ORGANIC
LETTERS

2002
Vol. 4, No. 6
1043−1045

Practical Os/Cu-Cocatalyzed Air Oxidation of Allyl and Benzyl Alcohols at Room Temperature and Atmospheric Pressure

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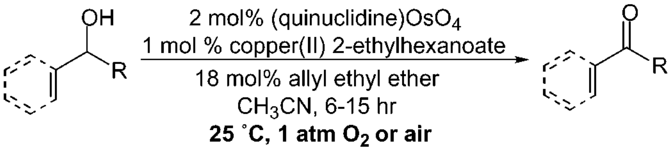
Received January 30, 2002

ABSTRACT



A new protocol for the oxidation of primary and secondary allyl and benzyl alcohols at room temperature and using 1 atm of air is described. The procedure uses low loadings of copper salts and osmium tetroxide, which is activated with quinuclidine and prereduced with an alkene. Chemoselectivity for allyl and benzyl alcohols is very high, no overoxidation is observed, and the reaction takes place under neutral conditions.

Molecular oxygen is an ideal oxidant for both economic and ecological reasons. While oxidations using air or dioxygen are widely practiced in industry,[1] where the scale of the reactions makes detailed optimization practical, the lack of general, selective, easy, and safe methods has impeded the adoption of aerobic methods for reactions run on a smaller scale. For example, molecular oxygen is seldom used in organic synthesis to oxidize alcohols to aldehydes or ketones, largely because the existing aerobic methodologies, even with notable recent improvements,[2] require using oxygen at elevated temperatures or pressures, which is inconvenient and presents a risk of explosion.[3] Some recent reports have described aerobic oxidations under ambient conditions.[3−5] However, these protocols still suffer from low conversions or high catalyst loadings, or require acidic media. Here we report a selective aerobic oxidation of benzylic and allylic alcohols cocatalyzed by readily available osmium and copper complexes under neutral conditions. This procedure is rapid and efficient and operates at ambient temperature and pressure. In fact, it is competitive with currently used stoichiometric oxidants such as manganese dioxide in its ease, selectivity, and even expense.

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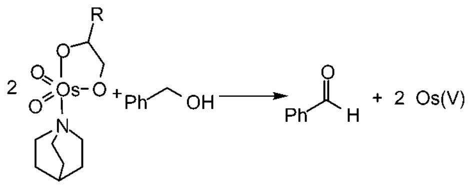
10.1021/ol025648q CCC: $22.00

Osmium tetroxide and its amine adducts have been used extensively in oxidation chemistry because of their rapid reaction with alkenes to form cyclic osmate esters, which, upon reductive or oxidative hydrolysis, yield the *syn* diols.[6] Osmylation is remarkably chemoselective; for example, allyl alcohols have been oxidized routinely to give triols, with no evidence of alcohol oxidation.[7] We were thus surprised to find that osmate(VI) esters derived from monosubstituted alkenes react readily with allylic and benzylic alcohols to give α,β-unsaturated aldehydes or ketones (eq 1). While this reaction works best with quinuclidine-ligated glycolates prepared from $(C_7H_{13}N)OsO_4$ (**1**),[8] even donor-free osmate esters will oxidize allylic and benzylic alcohols in organic solvents.



(1)

Oxidation of benzyl or allyl alcohols with osmium(VI) diolates results in formation of only half a mole of aldehyde or ketone relative to osmium, even when reactions are allowed to stand for prolonged periods in the presence of air. This suggests that the osmium is reduced to the +5 oxidation state and is then inert to further redox reactions under these conditions. We therefore sought a cocatalyst that could reoxidize the osmium to the +6 oxidation state using dioxygen as the stoichiometric oxidant. Copper seemed a logical choice for this role, given the extensive use of copper salts as oxygen-activating cocatalysts.[3,9] Indeed, addition of catalytic quantities of a variety of copper compounds enables the oxidation to take place with catalytic amounts of osmium at reasonable rates *at room temperature*. In fact, rates are high enough that the reactions appear to be mass transport limited when they are simply stirred under an O_2 atmosphere, and actual bubbling of oxygen through the solution is required to achieve optimal rates.

