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Efficient and selective catalytic oxidative cleavage of α-hydroxy ketones using vanadium-based HPA and dioxygen

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The combination of $H_{3+n}[PMo_{12-n}V_nO_{40}]$·aq (HPA-*n*, *n* = 3) and dioxygen provides a clean and regioselective reagent for the homolytic cleavage of various representative α-hydroxy ketones (primary to tertiary) and turns out to be as efficient for the catalytic ring opening of chiral natural products.

Keggin type mixed-addenda heteropolyanions such as $[PMo_{12-n}V_nO_{40}]^{(3+n)-}$, denoted HPA-*n* (*n* = 1, 2, 3, *etc.*), have found many applications in catalysis.[1] Recently, their variable redox and acid–base properties have been used for the catalytic cleavage of different cycloalkanones by dioxygen.[2,3] Carboxylic acids, including adipic acid were obtained with high yields and selectivities. Early mechanistic studies showed clearly that the α-ketol (α-hydroxy ketone) is not a major intermediate during cyclohexanone oxidation. In fact, 2-hydroxycyclohexanone is converted to adipic acid with a better yield.

The oxidative cleavage of carbon–carbon bonds in α-ketols is widely used in organic synthesis. In many synthetic schemes, including that of Taxol®, ring opening strategies are based on prior formation of α-hydroxy ketones.[4] Most of the published procedures use stoichiometric reagents.[5] Efforts have been made to find dioxygen-based catalytic pathways running either with Bi(0)/Bi(III) salts or moisture-sensitive dichloro(ethoxy)-oxy vanadium complexes.[6] In this communication, we report on the synthetic utility of the reaction catalysed by robust oxidation-resistant compounds like vanadium-based HPA and present a general route for the selective homolytic carbon–carbon bond cleavage of α-hydroxy ketones.

Using 2-hydroxycyclohexanone (**1a**) and $H_6[PV_3Mo_9O_{40}]$·aq as the catalyst precursor, the reaction was carried out either in methanol or in an acetic acid–water mixture at 65 °C. Dioxygen consumption was monitored by a gas burette system. Colour changes of the initial solutions from orange to blue-green and finally orange-brown were observed in both cases. They are consistent with the variation of the oxidation state of vanadium [V(V)/V(IV)] and the overall reaction can be interpreted in terms of a vanadium-catalysed process assisted by dioxygen. Under dinitrogen the solution remained blue and there was no significant reaction. The results are summarized in Table 1.

Regioselective cleavage of **1a** gave adipic acid or its dimethyl ester (Scheme 1) as the major products in acetic acid or methanol, respectively (runs 1 and 2). As shown in a blank experiment, adipic acid (**2a**) conversion to dimethyl adipate (**2b**) was also catalysed by 'HPA-3'† in methanol (100% yield in 1.5 h).

The *in situ* esterification yield, as determined by comparison of the diester (**2b**) amounts before and after addition of an ethereal solution of diazomethane was about 85–90%. Very low yields (< 1%) of glutaric acid derivatives were obtained. In methanol, the major by-products identified as methyl 6-oxohexanoate (**2c**) and methyl 6,6-dimethoxyhexanoate (**2d**) also arise from the cleavage of the C(O)–CH(OH) bond.

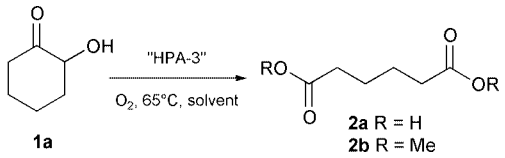
The conversion of the 2-hydroxycyclohexanone dimer to the monomer with accessible hydroxy and carbonyl groups proved to be an important prerequesite for the exclusive scission of this bond. Otherwise, significant amounts of 2-methoxybutanedioate were formed. In fact, the availability of both groups is not necessary for the occurrence of the desired reaction in methanol, as shown in Table 1 (runs 3 and 4). Comparison of the conversion rates (not shown) of 2,2-dimethoxycyclohexanol, a potential intermediate under acidic conditions, and 2-methoxycyclohexanone showed clearly the negative effects of the OH substituent. These results are consistent with a mechanism in which there is substrate pre-coordination to $[VO_2]^+$ species.[2,7]

