

## DoE (Design of Experiments) Assisted Allylic Hydroxylation of Enones Catalysed by a Copper–Aluminium Mixed Oxide

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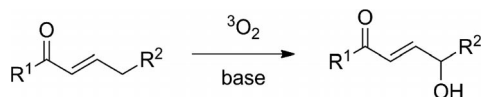
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The allylic hydroxylation of enones using dioxygen as the oxidant has been studied. The reaction was first examined in the absence of any catalyst, using  $\beta$ -ionone as a model substrate. Then a new copper–aluminium mixed oxide, Cu–Al Ox, was prepared and characterized in order to be used as a catalyst. This oxide showed good activity, and provided the corresponding  $\gamma$ - or  $\varepsilon$ -hydroxylated enones, starting from different  $\alpha,\beta$ - or  $\alpha,\beta,\gamma,\delta$ -unsaturated ketones. In all cases, the

yields were significantly improved compared to experiments run in the absence of the catalyst. The reaction was selective, and the formation of epoxides or other overoxidation products was detected only to a minor extent. The described procedure is a technically straightforward synthetic alternative to those methods described to date involving many reaction steps or toxic reagents. The reactions were optimized using design of experiments techniques (DoE).

### Introduction

The  $\gamma$ -hydroxylation of  $\alpha,\beta$ -unsaturated ketones using oxygen as the oxidant in the presence of a base is a reaction that has been known since the beginning of the last century (Scheme 1).<sup>[1–4]</sup> In the 1950s, Hawkins and the McQuillin group both published the results of their pioneering studies into the mechanism of this reaction, using substrates such as cyperone, mesityl oxide, and isophorone, among others.<sup>[5,6]</sup>



Scheme 1.  $\gamma$ -Hydroxylation of  $\alpha,\beta$ -unsaturated ketones.

The reaction of ketones with oxygen is usually sluggish, and frequently it results in the cleavage of the molecule. It typically involves species containing O–O bonds, and the weakness of these bonds results in the characteristic instability of the molecules. Such species are prone to undergo reactions such as Hock cleavage, Kornblum–DeLaMare reactions, Hock dehydration, rearrangements into dioxetane rings, etc.<sup>[7]</sup>

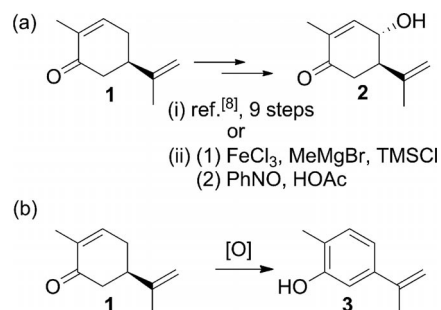
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Bearing this in mind, it is not surprising that this reaction has not found extensive use in organic synthesis. Usually, the desired hydroxy enone is accompanied by a plethora of other oxidation products, mainly epoxides or overoxidation products, resulting in very low yields.<sup>[7]</sup>

Evidence for the difficulty of this type of transformation can be seen in the preparation of (+)-5 $\beta$ -hydroxycarvone (**2**) by Yoshikoshi et al.<sup>[8]</sup> Instead of a direct oxidation of carvone (**1**), it required a nine-step synthetic sequence to produce the desired hydroxy enone (i.e., **2**; Scheme 2a). More recently, Yang et al. have reported the preparation of this compound in two steps, using nitrosobenzene to oxidize the corresponding silyl enol ether of the enone.<sup>[9]</sup> The toxicity of nitrosobenzene makes it desirable to find new alternative ways to perform this transformation (Scheme 2a). In addition, hydroxy enone **2** is very prone to undergo aromatization to produce phenol **3** (Scheme 2b).



Scheme 2. (a) Synthesis of 5- $\beta$ -hydroxycarvone (**2**); (b) oxidative aromatization of carvone (**1**). TMS = trimethylsilyl.

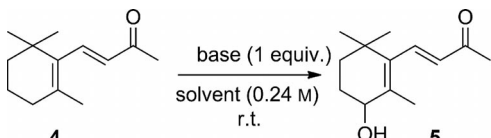
In this paper, we present the results of our efforts to achieve the oxidation of  $\alpha,\beta$ - and  $\alpha,\beta,\gamma,\delta$ -enones, using dioxygen (from the air) as the oxidant in the presence of a copper–aluminium mixed oxide, to give the corresponding  $\gamma$ -hydroxylated compounds. The products obtained may be used as building blocks in the synthesis of more complex molecules such as terpenes, and this represents the final goal of our investigation.

## Results and Discussion

### Study of the Influence of Bases, Solvents, and Oxidants in the Reaction

Our studies began using  $\beta$ -ionone (**4**) as a model substrate. Although this compound is an  $\alpha,\beta,\gamma,\delta$ -unsaturated ketone, it was chosen as a model compound since it is an affordable commercially available material that has previously been used in studies of the autoxidation of enones.<sup>[10]</sup> With this substrate, we carried out a preliminary screening of solvents and bases. After some experimentation, it was found that a protic solvent and a strong base were necessary. The best result was obtained with *t*BuOK as the base and EtOH as the solvent (Table 1, Entry 9).

