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An Effective Method for Allylic Oxidation of Δ^5-Steroids Using *tert*-Butyl Hydroperoxide

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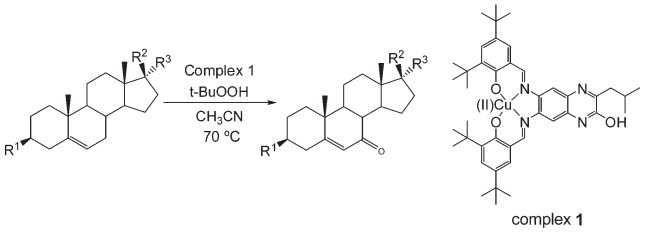
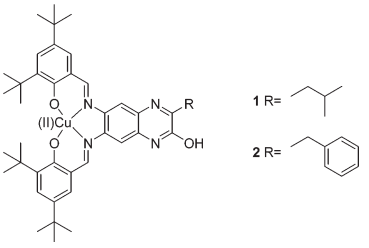


An allylic oxidation method for Δ^5-steroids using TBHP as oxidant with a 2-quinoxalinol salen Cu(II) complex as catalyst is reported. A variety of Δ^5-steroidal substrates are selectively oxidized to the corresponding enones. Excellent yields are achieved (up to 99% under optimized conditions) while significantly reducing reaction times required as compared to other current methods.

Because of the biological and physiological properties of their 7-keto-Δ^5-steroid oxidation products, Δ^5-steroids have attracted attention as highly useful synthetic building blocks.[1−10] Easy access to the 7-keto-Δ^5-steroids can be achieved via allylic oxidation of Δ^5-steroids. Although a variety of chromium(VI) compounds have been used in the synthetic modifications of steroids,[4,11−15] complications in applying these methods remain because of the harsh reaction conditions required and difficult workup and/or purification procedures. In addition, the accumulations of chromic acid or chromium salt wastes that are the side products of these reactions are of great environmental concern.[16] To complete such modifications in a more environmentally friendly yet still efficacious manner, many other metal complexes/salts have been employed, such as sodium chlorite,[17] copper iodide,[5] dirhodium caprolactamate,[18] ruthenium trichloride,[19] bismuth salt,[20] cobalt acetate,[21] palladium(II) salts,[22] and manganese-(III) acetate;[23] however, numerous limitations remain. All of the available methods must strike a balance between good yields and functional group compatibility while continuing to suffer from long reaction time requirements. Oxidations using manganese(III) acetate and dirhodium caprolactamate as catalysts are two more recent representative examples of the current methods.[17,21] The use of manganese(III) acetate allowed for excellent yields in Δ^5-steroidal oxidation under ambient temperature when *tert*-butyl hydroperoxide was used as oxidant. The reaction times were reduced remarkably when the reaction mixture was heated, but with a loss in yield. This method also does not exhibit compatibility with sensitive functionalities near allylic sites (e.g., hydroxyl group).[21] The use of the dirhodium caprolactamates as catalysts in such an allylic oxidation showed a wide tolerance for a variety of functional groups, and yet it also had decreased yields.[17]



Previously, we have reported a new catalytic system that consists of 2-quinoxalinol salen copper(II) complex **2** as a catalyst using *tert*-butyl hydroperoxide (TBHP) as an oxidant.[24] The 2-quinoxalinol salen copper(II) system was demonstrated

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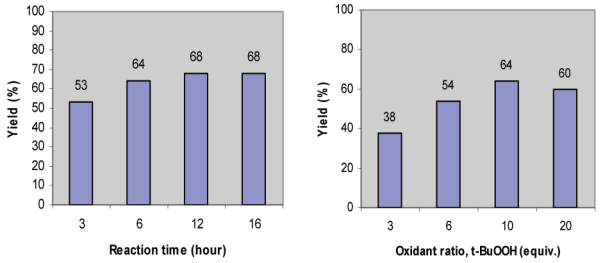
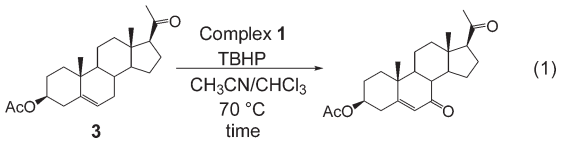


FIGURE 1. Isolated yields with reaction time and isolated yields with oxidant ratio.

to oxidize benzylic methylenes into carbonyl groups in near-quantitative yields with the use of catalyst loading of 1 mol % and 3 equiv of TBHP when different functional groups remained intact. On the basis of our previous success in this related study, we sought to modify this system to develop mild conditions that would retain satisfying yields, efficacious for allylic oxidations.