The use of 'HPA-3' as a catalyst for the aerobic C–C bond cleavage of α-ketols was then applied successfully to a range of representative substrates (Table 2). For all the benzoyl derivatives (**3a–d**), the reactions could be carried out at room temperature with completion of dioxygen uptake within 5 h. Methyl benzoate and/or benzoic acid were formed with 90–100% selectivity. Quantitative yields of other benzoyl derivatives or cyclohexanone are obtained with **3b** or **3d** respectively. In accordance with published results,[2,7] the outcome with 2-hydroxy-2-phenylacetophenone (**3b**, benzoin) was much more sensitive to the nature of the solvent. Significant amounts of 1,2-diphenylethanedione (benzil) were produced in AcOH–H_2O, whereas only carbon–carbon bond cleavage products (benzaldehyde and its dimethyl ketal) and methyl benzoate were formed at room temperature in methanol.

Table 1 Oxidation of 2-hydroxycyclohexanone (**1a**) or its derivatives with dioxygen catalysed by 'HPA-3'[a]

Run	Substrate	Solvent	*t*/h	Conv. (%)[b]	Yield (%)[b]
1	2-Hydroxycyclohexanone	MeOH	10	100	90 (**2a** + **2b**)
2	2-Hydroxycyclohexanone	AcOH–H_2O	3.5	100	80 (**2a**)
3	2,2-Dimethoxycyclohexanol	MeOH	7	100	83 (**2a** + **2b**)
4	2-Methoxycyclohexanone	MeOH	54	67	52 (**2b**)

[a] *Reaction conditions*: substrate (7.7 mmol), 'HPA-3' (0.078 mmol), MeOH (7 ml) or AcOH–H_2O (6.3 : 0.7 ml), dioxygen pressure (0.1 MPa), temperature (65 °C) stirred at 1000 rpm; [b] Conversions (% of substrate consumed) and yields [(mmol of product per mmol substrate) × 100] were determined by GC analysis (OV1701) after the addition of an ethereal solution of diazomethane to the crude mixture using methyl heptanoate as internal standard. Products were identified by GC-MS (RTX5-MS).



Scheme 1

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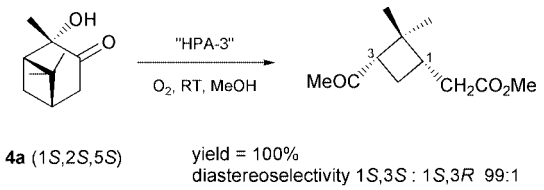
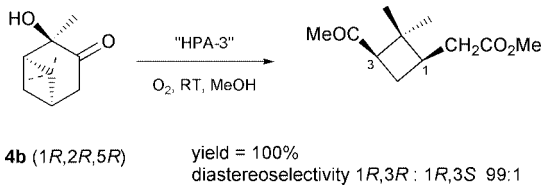
Table 2 'HPA-3'-catalysed oxidative cleavage of α-ketols[a]

Run	α-Ketol	Solvent	Conv. (%)[b]	Product(s) [Yield (%)][b]	O_2/Subst. (molar ratio)
5	2-Hydroxyacetophenone[c] (**3a**)	MeOH	100	$PhCO_2Me$ (97)	1.2
6	2-Hydroxyacetophenone[c] (**3a**)	AcOH–H_2O	100	$PhCO_2H$ (100)	1.05
7	2-Hydroxy-2-phenylacetophenone (**3b**)	MeOH	100	$PhCO_2Me$ (110); PhCHO (45); $PhCH(OMe)_2$ (45)	0.77
8	2-Hydroxy-2-phenylacetophenone (**3b**)	AcOH–H_2O	100	$PhCO_2H$ (81); PhCHO (1); PhCOCOPh (47)	0.75
9	2-Hydroxy-2-methylpropiophenone[c] (**3c**)	MeOH	100	$PhCO_2Me$ (97)	0.70
10	2-Hydroxy-2-methylpropiophenone[c] (**3c**)	AcOH–H_2O	100	$PhCO_2H$ (100)	0.50
11	1-Hydroxycyclohexyl phenyl ketone (**3d**)	MeOH	100	$PhCO_2Me$ (100); C_6H_{10}(=O) (100)	0.80
12	1-Hydroxycyclohexyl phenyl ketone (**3d**)	AcOH–H_2O	60	$PhCO_2H$ (54); C_6H_{10}(=O) (60)	0.35