Table 1. Influence of the solvent and base on the  $\varepsilon$ -hydroxylation of  $\beta$ -ionone.<sup>[a]</sup>

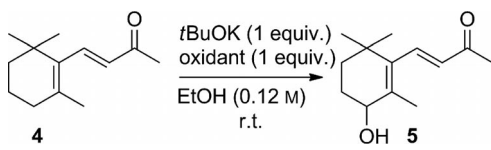


Entry	Base	Time [h]	Yield [%] <sup>[b]</sup>		
			EtOH	MeOH	2-Propanol
1	MeOK	2	19	5	16
2	MeOK	5	30	10	31
3	MeOK	24	42	33	37
4	KOH	2	18	5	11
5	KOH	5	29	10	18
6	KOH	24	36	30	21
7	<i>t</i> BuOK	2	25	6	10
8	<i>t</i> BuOK	5	36	13	14
9	<i>t</i> BuOK	24	45	38	17

[a] Reaction conditions: **4** (2.36 mmol), base (2.36 mmol), solvent (10 mL), room temp. [b] Determined by GC. Only alcohol **5** and starting material **4** were detected.

The reaction time was also studied, and we found that 24 h was an optimal time. Longer reaction times resulted in lower yields, probably due to overoxidation of the products. Although the autoxidation of enones proceeds with  $O_2$  as the oxidant, a series of experiments was performed with different oxidizing reagents ( $KMnO_4$ ,  $SeO_2$ , DIB [(diacetoxyiodo)benzene], etc.), but, as expected, the best results were obtained with atmospheric  $O_2$  (Table 2).

Table 2. Influence of the oxidant on the  $\varepsilon$ -hydroxylation of  $\beta$ -ionone (**4**).<sup>[a]</sup>



Run	Oxidant	Yield [%] <sup>[b]</sup>		
		2 h	5 h	20 h
1	$KMnO_4$ <sup>[c]</sup>	0	0	0
2	$KO_2$	0	5	14
3	$SeO_2$ <sup>[d]</sup>	0	0	0
4	DIB <sup>[d]</sup>	0	0	0
5	<i>t</i> BuOOH	5	6	11
6	$NaI/H_2O_2$ <sup>[e]</sup>	2	5	15
7	$NaOCl/H_2O_2$ <sup>[d,f]</sup>	0	0	2
8	$MnO_2$	9	16	36
9	$O_2$ <sup>[g]</sup>	25	36	45

[a] Reaction conditions: **4** (1.18 mmol), base (1.18 mmol), oxidant (1.18 mmol), solvent (10 mL), room temp. [b] Determined by GC. [c] Complex mixture. [d] Starting material recovered. [e]  $NaI$  (1.18 mmol)/ $H_2O_2$  (2.36 mmol). [f]  $NaOCl$  (1.18 mmol)/ $H_2O_2$  (2.36 mmol). [g] Oxygen from air (1 atm).

### DoE Optimization of the $\beta$ -Ionone $\varepsilon$ -Hydroxylation Reaction

To determine the importance of the different factors involved in the reaction, we decided to use a DoE (design of experiments) approach. This statistic tool is commonly used in analytical chemistry or chemical engineering, but it is rarely used in synthetic organic chemistry.<sup>[11–15]</sup> The design of experiments approach, in contrast to the classical OVAT method (changing one variable at a time), allows us to study a system by changing many variables at the same time. A matrix delimited by low and high levels of each variable involved in the reaction is defined. The yield is considered to be the response of the system to the changes of each variable, and the final objective is to obtain a model that accounts for the yield as a function of all of the variables. Thus, one can take into account interactions between the variables, and a wide knowledge of the system can be obtained from a reduced number of experiments.<sup>[16]</sup>

Based on our preliminary screening, we decided to use EtOH as the solvent and *t*BuOK as the base. The time was set to 24 h, and all the runs were carried out at room temperature.

The roles of the substrate concentration and the number of equivalents of base used were the variables to be optimized by DoE. Since there were only two variables, we decided to use a three-level full-factorial design. A full-factorial designed experiment includes all possible combinations of levels for all of the variables.

The range of the substrate concentration spanned from 0.10 M (low level) to 1.20 M (high level), with 0.65 M as the central point. The values chosen for the amounts of *t*BuOK were 1 (low level), 3 (central point), and 5 equiv. (high level).

The results of the experiments are shown in Table 3. Figures 1 and 2 show the Pareto plot and the response-surface graph, respectively. The vertical line in the Pareto plot (Figure 1) indicates a level of 95% confidence. Horizontal bars that cross this line represent variables with greater influence on the yield of the reaction for that level of confidence.

Table 3. Three-level full-factorial design for the oxidation of  $\beta$ -ionone (4).