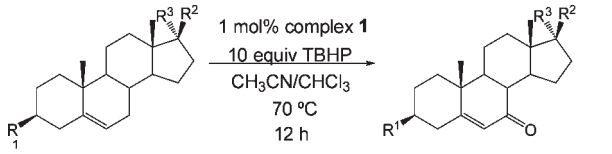
(1)

We began by using 2-quinoxalinol salen copper(II) complex **1** as catalyst and pregnenolone acetate **3** as substrate (eq 1). Two factors were varied to determine the optimal reaction conditions: reaction time and oxidant ratio. The oxidation was performed on a millimole scale using 1 mol % of catalyst complex **1**. $CH_3CN/CHCl_3$ (50/50) was chosen as solvent to dissolve steroids. The solution was heated to 70 °C, and then the TBHP was added. When the reaction was completed, the solution was concentrated under reduced pressure, and the residue was purified by flash column chromatography using hexane/ethyl acetate as eluent. Initially, we used 10 equiv of TBHP to determine the optimal reaction time (Figure 1). The isolated yields slightly increased when the reaction time was extended from 3 to 12 h, and did not change when the time was elongated from 12 to 16 h. There is little difference in isolated yields between 6 and 16 h, so we set the time to 6 h to optimize the oxidant ratio (Figure 1).

A generally increasing trend of isolated yields was observed as the oxidant ratio was increased from 3 equiv to 20 equiv. The highest yield was achieved when 10 equiv of TBHP was used, and the additional amount of oxidant did not result in a higher yield. It is notable that the remaining starting material, pregnenolone acetate, was recovered after this time. When carried out at ambient temperature, the reaction rate was found to be much slower (51% yield for 24 h and 65% for 48 h). In the absence of complex **1**, only 39% yield was obtained after heating 6 h at 70 °C.

A variety of Δ^5-steroidal substrates were oxidized using the optimized condition with 1 mol % of catalyst loading and 10 equiv of oxidant TBHP heated to 70 °C for 12 h (Table 1). The even more challenging oxidation of 3-hydroxy-Δ^5-steroids can also be successfully realized with a small decrease in yields (entry 5 and 6); however, in all cases, unreacted steroidal starting materials were recovered. Given the fact that structurally similar salen copper(II) complexes have been shown to

TABLE 1. Oxidation of Steroids Using Optimized Condition



entry	substrate	yield (%)
1	R^1 = OAc, R^2 = Ac, R^3 = H	64
2	R^1 = OAc, R^2 = C_8H_{17}, R^3 = H	62
3	R^1 = OBz, R^2 = Ac, R^3 = H	55
4	R^1 = OTHP, R^2 = C_8H_{17}, R^3 = H	61
5	R^1 = OH, R^2 = C_8H_{17}, R^3 = H	44
6	R^1 = OH, R^2 = Ac, R^3 = H	53
7	R^1 = Cl, R^2 = C_8H_{17}, R^3 = H	49

slowly decompose in most organic solvents[25] and the observation that the color of solution changes from its initial red to yellowish, it would appear that the ligand−metal complex **1** was consumed as the reaction proceeded.

To verify this hypothesis, we carried out the oxidation of cholesteryl chloride in CH_3CN and $CHCl_3$ independently. Interestingly, the reaction in CH_3CN had an isolated yield of 57% while the one in $CHCl_3$ only had 28% yield, despite the fact that complex **1** has much better solubility in $CHCl_3$ than in CH_3CN. According to the consensus radical mechanism of current allylic oxidation methods using TBHP,[18,23,26] the reason behind the low yield is likely stabilizers present in the $CHCl_3$ that can function as radical scavengers. The reaction was then carried out again with $CDCl_3$ as solvent, achieving 48% yield. Although a negative factor was found, the mystery of complex **1** appearing to be consumed over the course of the reaction remained.

It was thus decided to change the reaction procedure conditions to limit the exposure time of the catalyst, so in additional experiments complex **1** and TBHP were added in portions to the reaction mixture every 2 h. With this further optimization, new reaction conditions were developed in which CH_3CN heated to 70 °C was used as solvent, and 0.5 mol % of complex **1** and 5 equiv of TBHP were added simultaneously with multiple portions used.