This behavior contrasts with two other recent reports of air oxidations of alcohols catalyzed by osmium. Most closely related is a report by Osborn of aerobic oxidation of alcohols catalyzed by OsO_4 in the presence of CuCl, pyridine, and molecular sieves.[10] Under these conditions, reaction temperatures of 100 °C were generally required to achieve high conversions (although isolated examples proceeded at room temperature). Activation of the osmium by forming the glycolate appears to significantly improve both the reactivity and the selectivity of the system, allowing reactions to proceed at room temperature and without any oxidation of aliphatic alcohols (see below). Beller recently reported that good activity for air oxidation of benzylic and secondary aliphatic alcohols by osmium can be achieved at modestly elevated temperature (50°) using a buffered basic aqueous/organic biphase even in the absence of cocatalyst.[11] Allyl alcohols presumably cannot be oxidized selectively, however, since these conditions have been reported to effect alkene dihydroxylation.[12]

Oxidation of a variety of alcohols can be carried out at atmospheric pressure in the presence of 2 mol % of alkene-activated $(C_7H_{13}N)OsO_4$ (**1**) and 1 mol % of copper 2-ethylhexanoate (Table 1). All of the allyl and benzyl alcohols react completely in acetonitrile within 6−18 h at room temperature, and the products can be isolated easily using a simple extractive workup.[13] Although CH_3CN appears to be the optimal solvent, other polar organic solvents such as acetone, chloroform, THF, or DMF can be used with only a modest decrease in activity. Use of the quinuclidine adduct of osmium tetroxide (**1**) is important for achieving high activity, as unligated OsO_4 is about 10 times less reactive, but **1** can be generated in situ by the addition of 2 equiv of quinuclidine to OsO_4 without any difference in performance compared to isolated **1**. While a variety of alkenes produce reactive glycolates, the best catalyst performance is obtained upon activation of **1** with allyl ethyl ether. Both copper(II) 2-ethylhexanoate and copper(II) acetylacetonate are effective as cocatalysts, but copper(II) halides are less satisfactory, presumably due to their low solubility at room temperature.

Oxidation of allyl and benzyl alcohols gives only the corresponding α,β-unsaturated aldehydes or ketones, with the only deviations from essentially quantitative yield occurring with substrates such as nerol or geraniol, which give

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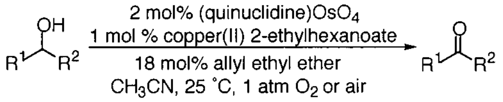
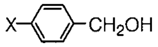
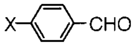
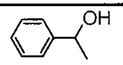
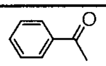
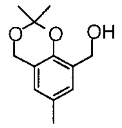
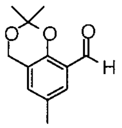
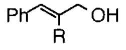
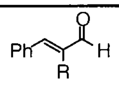
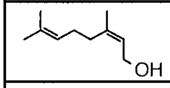
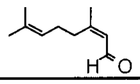
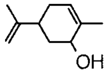
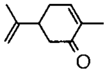
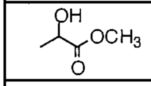
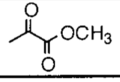
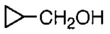
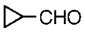
(13) **Typical experimental procedure: oxidation of 4-methoxybenzyl alcohol.** Into a 15 mL two-necked flask is added a solution of copper(II) 2-ethylhexanoate (20 mg, 0.057 mmol, 1 mol %) and 4-methoxybenzyl alcohol (755 mg, 5.46 mmol) in 3 mL of CH_3CN. Oxygen gas, which is presaturated with CH_3CN by passing it through a gas dispersion tube in a 100 mL two-neck flask filled with acetonitrile, is admitted to the reaction vessel using a needle. Oxygen is bubbled through the reaction mixture at a moderate rate (∼ 3 bubbles/s) and vented through a mineral oil bubbler. In a separate vial, the osmium reagent is generated by adding allyl ethyl ether (100 μL, 0.93 mmol, 18 mol %) to a suspension of (quinuclidine)-OsO_4 (40 mg, 0.109 mmol, 2 mol %) in 0.6 mL of CH_3CN. After allowing this osmium-containing solution to stand for 1 min after addition of the alkene, it is added to the solution containing the substrate and copper. Upon completion of the reaction, the reaction mixture is diluted with Et_2O (10 mL) and H_2O (10 mL) and the ether layer separated from the aqueous layer and a black precipitate. The aqueous layer is washed with Et_2O (2 × 10 mL), the organic layers are washed once with 7 mL of 7% aqueous Na_4-EDTA to remove copper and dried over $MgSO_4$, and the ether is evaporated. The product is filtered through a small plug of silica gel using Et_2O/hexane (3:1) to give pure 4-methoxybenzaldehyde (659 mg, 88%).