Entry	Concentration of $\beta$ -ionone (4) [M]	<i>t</i> BuOK [equiv.]	Yield of 5 [%]
1	0.10	1	50
2	0.65	1	48
3	1.20	1	36
4	0.10	3	46
5	0.65	3	4
6	1.20	3	0
7	0.10	5	39
8	0.65	5	0
9	1.20	5	0
10	0.65	3	3
11	0.65	3	4
12	0.65	3	16

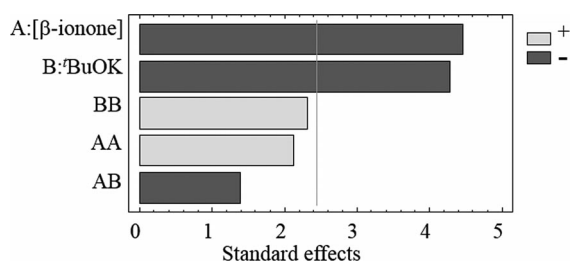


Figure 1. Pareto plot for the oxidation of  $\beta$ -ionone (4).

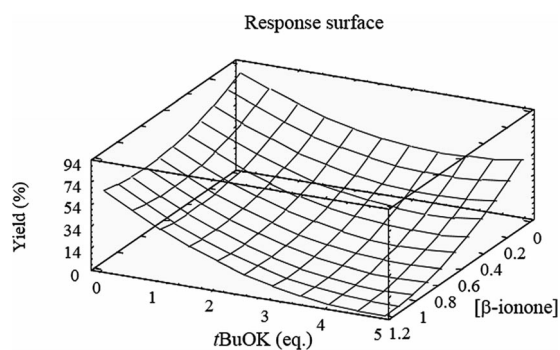


Figure 2. Calculated response surface for the oxidation of  $\beta$ -ionone.

In this case, the graph shows significant negative effects for the concentration and the number of equivalents of *t*BuOK used. No interaction was observed between these two variables.

Analysis of the response-surface graph reveals that the higher the concentration of  $\beta$ -ionone (4), the lower the yield is. The maximum yield was found at a  $\beta$ -ionone concentration of 0.1 M, using 1.0 equiv. of *t*BuOK. Given that the maximum yield was obtained at the lower limiting level of

the number of equivalents of *t*BuOK, we performed some additional runs outside the established experimental domain. But these experiments using less than 1.0 equiv. of *t*BuOK did not lead to further improvements in the yield. Eventually, we found that when 1.2 equiv. of *t*BuOK was used, the yield increased to 55%.

### Catalytic Activity of Cu–Al Ox, a Copper–Aluminium Mixed Oxide

Despite the improvement in the yield resulting from the statistical study of the reaction, it was clear that the conditions had the potential to be improved further. So we focussed our attention on heterogeneous catalysis. A survey of the literature showed that clays and hydrotalcites have often been described as catalysts for different organic reactions.<sup>[17–22]</sup> Commercially sourced hydrotalcite did not affect the outcome of our reaction with any substrate. It has also been published that the use of some copper sources may help to decrease the formation of epoxides and other by-products in the autoxidation of similar enones.<sup>[23]</sup> After some experimentation, a copper–aluminium mixed oxide, (hereafter called Cu–Al Ox), was synthesized. This new mixed oxide showed remarkable catalytic behaviour in the hydroxylation of enones. This material was prepared by a modification of the procedure developed by Guida et al. for the synthesis of hydrotalcites (see Experimental Section).<sup>[24]</sup>

To ensure the reproducibility of the Cu–Al Ox preparation, it was submitted to a characterization process. Figure 3 shows a typical SEM (scanning electron microscopy) image of the Cu–Al Ox catalyst prepared in this work. It has the form of a fine powder, which, although showing some irregularities in morphology and size, in general consists of micron-sized well-rounded grains. This study was complemented by granulometric measurements, which indi-

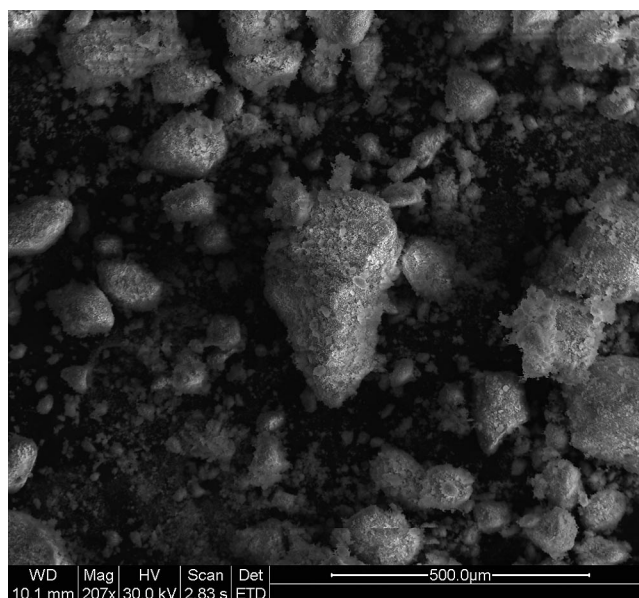


Figure 3. Scanning electron micrograph of the catalyst Cu–Al Ox.

cated a mean particle size of 1  $\mu\text{m}$ . In addition, a textural study was performed using  $\text{N}_2$  physisorption (see Supporting Information).

The results of compositional analysis performed by ICP (inductively coupled plasma mass spectrometry) and XRF (X-ray fluorescence) are summarized in Table 4. There is good agreement between data obtained by the two techniques. Moreover, they are relatively consistent with the Cu/Al atomic ratio selected for catalyst preparation.

