Direct, efficient, and inexpensive formation of α-hydroxyketones from olefins by hydrogen peroxide oxidation catalyzed by the 12-tungstophosphoric acid/cetylpyridinium chloride system

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The direct ketohydroxylation of a variety of 1-aryl-1-alkenes with H_2O_2, catalyzed by the inexpensive 12-tungstophosphoric acid/cetylpyridinium chloride system under very mild conditions, was achieved. Various acyloins were obtained in good yields and high regioselectivies.

α-Hydroxyketones (acyloins) are important building blocks in organic synthesis and form parts of the structures of various biologically active compounds, such as cortisone acetate **1** and daunomycinone **2**[1,2] (Fig. 1).

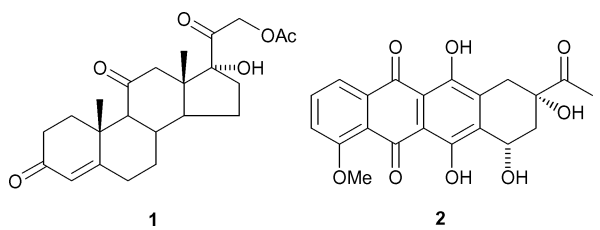
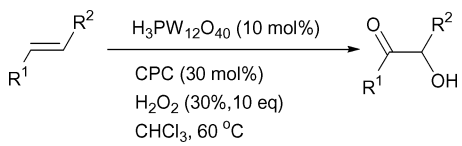


Fig. 1 Acyloin substructure in cortisone acetate **1** and daunomycinone **2**.

It is known that acyloins can be prepared by the benzoin condensation, the acyloin condensation, the α-hydroxylation of carbonyl compounds and the oxidation of diols, whereas the direct oxidation of C–C double bonds has only rarely been reported.[3] Since, in these cases, toxic cyanide compounds must be employed, or the reaction must be performed under an inert atmosphere with dry solvent, the development of an efficient and convenient method to obtain α-hydroxyketones would be significant. Recently, a new straightforward oxidation of C–C double bonds to α-hydroxyketones using catalytic amounts of $RuCl_3$ and stoichiometric amounts of Oxone under buffered conditions has been reported by Plietker.[4] A variety of substituted olefins were oxidized to α-hydroxyketones in good-to-excellent regioselectivities and yields by this method.

Heteropoly acids (HPA) such as 12-molybdophopsphoric acid (MPA) or 12-tungstophosphoric acid (WPA) are often used, not only for the oxidation of organic substrates, but also for many acid-catalyzed reactions, because they possess the dual catalytic functions of oxidizing ability and strong acidity.[5] It has been reported that the combination of HPA with cetylpyridinium chloride (CPC) could catalyze the epoxidation of olefins such as 1-octene, the ketonization of alcohols and diols, and the oxidative cleavage of 1,2-diols and olefins.[5]

We have found that direct ketohydroxylation of some olefins with H_2O_2 could be achieved under similar conditions. It turns out that when olefins are treated with hydrogen proxide in chloroform containing a catalytic amount of WPA (10 mol%) combined with CPC (30 mol%) as phase-transfer catalyst at 60 °C, α-hydroxyketones can obtained in good-to-excellent yields with good regioselectivities (Scheme 1). There are a number of interesting features of this methodology worth pointing out: (i) $H_3PW_{12}O_{40}$ is less expensive and less toxic than RuO_4 or OsO_4; (ii) H_2O_2 as the oxidant is of great advantage to the environment and industry because it generates H_2O as the sole by-product, it has a high content of active oxygen species, and it is less expensive than organic peroxides and peracids; (iii) the experiment is easy to carry out, because no special precautions such as high temperature, inert gas atmosphere or dry solvents are necessary.



Scheme 1

We choose styrene as our working model to study the influences of the catalyst, phase-transfer catalyst, solvents and temperatures (Table 1).

