16b**, and copies of ^1H NMR, $\{^1H\}^{13}C$ NMR, and HRMS spectra for ketol **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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