[a] *Reaction conditions*: substrate (7.7 mmol), 'HPA-3' (0.078 mmol), MeOH (7 ml) or AcOH–H_2O (6.3:0.7 ml), dioxygen pressure (0.1 MPa), room temperature. [b] See Table 1. [c] Formaldehyde and acetone or their oxidized derivatives were not determined.



4a (1*S*,2*S*,5*S*) yield = 100%
diastereoselectivity 1*S*,3*S* : 1*S*,3*R* 99:1



4b (1*R*,2*R*,5*R*) yield = 100%
diastereoselectivity 1*R*,3*R* : 1*R*,3*S* 99:1

Scheme 2

Clean oxidation of **3d** to methyl benzoate or benzoic acid and cyclohexanone was only possible at room temperature; otherwise subsequent cleavage of the cycloalkanone becomes significant.[3] The oxygen consumed–substrate molar ratio was in good agreement with the stoichiometric values (Table 2). The dioxygen uptake for primary α-ketols (**3a**) was roughly twice that for tertiary ones (**3c**,**d**) as expected for pure C–C bond cleavage (runs 6, 10 and 12).

The same experimental procedure was successfully applied to natural compounds. For example, the oxidative cleavage of (1*S*,2*S*,5*S*)-2-hydroxypinan-3-one(**4a**) or its enantiomer (**4b**) led to the diastereoselective formation of methyl esters‡ of the corresponding *cis*-pinonic acids§ with 100% conversion (Scheme 2).

The epimerization of the cyclobutane carbon atom (C3) linked to the acyl group under acidic conditions is well-documented[8] but this competing reaction did not exceed 10% at 65 °C and did not occur at all at room temperature.

Cyclobutane-derived amino-acids and related peptides isolated from natural sources display interesting biological properties, and methyl pinonates are very important chiral cyclobutane synthons. However, stereoselective methodologies based usually on α-pinene oxidation are scant[9] and our approach corresponds to a convenient green alternative.

In conclusion, the present study has proved that the aerobic oxidative cleavage of α-hydroxy ketones (or α-hydroxy ketals) catalysed by 'HPA-3' could replace stoichiometric polluting reagents either for large-scale products or for fine chemicals synthesis. We are currently investigating the mechanism as well as the supported counterpart of these catalysts.

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Notes and references

† The heteropolyacids 'HPA-3' were prepared according to described procedures.[10] Their elemental analysis gave P, 1.7, Mo, 45.5, V, 7.75% which is consistent with the formula '$H_6[PV_3Mo_9O_{40}]\cdot 11H_2O$'. Solid HPA-*n* and their aqueous solutions are multi-component systems: they contain several polyanions, positional isomers of these, $[VO_2]^+$ and often traces of V(IV).

‡ Methyl esters obtained from the oxidation of (1*S*,2*S*,5*S*) or (1*R*,2*R*,5*R*)-2-hydroxypinan-3-one were characterized by their $[MNH_4]^+$ and $[MH]^+$ signals at 216 and 199 Da, respectively, using GC-MS/CI$^+$ (NH_3). Complete retention of configuration of both asymmetric carbon atoms in the 1*S*,3*S* and 1*R*,3*R* compounds was established by NOE ^{1}H NMR studies. Specific rotations of the diastereoisomeric mixtures isolated from the oxidation of (1*S*,2*S*,5*S*)-2-hydroxypinan-3-one at 65 °C or its enantiomer (1*R*,2*R*,5*R*) at RT were +65.1 deg cm^2 g^{-1}(*c* 2.17, $CHCl_3$) and −81.4 10^{-1} deg cm^2 g^{-1}(*c* 5.03, $CHCl_3$), respectively, in accordance with data for the pure compounds.[11]

§ The IUPAC name for pinonic acid is 3-acetyl-2,2-dimethylcyclobutaneacetic acid.

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