Table 4. Compositional analysis [wt.-%] of the catalyst studied (n.a.: not available by means of this technique; n.d.: not detected).

Element	ICP	XRF	EDS <sup>[a]</sup>
Cu	61.2	64.9	63.3 $\pm$ 8.5
Al	7.9	9.5	9.1 $\pm$ 1.6
O	n.a.	25.2	22.0 $\pm$ 5.4
C	n.a.	n.a.	5.4 $\pm$ 1.6
Cl	n.a.	0.03	n.d.

[a] Data correspond to the average of values obtained for different analysed areas.

Table 4 also includes the elemental composition according to EDS (energy-dispersive X-ray spectroscopy) analysis performed over different areas of the surface of the catalyst sample. These data deserve several comments. First of all, it should be noted that in general, they also agree with the data obtained by ICP and XRF. Second, although some copper-rich (77.8 wt.-%) and aluminium-rich (15.4 wt.-%) areas were found, both elements were detected along with oxygen in all zones measured. This relatively homogeneous composition fits well with the formation of a mixed phase. The presence of a minor amount of carbon is also notable, and this could reasonably be derived from residual carbonates that might in principle come either from the sodium carbonate used for the catalyst preparation or from further reaction of the precipitate with  $\text{CO}_2$  during its exposure to air. This finding contrasts with the absence of chlorine, which confirms that the chlorides originally present in the starting materials for the catalyst synthesis were completely removed in the course of the preparation of the material.

A structural study of the catalyst by X-ray diffraction did not reveal the presence of a hydroxalcite phase. Some small and not well-defined peaks that could be due to CuO, tenorite phase, were detected.<sup>[25]</sup> These results suggest that an amorphous copper–aluminium mixed oxide must mainly have been formed. This fact is in good agreement with many references in the literature that point out the difficulty in obtaining crystalline hydroxalcite-like compounds with  $\text{Cu}^{2+}$  compared to with other divalent metals from  $\text{Mg}^{2+}$  to  $\text{Mn}^{2+}$ , due to the well known Jahn–Teller effect.<sup>[26–29]</sup>

### DoE Optimization of the $\gamma$ -Hydroxylation Using Cu–Al Ox as a Catalyst

The addition of the Cu–Al Ox catalyst to the reaction mixture produced a substantial improvement in the yield of the reaction. To ensure that this improvement was due to

the catalytic activity of Cu–Al Ox, several runs using the Cu–Al Ox precursors under different conditions and with different substrates were also carried out, with negative results. Furthermore, blank experiments in the absence of Cu–Al Ox led to poorer yields.

The scope of the reaction was investigated with different  $\alpha,\beta$ -unsaturated ketones. The initial conditions used were those optimized for  $\beta$ -ionone, but we soon discovered that every substrate would have to be studied separately. We also observed that the yield improved when the Cu–Al Ox was stirred with ethanol for 10 min prior to the addition of the substrate and the base. This fact seems to suggest that the Cu–Al Ox requires preactivation for catalysis to take place. We used either three-level full-factorial design or Box–Behnken experiments, now including the amount of the Cu–Al Ox as a new variable. In all cases except for testosterone, the reaction time was limited to 24 h.

The case of carvone (**1**) was especially interesting. As mentioned above, this substrate is very reluctant to provide the corresponding  $\gamma$ -hydroxy derivative **2**, in part due to its tendency to aromatize by elimination of the hydroxy group (Scheme 2b). To determine the best conditions for its oxidation, a three-level factorial design was performed with the following range of variables: (a) carvone concentration: 0.10, 0.38, and 0.65 M; (b) amount of Cu–Al Ox: 5.0, 52.5, and 100.0 mg; (c) amount of *t*BuOK: 0.50, 1.75, and 3.00 equiv. The resulting yields are shown in Table 5. Under

Table 5. Three-level full-factorial design experiment for the  $\gamma$ -hydroxylation of carvone (**1**).

Entry	Concentration of <b>1</b> [M]	Cu–Al Ox [mg]	<i>t</i> BuOK [equiv.]	Yield of <b>2</b> [%]
1	0.65	5.0	3.00	22
2	0.38	5.0	0.50	23
3	0.10	52.5	3.00	10
4	0.38	100	3.00	27
5	0.65	5.0	1.75	17
6	0.65	52.5	3.00	34
7	0.38	52.5	3.00	27
8	0.38	52.5	1.75	25
9	0.38	5.0	3.00	14
10	0.65	100	0.50	26
11	0.10	52.5	1.75	11
12	0.65	52.5	0.50	23
13	0.38	100	0.50	27
14	0.10	100	1.75	12
15	0.65	100	1.75	31
16	0.65	52.5	1.75	18
17	0.65	100	3.00	0 <sup>[a]</sup>
18	0.10	52.5	0.50	42
19	0.38	52.5	1.75	20
20	0.65	5.0	0.50	18
21	0.10	5.0	0.50	27
22	0.38	52.5	0.50	18
23	0.10	100	0.50	24
24	0.38	52.5	1.75	14
25	0.10	5.0	1.75	4
26	0.10	5.0	3.00	4
27	0.38	100	1.75	23
28	0.10	100	3.00	13
29	0.38	5.0	1.75	9

[a] Only aromatic phenol **3** was detected.

the optimal conditions, a yield of 42% was achieved. The resulting  $\gamma$ -hydroxy derivative (i.e., **2**) represents an important synthon for the synthesis of 8-hydroxylated terpenes.