Table 1 Effects of the catalyst, solvent, and temperature on the ketohydroxylation of styrene[a]

Entry	Catalyst	Solvent	T/°C	Yield (%)[b]
1	WPA/CPC	$CHCl_3$	60	86.4
2	WPA	$CHCl_3$	60	nd
3	CWP[c]	$CHCl_3$	60	42.4
4	WPA/CPC	CH_2Cl_2	40	62.5
5	WPA/CPC	CH_3CN	60	36.4
6	WPA/CPC	$PhCH_3$	60	73.9
7	WPA/CPC	H_2O	60	nd
8	WPA/CPC	$CHCl_3$	−20	nd
9	WPA/CPC	$CHCl_3$	4	10

[a] All reactions were performed on a 6.5 mmol scale in $CHCl_3$ (15 mL) using WPA ($H_3PW_{12}O_{40}$, 0.4 mol%), CPC (1.2 mol%) and 10 equiv. of H_2O_2 (30%), and were stopped after 24 h. [b] Isolated yields (nd = not determined). [c] CWP: prepared according to ref. 5.

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To evaluate the potential of $H_3PW_{12}O_{40}$ for the ketohydroxylation of styrene, three different catalyst systems were tested (entries 1–3). Combination of WPA with CPC produced *in situ* was found to be more effective than $[\pi\text{-}C_6H_5NC_{16}H_{33}]_3[PO_4(WO_3)_4]$ (CWP).

When the WPA/CPC combination (which produces CWP with evolution of hydrogen chloride) was employed as the catalyst, the reaction medium is acidic, while in the CWP-catalyzed reaction, the medium is not acidic. The fact that ketohydroxylation proceeded more rapidly with the WPA/CPC combination suggested that the tungsten-catalyzed reaction is accelarated in acidic media. WPA alone could not catalyze the ketohydroxylation of styrene (entry 2), probably due to its poor solubility in organic solvents. Therefore, the reaction was conducted in various solvents using the WPA/CPC catalyst. It was observed that chloroform was the best solvent. The same reaction in toluene or acetonitrile led to a considerable decrease of the yield (entries 1, 4–7). A lower temperature decreased the conversion significantly (entry 9), while no reaction was found at −20 °C.

It is noteworthy that the insoluble WPA/CPC dissolved slowly under the action of H_2O_2, to form the real catalyst, which subsequently led to homogeneous catalytic direct oxidation of C–C double bond. During the reaction, the system gradually changed from turbid to clear. The infrared spectra (Fig. 2) showed that the H_2O_2-treated WPA/CPC (spectrum 2) has a peroxo-bond absorption peak ν(O–O) at 840 cm^{-1} and 846 cm^{-1}, while CWP itself (spectrum 1) does not have a peroxo-bond absorption peak at about 840 cm^{-1}. Instead, an absorption peak at 895 cm^{-1}, which corresponds to the asymmetric vibration of W–O–W, was found.