Table 1. Os/Cu-Cocatalyzed Oxidations of α,β-Unsaturated Alcohols



Reactant	Product	Time (hr)	Yield (%)[a]
			
X = H		6	98
OCH_3		6	97 (88)
NO_2		10	98
SCH_3		6	97
		8	97
		8	97
			
R = H		15	96
CH_3		15	97
		13	98 (85)[b]
		12	98
		17	17
		17	15

[a] Yields determined by ^{1}H NMR; values in parentheses indicate isolated yields. [b] Product contains 4% geranial.

a small amount (<5%) of double bond isomerization. Overoxidation to the carboxylic acid is never observed. Alkenes are not dihydroxylated under these conditions, and even easily oxidized functional groups such as sulfides are tolerated, as are acid-sensitive groups such as acetals. Most remarkably, as long as the gas is bubbled through the reaction solution rapidly enough to prevent mass transfer limitations, the reaction can be performed as effectively *using air* as it can with pure oxygen.

The oxidation is highly chemoselective, with only allylic and benzylic alcohols reacting at appreciable rates. Simple aliphatic primary and secondary alcohols are completely inert to osmium(VI), and their presence does not interfere with the oxidation. While many catalytic air oxidations proceed more rapidly with allylic and benzylic substrates, the essentially complete chemoselectivity observed here is very unusual and is not shared even by other osmium-catalyzed processes.[10,11] In contrast to simple aliphatic alcohols, alcohols flanked by electron-withdrawing groups such as esters and ketones are oxidized catalytically by osmium/copper. However, their rates of oxidation are much slower than those of allylic and benzylic alcohols. Cyclopropanemethanol is also oxidized very slowly and cleanly forms cyclopropanecarboxaldehyde without any sign of ring-opened products, indicating that long-lived radicals are not involved in the oxidation.

The presence of water has no effect on the reaction, with equal rates observed in wet acetonitrile or in the presence of molecular sieves. Oxidation is, however, completely inhibited in the presence of 1,2- or 1,3-diols. This may indicate that diol dissociates from the osmium(VI) glycolate to form the catalytically active species or may simply be due to conversion of the active monoglycolate complex to an inactive bis(diolate) complex.[14]

The standard reagent currently used for selective oxidation of allylic and benzylic alcohols is manganese dioxide.[15] While MnO_2 shows excellent chemoselectivity, there are sometimes problems associated with the generation and storage of active material, and the universal need to employ a large excess of the reagent results in the generation of substantial quantities of inorganic waste. The aerobic protocol described here is as chemoselective as MnO_2, and since it uses commercially available reagents and operates at room temperature and atmospheric pressure, it is as convenient to employ. Despite the use of the relatively expensive osmium, the low catalyst loadings mean that it is actually economically competitive with the obligate use of superstoichiometric MnO_2, while generating far less waste. For these reasons, we envision this procedure supplanting the use of manganese dioxide for this class of oxidations and substantially furthering the use of air as a stoichiometric oxidant in lab-scale organic synthesis.

Acknowledgment. Support from a DuPont Young Professor Award, from the Camille and Henry Dreyfus Foundation (New Professor Award), and from the Dow Chemical Company (Innovation Recognition Program) is gratefully acknowledged.

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