For each substrate, different numbers of portions were tested to find optimal conditions. Cholesteryl acetate needs 3 portions (each addition contains complex **1** (1.8 mg, 0.0025 mmol) and *t*-BuOOH (0.5 mL, 2.5 mmol)) to achieve 99% yield (Table 2, entry 1); benzoyl protected pregnenolone required 5 portions to get 77% yield (Table 2, entry 2). Simple cholesterol only needs 2 portions (Table 2, entry 3) while pregnenolone and cholesteryl chloride need 4 portions (Table 2, entries 4 and 5). Generally excellent yields were obtained albeit unprotected substrates have generally lower yields than the protected ones. The addition of subsequent portions of catalyst and oxidant did not increase yields. The benzoyl protected cholesterol is oxidized in significantly lower yield than other protected steroids although 5 portions were added due to the insolubility of substrate in CH_3CN.

We also performed a theoretical study and computational modeling to investigate the origins of regioselectivity.

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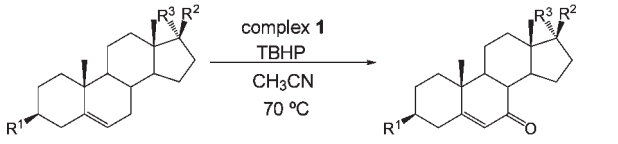
TABLE 2. Oxidation of Steroids Using Further Optimized Condition



entry	susbtrate	yield (%)
1	R^1 = OAc, R^2 = C_8H_{17}, R^3 = H	97[a]
2	R^1 = OBz, R^2 = Ac, R^3 = H	77[b]
3	R^1 = OH, R^2 = C_8H_{17}, R^3 = H	69[c]
4	R^1 = OH, R^2 = Ac, R^3 = H	88[d]
5	R^1 = Cl, R^2 = C_8H_{17}, R^3 = H	99[d]

[a]3 portions of TBHP and complex **1** were used. [b]5 portions of TBHP and complex **1** were used and 1 mL of $CHCl_3$ was added to help dissolve the substrate. [c]2 portions of TBHP and complex **1** were used. [d]4 portions of TBHP and complex **1** were used.

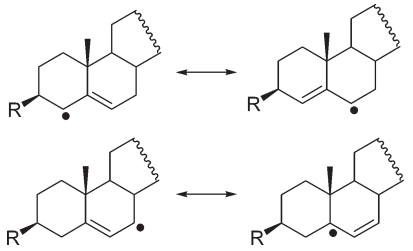
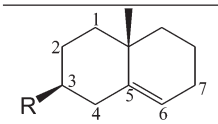


FIGURE 2. Resonance structures of radical species.

TABLE 3. Calculations of Free Energies of Model Radicals

Model molecule	Relative stability of C7 vs C4 radical[a] (kcal/mol)
	
4 R=OAc	-3.43
R=OH	-4.65
R=Cl	-2.85
R=OBz	-3.38
R=OTHP	-3.30

[a]Value reported as ΔG at 298K.

For Δ^5-steroids, the two allylic sites do not have much difference in reactivity at first glance; however, only 7-keto products were obtained exclusively. From the resonance structures, the difference becomes clear (Figure 2). Species bearing a radical at the 7-position will have two possible resonance structures, one of which is a tertiary radical that can significantly lower the energy, while the species bearing a radical at the 4-position also has two possible resonance structures, but neither contributes to the lower energy state. Of course, the preference of reactivity is also affected by the conformation of the sterol.

This hypothesis was supported by ab initio computational studies at the B3LYP/6-31G(2d,p) level using the Gaussian03 package (Table 3). Compound **4** was selected as a model to examine the energy difference between the species bearing radicals at two different sites. The free energy at 298 K of the 7-position radical is less than that of the 4-position radical by 3.43 kcal/mol. This relative stability becomes more significant (6.21 kcal/mol) when calculations with the more complicated steroid molecule (pregnenolone acetate **3**) were performed with the same level of theory. A series of calculations were carried out toward the model compound **4** bearing different functional groups. In each case, compounds with the radical at the 7-position were more stable than those at the 4-position. It is interesting that the trend of energy difference bearing different functional groups is in agreement with the trend of numbers of portions needed for the corresponding substrates (see Table 2, entries 1, 3, and 5).