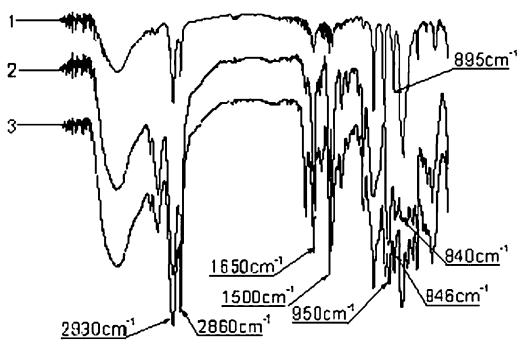


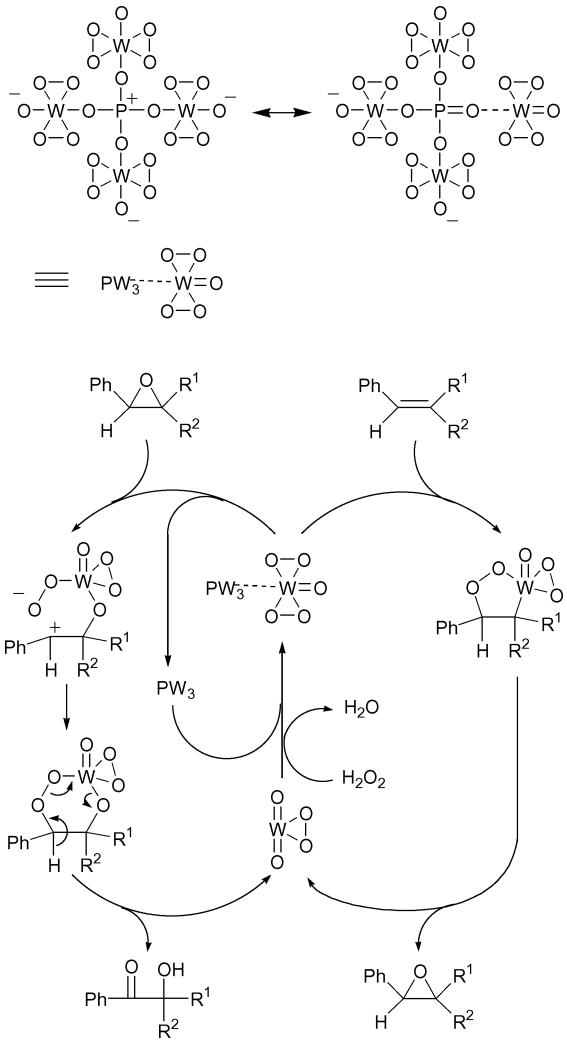
Fig. 2 Infrared spectra of (1) CWP, (2) H_2O_2 (30%)-treated CWP, and (3) recovered H_2O_2 (30%)-treated catalyst.

After extraction of the product, the aqueous phase was evaporated, which allowed the recovery of the catalyst. As shown in Table 2, the recovered catalyst can be recycled at least once without significant loss of activity.

Table 2 Recycling the catalyst for the ketohydroxylation of styrene

Run [a]	Yield (%) [b]
1	86.4
2	81.8
3	71.5
4	64.7

[a] All reactions were performed under the conditions of entry 1, Table 1, except that the catalyst was recovered from the preceding run. [b] Isolated yield.



Scheme 2 A proposed mechanism.

A mechanistic explanation is proposed as shown in Scheme 2. According to previous mechanistic research on the WPA/CPC-catalyzed epoxidation of olefins with hydrogen peroxide, when mixed with commercially available 35% H_2O_2, $H_3[PW_{12}O_{40}]$ is oxidized to $\{PO_4[WO(O_2)_2]_4\}^{3-}$, which was identified as the real catalyst.[7] This peroxo tungsten complex behaves as a 1,3-dipolar reagent, M^+–O–O^-, which reacts with the olefin to form a five-membered dioxametallocycle adduct. Degradation of the adduct produces the corresponding epoxide[8] and a PW_3 species, which quickly turns to the peroxo tungsten catalyst in the presence of hydrogen peroxide. The electrophilic attack of the peroxo tungsten complex on the above epoxide results in the formation of a six-membered cyclic intermediate, which degrades to produce the final oxidation product, a hydroxyketone, together with a PW_3 moiety, which is oxidized back to the peroxo tungsten catalyst and then enters the next cycle. As evidence for the above mechanism, phenyloxirane could be oxidized to the corresponding hydroxyketone in high yield under the reaction conditions (entry 19, Table 3). The fact that 1,1-disubstituted and trisubstituted ethylenes did not give hydroxyketones is another piece of evidence for this, because, according to the above mechanistic explanation, a hydrogen atom α- to the phenyl group is necessary. In the absence

Table 3 WPA/CPC-catalyzed oxidation of various olefins[a]

