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Solvent Effect on Ruthenium Catalyzed Dihydroxylation

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Abstract: The effect of different solvents on flash dihydroxylation is compared and for the first time, the replacement of ethyl acetate with acetone was shown to give a successful, *catalytic cis*-dihydroxylation of the alkene moiety in cholesteryl acetate and the ruthenium catalytic cycle could be maintained by methanesulfonamide in the absence of acetonitrile. © 1999 Elsevier Science Ltd. All rights reserved.

Recently, we have disclosed a catalytic ruthenium system for the rapid oxidation of alkenes to *vic*-diols. This novel *cis*-dihydroxylation protocol was coined 'flash dihydroxylation'.[1,2] In this communication, we report our studies of the influence of solvents on flash dihydroxylation and demonstrate that the first successful, catalytic *cis*-dihydroxylation of cholesteryl acetate could be accomplished using acetone-MeCN-H_2O solvent system in a ratio of 3:3:1, respectively.

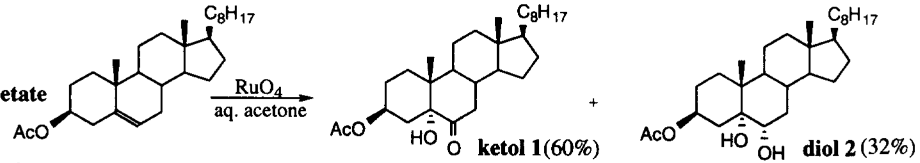
Initially, the ruthenium catalyzed flash dihydroxylation was discovered with a two-phase solvent system containing CCl_4-MeCN-H_2O in a respective ratio of 3:3:1. Subsequently we found that ethyl acetate-MeCN-H_2O in the same solvent ratio (Method A) gave even better yields of diols. This is probably due to the better solubility of the resultant diols in ethyl acetate than in CCl_4. On the other hand, the higher solubility of the resultant diols in water than in the organic solvent is not desirable because that leads to competitive glycol cleavage reactions by $NaIO_4$ in the aqueous layer and hence to lower yields. For example, the reaction of 1-decene or cyclohexene in CCl_4-MeCN-H_2O only furnished the corresponding cleavage products (carbonyl compounds) in 28% and 40% yields, respectively, and no desired diols were detected or isolated (c.f. Table 1, entries 1 and 2). In view of this, we wanted to investigate further the influence of different solvents on flash dihydroxylation. However, RuO_4 is a vigorous oxidant,[3] and thus the number of solvents that can be used is limited. The most suitable common organic solvents are CCl_4, $CHCl_3$, acetone, and ethyl acetate, all of which resist oxidation by RuO_4.

An alternative solvent system of MeCN-H_2O in a ratio of 6:1 (Method B) was found to complement the existing solvent system (Method A) and gave better results in most cases (see entries 2-5 in Table 1). It is important to note that MeCN prevents catalyst inactivation and is crucial for the increased effectiveness and reliability of the catalytic RuO_4 oxidations.[4] The drawback of this solvent system is that it is homogenous and hence promotes glycol cleavage reactions.

Recently, Sica and co-workers have studied the oxidation of a number of tri- and tetra-substituted steroidal alkenes with *stoichiometric* ruthenium tetraoxide and observed that the reaction products consisted of a mixture of α-ketols, 1,2-diols and sometimes fission products.[5-7] The example that gave the best yield of *vic*-diol is shown in Figure 1 in which cholesteryl acetate was treated with a stoichiometric amount of RuO_4 (prepared from RuO_2 and $NaIO_4$) in aqueous acetone to give ketol **1** and diol **2** in 60% and 32% yields, respectively.

Figure 1

cholesteryl acetate



ketol 1(60%) **diol 2** (32%)

When Method A or B was applied to cholesteryl acetate, the reaction stopped after 2 turnovers because it formed a rather stable complex with ruthenium. This problem was also encountered in the OsO_4 catalyzed dihydroxylation of cholesteryl acetate.[8] Replacement of the ethyl acetate with acetone (Method C) gratifyingly could effect the ruthenium dihydroxylation catalytically (entry 7) and gave good yields of the vicinal diol **2**. However, this method gave poorer yields of diols for other alkenes (see entries 1-6) and the byproducts are mostly carbonyl compounds. This is probably attributable to the facile glycol cleavage of the resultant diols in the homogeneous solution of Method C.

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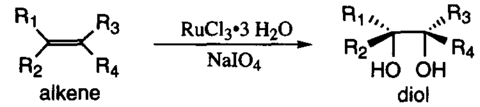
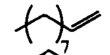
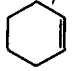
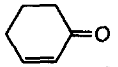
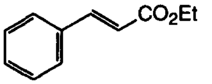
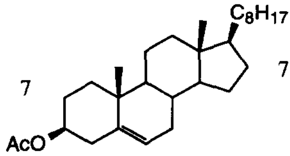
Interestingly, it was observed for the first time that the catalytic cycle could be maintained by replacing the MeCN with one millimole of methanesulfonamide (Method D). However, the yields of diols from electron deficient alkenes were disappointing (see entries 4-6). Methanesulfonamide had been used to hydrolyze the tetra-substituted osmium(VI) ester complex in osmium tetraoxide catalyzed dihydroxylation reactions.[9] Presumably, the ruthenium(VI) ester was formed initially and then broken down by the methanesulfonamide to give the diol. The ruthenium species was then oxidatively regenerated by $NaIO_4$ for dihydroxylation. Although this method gave 12% yield of the cholesteryl diol **2**, unfortunately, combining methanesulfonamide with ethyl acetate-MeCN-H_2O (3:3:1, Method A) did not show any improvement of the reaction even for the tetra-substituted alkenes.

In conclusion, the first successful catalytic dihydroxylation of cholesteryl acetate was realized using acetone-MeCN-H_2O in a ratio of 3:3:1 as the solvent system and methanesulfonamide was shown to be able to replace MeCN in maintaining the ruthenium catalytic cycle.

Table 1[a] Solvent Effect on Ruthenium Catalyzed Dihydroxylation.



Entry	Alkene	Time (min)	A	B	C	D
			%	%	%	%
1		0.5	67	54	53	56
2		3	58	72	55	54
3		3	36	51	32	41
4		3	55	69	50	30
5		3	77	84	75	44
6		3	90	89	80	30
7		720	stopped after 2 turnovers	stopped after 2 turnovers	68 diol 10 ketol	12 diol 84 recovery

[a] All the reactions were performed in 1 mmol of alkene, 0.07 mmol $RuCl_3 \cdot 3\,H_2O$ and 1.5 mmol $NaIO_4$. Solvent sysem of Method A is (EtOAc-MeCN-H_2O, 3:3:1). Solvent sysem of Method B is (MeCN-H_2O, 6:1). Solvent sysem of Method C is (acetone-MeCN-H_2O, 3:3:1). Method D is 1 mmol of methanesulfonamide in solvent system (EtOAc-H_2O, 6:1). % indicates the percentage yield of the diol product.

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