In summary, we have demonstrated a novel system for allylic oxidation of Δ^5-steroids. This method is tolerant with a variety of functional groups, has low sensitivity to air or water, and excellent yields (up to 99%) can be realized.

Experimental Section

Synthesis of 2-Quinoxalinol Salen Copper(II) Complex 1. The 2-quinoxalinol salen ligand was synthesized following a published procedure.[27] In a 100 mL round-bottomed flask charged with a stirrng bar, 0.20 mmol of 2-quinoxalinol salen ligand (133 mg) and 0.24 mmol of $Cu(OAc)_2 \cdot H_2O$ (48 mg) were dissolve with 20 mL of DCM and 20 mL of methanol. After 1.2 mmol of triethylamine (0.20 mL) was added, the reaction was stirred for 2 h at refluxing temperature. After solvent was removed, the resulting dark red solid was washed with water and cold ether 3 times each. A product of 127 mg of solid was obtained (87%).

2-Quinoxaninol Salen Copper(II) Complex 1. IR (KBr): 3429 (br), 2955, 2909, 2868, 1661, 1556, 1524, 1495, 1462, 1423, 1385, 1202 cm^{-1}. UV−vis ($CHCl_3$) 250 (ε = 35 600 M^{-1} cm^{-1}), 285 (ε = 27 140 M^{-1} cm^{-1}), 330 (ε = 31 340 M^{-1} cm^{-1}), 460 nm (ε = 39 280 $M^{-1}cm^{-1}$). Formula (M + H): $C_{42}H_{55}N_4O_3Cu$. HRMS: found 726.3575 (M + H), calcd 726.3570 (M + H).

Representative Procedure for Allylic Oxidation Using Optimized Condition (Table 1). To a 50 mL round-bottomed flask charged with a stirring bar, were sequentially added pregnenolone acetate (**3**) (358 mg, 1 mmol), complex **1** (7.3 mg, 0.01 mmol), CH_3CN (10 mL), $CHCl_3$ (10 mL), and *t*-BuOOH (2 mL, 10 mmol). After the reaction was stirred at 70 °C for 12 h, solvent was removed under reduced pressure. The residue was purified by flash column chromatography with hexane/ethyl acetate (5:1) as eluent to yield product as a white solid (239 mg).

3β-Acetoxypregn-5-ene-7,20-dione (Entry 1, Table 1). IR (solid): 1730, 1707, 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.72 (d, J = 1.6 Hz, 1H), 4.75−4.69 (m, 1H), 2.59−1.26 (comp, 18H), 2.12 (s, 3H), 2.05 (s, 3H), 1.22 (s, 3H), 0.64 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 209.7, 201.2, 170.3, 164.3, 126.4, 72.0, 62.2, 49.9, 49.6, 45.2, 44.4, 38.3, 37.7, 37.6, 35.9, 31.6, 27.2, 26.4, 23.5, 21.2, 21.0, 17.2, 13.2. ^1H, ^{13}C NMR, and IR data were in accordance with literature values.[18]

3β-Acetoxycholest-5-ene-7-one (Entry 2, Table 1). IR (solid): 1728, 1671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.70 (d, J = 1.6 Hz, 1H), 4.76−4.67 (m, 1H), 2.58−1.00 (comp, 26H), 2.05 (s, 3H), 1.21 (s, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.68 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 201.9, 170.2, 164.0, 126.6, 72.2, 54.7, 49.9, 49.8, 45.4, 43.1, 39.4, 38.6, 38.3, 37.6, 36.2, 36.0, 35.7, 28.5, 28.0, 27.3, 26.3, 23.8, 22.8, 22.6, 21.2, 21.1, 18.8, 17.2, 11.9. ^1H, ^{13}C NMR, and IR data were in accordance with literature values.[18]

3β-Benzoyloxypregn-5-ene-7,20-dione (Entry 3, Table 1). IR (solid): 1707, 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (d,

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J = 7.2 Hz, 2H), 7.57 (t, 1H), 7.45 (t, 2H), 5.77 (d, J = 1.6 Hz, 1H), 5.02−4.94 (m, 1H), 2.78−0.68 (comp, 24H), 2.14 (s, 3H), 1.27 (s, 3H), 0.68 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 209.9, 201.4, 166.0, 164.4, 133.2, 130.4, 130.3, 129.7, 128.5, 126.8, 72.8, 62.4, 50.1, 49.8, 45.4, 44.6, 38.6, 38.0, 37.8, 36.2, 31.8, 27.6, 26.6, 23.8, 21.3, 17.5, 13.4. ^{1}H, ^{13}C NMR, and IR data were in accordance with literature values.[18]