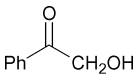
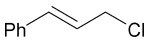
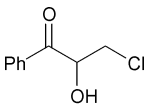
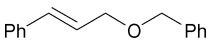
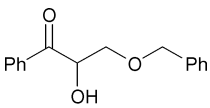
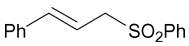
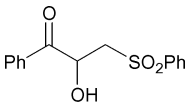
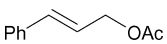
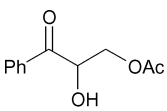
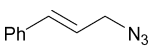
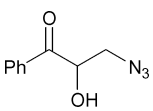
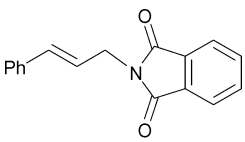
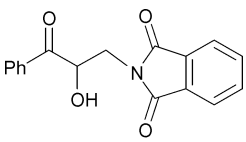
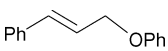
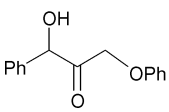
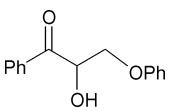
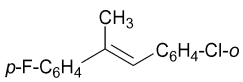
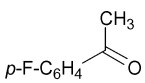
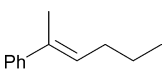
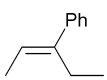
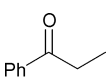
Entry	Substrate	Product	Time/h	Yield (%)[b]
1[c]	**1**	 **2**	24	86.4
2	 **3**	 **4**	48	74.6
3	 **5**	 **6**	24	75.7
4	 **7**	 **8**	48	73.0
5	 **9**	 **10**	48	78.5
6	 **11**	 **12**	17	75.6
7	 **13**	 **14**	20	79.4
8	 **15**	 **16a**  **16b**	48	20, 22
9	 **17**	 **18**	48	76.2
10	 **19**	**20**	12	76.7
11	 **21**	 **22**	12	80.7

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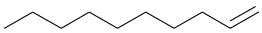
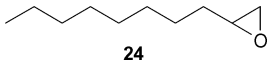
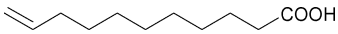
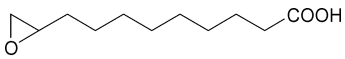
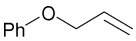
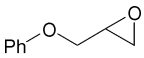
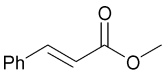
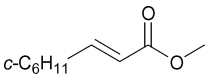
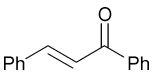
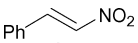
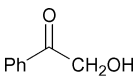
Table 3 (*Contd.*)

Entry	Substrate	Product	Time/h	Yield (%)[c]
12	 **23**	 **24**	15	87.8
13	 **25**	 **26**	24	87.5
14	 **27**	 **28**	24	nd
15	 **29**	—	24	nd
16	 **30**	—	24	nd
17	 **31**	—	24	nd
18	 **32**	—	24	nd
19	**33**	 **2**	$\frac{2}{3}$	93.1

[a] All reactions were performed on a 2 mmol scale in $CHCl_3$ (15 mL) using WPA ($H_3PW_{12}O_{40}$, 10 mol%), CPC (30 mol%), and 10 equiv. of H_2O_2 (30%) at 60 °C. [b] Isolated yields (nd = not determined). [c] The reaction was carried out under the conditions given in Table 1.

of WPA, styrene was not oxidized at all, even after 20 h of stirring with CPC/hydrogen peroxide at 60 °C. This excludes a radical pathway.

However, when extended to substrates other than styrene, the above conditions did not work. It was found that the amount of WPA and CPC must be increased to 10 mol% and 30 mol%, respectively, for the reaction to proceed at an acceptable rate.

We investigated the direct oxidation of various olefins under the modified conditions.[6] Table 3 shows the results of an intense screening of scope and limitations. It is important that many electron-rich alkenes were successfully transformed into the corresponding acyloins with remarkably high regioselectivities and yields (entries 1–7). We were even not able to detect any regioisomeric products from the crude mixtures. All the substrates that gave hydroxyketones as the products were 1-aryl-1-alkenes. In other words, an aromatic ring attached to the terminal sp^2 carbon is necessary for the hydroxyketonization to occur. Without this kind of substituent, only epoxidation was observed (entries 12–14). 1,1-Disubstituted and trisubstituted ethylenes cleaved during the course of oxidation (entries 9–11). It is noteworthy that the conversion is strongly dependent on the electronic properties of the C–C double bond. In general, electron-rich substrates are ketohydroxylated much faster than electron-poor starting materials; in fact, no reaction was observed with those alkenes that had moderately strong electron-withdrawing groups on C2 (entries 15–18).

In conclusion, we have demonstrated that various 1-aryl-1-alkenes can be oxidized by H_2O_2 to hydroxyketones in the presence of WPA/CPC under mild reaction conditions.

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References and notes

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