The Pareto plot shows that there is an important interaction between the concentration of carvone and the amount of base (Figure 4). Furthermore, the amount of Cu–Al Ox is significant at the 95% confidence level. In contrast, the role of *t*BuOK itself is not considered to be significant. This suggests the existence of a complex scenario with both heterogeneous and homogeneous phase reagents present. The corresponding response-surface graph is shown in Figure 5.

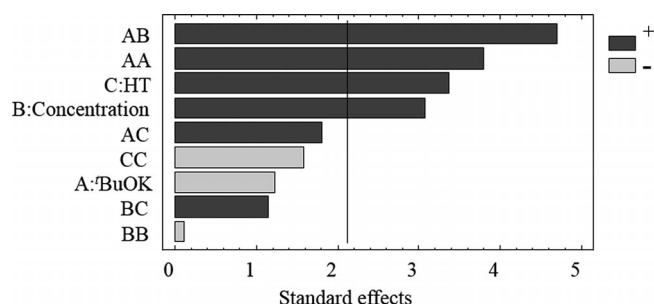


Figure 4. Pareto plot for the oxidation of carvone.

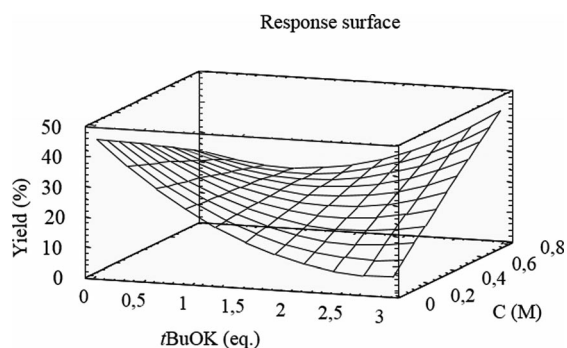
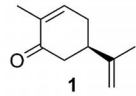
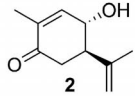
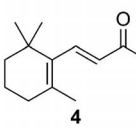
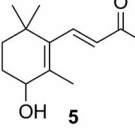
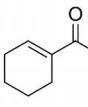
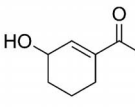
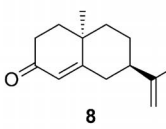
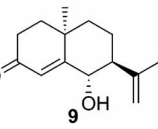
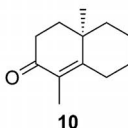
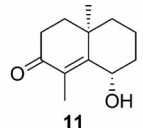
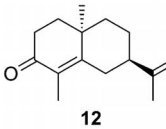
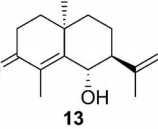
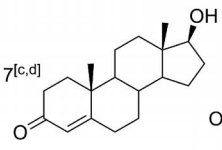
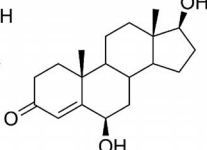


Figure 5. Calculated response surface for the oxidation of carvone.

The remaining substrates were studied in a similar way. The results are summarized in Table 6. An inspection of Table 6 reveals that notable improvements in the yield of the reaction can be obtained by addition of the appropriate amount of Cu–Al Ox. For instance, Table 6, Entry 3 shows that the yield of the reaction of acetylcyclohexene (**6**) was almost quadrupled by the addition of Cu–Al Ox.

The oxidation of nor-cyperone (**8**; Table 6, Entry 4), a substrate that is easily cleaved under oxidative conditions, proceeds with almost 50% yield. Cyperone itself (**12**; Table 6, Entry 6) proceeded quantitatively, providing 6 $\alpha$ -hydroxycyperone derivative **13** in synthetically useful yields. Table 6, Entry 7 shows the oxidation of a more complex ketone such as testosterone (**14**). The inertness of this substrate is well known, and a low yield (20%) of the product was isolated, although in the absence of Cu–Al Ox, only starting material was recovered.

Table 6. Oxidation of different substrates with Cu–Al Ox, *t*BuOK, and O<sub>2</sub>.