3β-[(Tetrahydropyran-2*R*,*S*-yl)oxy]-7-oxo-cholest-5-ene (Entry 4, Table 1). IR (solid): 1676, 1630 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.68 (d, J = 1.0 Hz, 1H), 4.72 (s, 1H), 3.55−3.64 (m, 1H), 3.45−3.49 (m, 2H), 0.93 (s, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 6H), 0.68 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 202.2, 165.6, 126.0, 97.4, 75.0, 62.9, 54.8, 50.0, 45.4, 43.1, 40.1, 39.5, 38.8, 38.5, 36.5, 36.2, 31.2, 29.4, 28.5, 28.0, 27.7, 26.3, 25.4, 23.8, 22.6, 21.2, 19.9, 19.0, 17.4, 12.0. ^{1}H, ^{13}C NMR, and IR data were in accordance with literature values.[28]

3β-Hydroxycholest-5-ene-7-one (Entry 5, Table 1). IR (solid): 1670 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.69 (d, J = 1.6 Hz, 1H), 3.71−3.64 (m, 1H), 2.54−1.00 (comp, 26H), 1.21 (s, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.68 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 202.6, 165.6, 126.0, 70.5, 54.8, 50.0, 49.9, 45.4, 43.1, 41.8, 39.5, 38.7, 38.3, 36.4, 36.2, 35.7, 31.1, 28.6, 28.0, 26.3, 23.8, 22.8, 22.6, 21.2, 18.9, 17.3, 12.0. ^{1}H, ^{13}C NMR, and IR data were in accordance with literature values.[18]

3β-Hydroxypregn-5-ene-7,20-dione (Entry 6, Table1 1). IR (solid): 1681, 1666 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.68 (d, J = 1.6 Hz, 1H), 3.67−3.63 (m, 1H), 2.52−1.18 (comp, 19H), 2.10 (s, 3H), 1.18 (s, 3H), 0.63 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 210.0, 201.8, 166.0, 125.8, 70.3, 62.3, 50.0, 49.8, 45.1, 44.4, 41.8, 38.4, 37.7, 36.4, 31.6, 31.0, 26.5, 23.6, 21.1, 17.3, 13.3. ^{1}H, ^{13}C NMR, and IR data were in accordance with literature values.[18]

3β-Chlorocholest-5-ene-7one (Entry 7, Table 1). IR (solid): 1669 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.68 (s, 1H), 3.86−3.82 (m,1H), 2.71 (d, J = 8.3 Hz, 2H), 2.43−2.36 (m, 1H), 2.26−2.15 (comp, 2H), 2.04−1.88 (comp, 4H), 1.57−1.05 (comp, 20H), 1.22 (s, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.68 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 201.9, 163.9, 126.2, 57.8, 54.8, 49.9, 49.8, 45.4, 43.1, 42.6, 39.5, 38.6, 38.1, 36.2, 35.7, 32.8, 28.5, 28.0, 26.3, 23.8, 22.8, 22.6, 21.1, 18.9, 17.2, 12.0. ^{1}H, ^{13}C NMR, and IR data were in accordance with literature values.[18]

Representative Procedure for Allylic Oxidation Using Further Optimized Condition (Table 2). To a 50 mL round-bottomed flask charged with a stirring bar were sequentially added cholesteryl chloride (203 mg, 0.5 mmol), complex **1** (1.8 mg, 0.0025 mmol), CH_3CN (10 mL), and *t*-BuOOH (0.5 mL, 2.5 mmol). Additional complex **1** (1.8 mg, 0.0025 mmol) and *t*-BuOOH (0.5 mL, 2.5 mmol) were added three times every 2 h. Solvent was then removed under reduced pressure. The residue was purified by flash column chromatography with hexane/ethyl acetate (15:1) as eluent to yield product as a white solid (201 mg).

Acknowledgment. We thank Dr. Peter Livant and Dr. Xiaoxun Li for helpful suggestions with NMR spectroscopy, and gratefully acknowledge funding for this project from Auburn University.

Supporting Information Available: Procedures, data from theoretical calculation, and ^{13}C NMR spectra of the of 7-keto-Δ5-steroid compounds produced (see Tables S1and S2). This material is available free of charge via the Internet at http://pubs.acs.org.

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