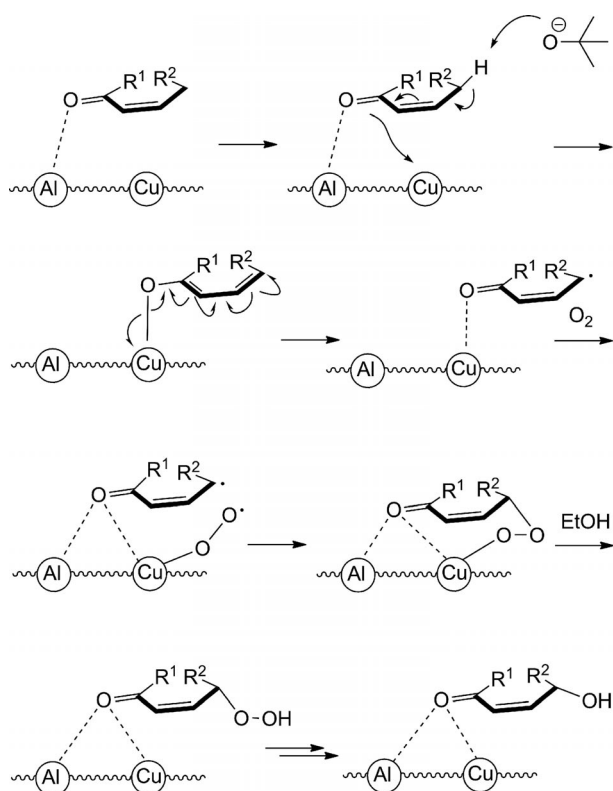
Entry	Substrate	Product (yield [%]) <sup>[b]</sup>	Conditions <sup>[a]</sup>
1		 (42/22)	0.10; 0.50; 83.9
2		 (72/55)	0.10; 1.20; 33.9
3		 (57/15)	0.65; 1.75; 69.5
4		 (48/15)	0.38; 0.50; 150.8
5		 (44/36)	0.25; 1.25; 67.5
6 <sup>[c]</sup>		 (100/60)	0.25; 1.25; 67.5
7 <sup>[c,d]</sup>		 (20/0)	0.09; 1.00; 161.5

[a] Concentration of substrate [M]; amount of *t*BuOK [equiv.]; amount of Cu–Al Ox [mg/mmol substrate]. [b] Yield with Cu–Al Ox/yield without Cu–Al Ox. [c] Isolated yield. [d] 3 d, 75% yield based on recovered material.

### Some Considerations About the Mechanism

The  $\gamma$ -hydroxylation reaction apparently involves the reaction of the enone with triplet dioxygen in the presence of

a base.<sup>[7]</sup> The reaction would be favoured by the presence of the acidic Al<sup>3+</sup> cations, which would coordinate to the carbonyl group of the ketone, attaching it to the catalyst surface. The experimental data seem to support an anionic mechanism involving the interaction between an enolate and molecular oxygen. However, this would mean a violation of the spin-conservation rule.<sup>[30]</sup> Alternatively, the enolate may be converted first into a free radical by donating an electron to an acceptor, before combining with triplet dioxygen (Scheme 3).



Scheme 3. Proposed mechanism for the oxidation of unsaturated enones with Cu–Al Ox, *t*BuOK, and O<sub>2</sub>.

According to Russell, this acceptor could be dioxygen itself.<sup>[7,31]</sup> Nevertheless, in the heterogeneous phase, it would be more likely that the copper ions may act as an electron sink to provide the corresponding radicals. Coordination of the O<sub>2</sub> molecule to the copper atoms would provide a way for the transfer of the oxygen atom to the enone. This transfer could be accomplished by the same copper atom attached to the carbonyl oxygen atom,<sup>[32]</sup> or it could be cooperatively assisted by a second copper atom in a different active centre. Finally, cleavage of the Cu–O bond would lead to the hydroxylated product. (Scheme 3).

## Conclusions

The treatment of  $\alpha,\beta$ - or  $\alpha,\beta,\gamma,\delta$ -unsaturated enones with a copper–aluminium mixed oxide, Cu–Al Ox, in the presence of *t*BuOK and O<sub>2</sub> yields the corresponding  $\gamma$ - or  $\varepsilon$ -hydroxylated derivatives in moderate to good yields. In all

cases, Cu–Al Ox catalyses the reaction, and the yields were higher than those observed in experiments in which the mixed oxide was not added. The vicinal presence of the Al<sup>3+</sup> and Cu<sup>2+</sup> cations seems to provide an appropriate environment for the catalytic process to take place. This study was carried out using DoE techniques. This approach is especially suitable for the optimization of reactions in which the involvement of many different species leads to a complex mechanism.

This procedure provides a route to valuable synthons such as (+)-5 $\beta$ -hydroxycarvone (**2**), a substrate whose preparation by previously described routes is problematic. We are currently using this compound in the synthesis of more complex terpenes, and the results of this work will be reported in due course.

## Experimental Section

**Catalyst Preparation:** The procedure for the preparation of the copper–aluminium mixed oxide (Cu–Al Ox) is based on that reported by Guida et al. for the synthesis of a typical hydroxalite material.<sup>[24]</sup> The molar ratio [Al]/(Cu + Al) is 0.315. A solution containing Na<sub>2</sub>CO<sub>3</sub> (1.27 g) and NaOH (5.20 g) in water (100 mL) was added dropwise over 1.5 h to a second solution containing CuCl<sub>2</sub> (5.0 g) and AlCl<sub>3</sub>·6H<sub>2</sub>O (4.0 g) in water (50 mL). The resulting blue suspension was stirred at 70 °C for 22 h. A gradual change in colour from blue to black was observed. The black precipitate was filtered, and the residue was washed with warm water. The solid was then dried in the oven at 105 °C for 24 h, after which time it was ground to a uniform consistency. Finally, it was left exposed to air for 3 d before use. The procedure was repeated several times, and the different batches of material had identical properties and catalytic behaviour.

**General Procedure for the  $\gamma$ - or  $\varepsilon$ -Hydroxylation of Enones:** The Cu–Al Ox catalyst (see below for Cu–Al Ox/substrate ratio) was suspended in EtOH with vigorous stirring for 10 min. The substrate (1 mmol) and *t*BuOK (the required amount) were added. The mixture was stirred under air for 24 h, after which time the reaction mixture was filtered through a Celite pad, which was then rinsed abundantly with methanol. The solvent was then removed from the filtrate under vacuum. The resulting oily residue was either analysed by GC or purified by silica gel column chromatography (mixtures of EtOAc/hexanes, according to TLC analysis).

**(*E*)-4-(3-Hydroxy-2,6,6-trimethylcyclohex-1-en-1-yl)but-3-en-2-one (**5**):** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.17 (br. d, *J* = 16.5 Hz, 1 H), 6.11 (d, *J* = 16.5 Hz, 1 H), 4.01 (br. t, *J* = 4.9 Hz, 1 H), 2.29 (s, 3 H), 1.92 (m, 1 H), 1.84 (br. s, 3 H), 1.72 (m, 1 H), 1.66 (m, 1 H), 1.58 (br. s, OH), 1.44 (m, 1 H), 1.06 (s, 3 H), 1.03 (s, 3 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 198.6, 142.9, 138.8, 134.4, 132.6, 69.4, 34.5, 34.4, 28.5, 28.0, 27.4, 27.0, 18.2 ppm. IR (film):  $\tilde{\nu}$  = 3422, 2939, 1667, 1607, 1361, 1256, 1022, 996, 577 cm<sup>-1</sup>. HRMS (ESI): calcd. for C<sub>13</sub>H<sub>21</sub>O<sub>2</sub> [M + H]<sup>+</sup> 209.1542; found 209.1550.

**5 $\beta$ -Hydroxycarvone (**2**):** [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +110.72 (*c* = 2.00, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 6.69 (br. s, 1 H), 4.96 (m, 1 H), 4.93 (br. s, 1 H), 4.43 (br. d, *J* = 9.7 Hz, 1 H), 2.68 (ddd, *J* = 13.7, 9.7, 4.0 Hz, 1 H), 2.49 (dd, *J* = 16.3, 4.0 Hz, 1 H), 2.37 (dd, *J* = 16.3, 13.8 Hz, 1 H), 1.77 (m, 3 H), 1.74 (br. s, 3 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 198.4, 147.4, 143.0, 135.0, 114.6, 68.4, 52.6, 40.8, 19.0, 15.3 ppm. IR (film):  $\tilde{\nu}$  = 3411, 2922, 1668, 1321, 1260,

1100, 1037, 893, 796  $\text{cm}^{-1}$ . HRMS (ESI): calcd. for  $\text{C}_{10}\text{H}_{15}\text{O}_2$  [ $\text{M} + \text{H}$ ] $^+$  167.1072; found 167.1084.

**1-(3-Hydroxycyclohex-1-en-1-yl)ethanone (7):**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 6.74 (br. s, 1 H), 4.42 (m, 1 H), 2.30 (s, 3 H), 2.20 (m, 2 H), 1.95 (m, 1 H), 1.79 (m, 1 H), 1.56 (m, 2 H) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 199.7, 140.8, 140.5, 66.5, 31.4, 25.4, 23.0, 19.0 ppm. IR (film):  $\tilde{\nu}$  = 3366, 2932, 1662, 1361, 1261, 1025, 795, 698, 487  $\text{cm}^{-1}$ . HRMS (ESI): calcd. for  $\text{C}_8\text{H}_{13}\text{O}_2$  [ $\text{M} + \text{H}$ ] $^+$  141.0916; found 141.0926.

**6 $\alpha$ -Hydroxy-4-nor-methyl-7-epi-cyperone (9):**  $[\alpha]_{\text{D}}^{20}$  = -79.43 ( $c$  = 0.87,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 5.91 (s, 1 H), 4.86 (s, 1 H), 4.56 (s, 1 H), 4.38 (d,  $J$  = 2.5 Hz, 1 H), 2.60 (ddd,  $J$  = 17.8, 14.8, 5.3 Hz, 1 H), 2.53 (br. s, 1 H), 2.41 (ddd,  $J$  = 4.6, 2.2, 1.0 Hz, 1 H), 2.37 (m, 1 H), 2.25 (m, 1 H), 1.83 (dd,  $J$  = 14.4, 4.6 Hz, 1 H), 1.74 (br. s,  $J$  = 0.6 Hz, 3 H), 1.69 (ddd,  $J$  = 13.2, 5.2, 2.2 Hz, 1 H), 1.60 (m, 1 H), 1.46 (dd,  $J$  = 13.6, 4.2 Hz, 1 H), 1.42 (s, 3 H) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 200.2, 168.2, 144.6, 127.5, 112.5, 74.7, 47.0, 39.1, 35.2, 34.8, 34.4, 25.0, 22.7, 19.3 ppm. IR (film):  $\tilde{\nu}$  = 3388, 2925, 1669, 1447, 1261, 1002, 892, 697  $\text{cm}^{-1}$ . HRMS (ESI): calcd. for  $\text{C}_{14}\text{H}_{21}\text{O}_2$  [ $\text{M} + \text{H}$ ] $^+$  221.1542; found 221.1552.

**(4a*R*,8*S*)-8-Hydroxy-1,4a-dimethyl-4,4a,5,6,7,8-hexahydro-naphthalen-2(3*H*)-one (11):**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 4.91 (dd,  $J$  = 9.4, 6.4 Hz, 1 H), 2.61 (ddd,  $J$  = 17.5, 15.0, 5.3 Hz, 1 H), 2.41 (ddd,  $J$  = 17.5, 4.7, 2.5 Hz, 1 H), 2.02 (m, 3 H), 1.82 (s,  $J$  = 4.8 Hz, 3 H), 1.62 (m, 3 H), 1.46 (m, 2 H), 1.38 (s, 3 H) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 200.3, 159.6, 131.3, 66.7, 41.4, 39.1, 35.2, 34.1, 33.2, 24.6, 15.6, 10.4 ppm. IR (film):  $\tilde{\nu}$  = 3447, 2924, 1652, 1445, 1262, 1198, 1018, 615  $\text{cm}^{-1}$ . HRMS (ESI): calcd. for  $\text{C}_{12}\text{H}_{19}\text{O}_2$  [ $\text{M} + \text{H}$ ] $^+$  195.1385; found 195.1404.

**6 $\alpha$ -Hydroxy-7-epi- $\alpha$ -cyperone (13):**  $[\alpha]_{\text{D}}^{20}$  = +44 ( $c$  = 0.10,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 4.90 (d,  $J$  = 1.3 Hz, 1 H), 4.82 (d,  $J$  = 1.7 Hz, 1 H), 4.36 (d,  $J$  = 1.7 Hz, 1 H), 2.60 (ddd,  $J$  = 17.9, 14.8, 5.4 Hz, 1 H), 2.53 (br. s, 1 H), 2.40 (ddd,  $J$  = 17.9, 5.1, 2.2 Hz, 1 H), 2.21 (dddd,  $J$  = 13.6, 13.6, 5.3, 2.9 Hz, 1 H), 1.88 (s, 3 H), 1.82 (ddd,  $J$  = 14.8, 13.4, 5.1 Hz, 1 H), 1.72 (s, 3 H), 1.60 (ddd,  $J$  = 13.4, 5.4, 2.2 Hz, 1 H), 1.37 (s, 3 H), 1.52–1.36 (m, 1 H) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 200.5, 160.6, 145.8, 132.5, 111.9, 70.0, 48.2, 39.3, 35.6, 35.6, 34.6, 26.2, 23.5, 19.1, 10.9 ppm. IR (film):  $\tilde{\nu}$  = 3454, 2923, 2862, 1662, 1464, 1343, 1199, 1021, 991, 895, 748  $\text{cm}^{-1}$ . HRMS (ESI): calcd. for  $\text{C}_{15}\text{H}_{23}\text{O}_2$  [ $\text{M} + \text{H}$ ] $^+$  235.1698; found 235.1702.

**6 $\beta$ -Hydroxytestosterone (15):**  $[\alpha]_{\text{D}}^{20}$  = +17.20 ( $c$  = 0.12,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 5.81 (s, 1 H), 4.34 (t,  $J$  = 2.8 Hz, 1 H), 3.65 (m, 1 H), 2.52 (ddd,  $J$  = 17.2, 14.9, 5.0 Hz, 1 H), 2.38 (m, 1 H), 2.05 (m, 1 H), 2.03 (m, 1 H), 2.00 (m, 1 H), 1.98 (m, 1 H), 1.87 (m, 1 H), 1.72 (dd,  $J$  = 14.3, 4.4 Hz, 1 H), 1.61 (m, 1 H), 1.55 (m, 1 H), 1.45 (m, 1 H), 1.39 (m, 1 H), 1.38 (s, 3 H), 1.35 (m, 1 H), 1.21 (m, 1 H), 1.09 (m, 1 H), 0.98 (m, 1 H), 0.93 (m, 1 H), 0.81 (s, 3 H) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 200.4, 168.2, 126.6, 110.2, 81.8, 73.2, 53.9, 50.6, 43.1, 38.2, 37.3, 36.6, 34.4, 30.7, 29.9, 23.4, 20.8, 19.7, 11.2 ppm. IR (film):  $\tilde{\nu}$  = 3396, 2961, 1662, 1447, 1261, 1020, 802, 598  $\text{cm}^{-1}$ . HRMS (ESI): calcd. for  $\text{C}_{19}\text{H}_{29}\text{O}_3$  [ $\text{M} + \text{H}$ ] $^+$  305.2117; found 305.2125.

**Supporting Information** (see footnote on the first page of this article): General experimental methods;  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the  $\gamma$ -hydroxy enones; granulometry study; X-ray diffraction phase identification;  $\text{N}_2$  adsorption/desorption isotherm of Cu–Al Ox.

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