# Allylic Oxidation of Alkenes Catalyzed by a Copper–Aluminum Mixed Oxide

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Ⓢ *Supporting Information*

ABSTRACT: A strategy for the allylic oxidation of cyclic alkenes with a copper–aluminum mixed oxide as catalyst is presented. The reaction involves the treatment of an alkene with a carboxylic acid employing *tert*-butyl hydroperoxide as the oxidant. In all cases, the corresponding allylic esters are obtained. When L-proline is employed, the allylic alcohol or ketone is obtained. The oxidation of cyclohexene and valencene has been optimized by design of experiments (DoE) statistical methodology.
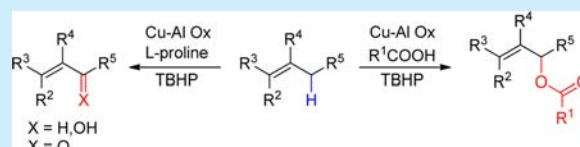
The allylic oxidation of an alkene is one of the simplest cases of C–H bond activation.[1] This transformation lacks a general methodology due to problems such as regio- and stereoselectivity, poor compatibility with other functional groups, overoxidation issues, etc. It is not common to find a total synthesis in which the key step lies in the allylic oxidation of an alkene, despite the fact that in many cases this sort of transformation could streamline a given route substantially.[2]

Classically, this transformation has been based mainly on the chemistry of Se, Cr, Pd, and Cu species.[3] Toxicity and cost are the main drawbacks of some of them, especially when the reagent has to be used in stoichiometric amounts. Additionally, remarkable efforts have been made by the White[4] and Doyle[5] groups based on Pd and Rh, respectively, leading to commercial versions of their catalysts.

A lesser known approach employs a copper source and a stoichiometric amount of an oxidant, usually a perester. This reaction is known as the Kharasch–Sosnovsky reaction.[6] First described in the later years of the 1950s, the reaction involves the oxidation of an alkene by *tert*-butyl peroxybenzoate in the presence of a copper or cobalt source, providing the corresponding benzoate ester (Figure 1a). An alternative is the employment of a carboxylic acid as the donor of acyloxy radicals, providing directly the corresponding allylic esters.[7]
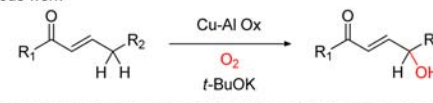
The Kharasch–Sosnovsky reaction is an interesting option that has not been fully exploited.[8] Recently, we have reported the preparation of a new copper–aluminum mixed oxide (Cu–Al Ox henceforth) that catalyzes the allylic hydroxylation of enones.[9] The electron-deficient double bond of the enone was oxidized with moderate to good yields employing Cu–Al Ox, *t*-BuOK, and molecular oxygen from the air as the oxidant (Figure 1b). In this work, we describe the allylic oxidation of cyclic alkenes catalyzed by Cu–Al Ox using *tert*-butyl hydroperoxide as the oxidant (Figure 1c).

Cu–Al Ox is prepared from CuCl₂ and AlCl₃·6H₂O by co-precipitation with Na₂CO₃ and NaOH in water. After heating at 70 °C for 22 h, removal of water, and drying first in an oven (105
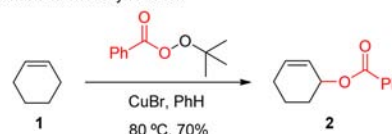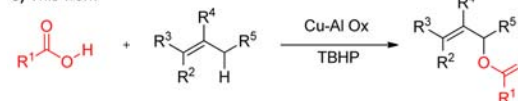

Figure 1. (a) Kharasch–Sosnovsky reaction; (b) use of Cu–Al Ox for the allylic oxidation of electron-deficient alkenes; (c) use of Cu–Al Ox for the allylic oxidation of electron-rich alkenes.
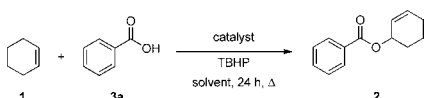
°C, 24 h) and then at open atmosphere (3 days), a fine powder is obtained. It consists of well-rounded grains in which copper and aluminum can be detected in all zones measured in a constant composition (Cu 63.3%, Al 9.1%, EDS measures).[9]

The optimal performance of Cu–Al Ox in the oxidation of alkenones prompted us to investigate its use in the allylic oxidation of electron-rich alkenes. To this end, we first carried out an exploratory screening employing cyclohexene **1** and benzoic acid **3a**. After some experimentation, good yields of cyclohexenyl benzoate **2** were obtained employing *tert*-butyl hydroperoxide (TBHP) as the oxidant.

It was also observed that the reaction was highly sensitive to the nature of the solvent, being quantitative when acetonitrile was employed (Table 1).

Table 1. Oxidation of Cyclohexene with TBHP[a]

entry	catalyst	solvent	temp (°C)	yield[b] (%)
1	Cu−Al Ox	hexane	69	20
2	Cu−Al Ox	CH₂Cl₂	40	82
3	Cu−Al Ox	pyridine	115	37
4	Cu−Al Ox	CH₃CN	82	100
5[c]	Cu−Al Ox	CH₃CN	82	9
6		CH₃CN	82	6
7	CuCl₂	CH₃CN	82	25
8	AlCl₃·6H₂O	CH₃CN	82	4
9[d]	CuCl₂, AlCl₃·6H₂O	CH₃CN	82	51

[a]All reaction were carried out using cyclohexene **1** (4.0 mmol), benzoic acid **3a** (1.0 mmol), TBHP (1.5 mmol), catalyst (60 mg), solvent (4 mL), 24 h. [b]Determined by GC. [c]Without TBHP, oxygen from air as oxidant(1 atm, vigorous stirring). [d]CuCl₂ (33 mg), AlCl₃·6H₂O (27 mg).

Several blank tests were run to evaluate the necessity of the use of Cu−Al Ox and the behavior of its parent precursors (entries 6−9). The presence of Cu−Al Ox was essential since the yield of the corresponding ester dropped to only 6% in its absence (entry 6). TBHP was needed for the reaction to proceed, and the oxygen from the air did not work as the oxygen source (entry 5). It was also observed that the use of any Cu−Al Ox precursors led lower yields, demonstrating the superior catalytic activity of Cu−Al Ox.

We next turned to the substrate scope of simple cycloalkenes and carboxylic acids (Scheme 1). The yields ranged from moderate to excellent. Several aromatic carboxylic acids bearing different groups were employed. The presence of either an electron-withdrawing or an electron-releasing group in the aromatic ring of the carboxylic acids seemed not to affect the outcome of the reaction. In the case of cyclohexene, the results were excellent with all tested acids. There was more disparity when cyclopentene **4** and cyclooctene **5** were used. In the case of cyclopentene, the presence of a methoxyl group in the *p*-position of the aromatic ring led to a 85% yield of the ester **13**. The same acid led to a moderate 36% yield of **18** when cyclooctene was employed.

More complex alkenes were also evaluated (Scheme 2). In the case of the monoterpene β-pinene **20**, the yields ranged from moderate to good. It is remarkable that no allylic transposition of the double bond was observed in contrast to other oxidation methods. In the case of the sesquiterpene valencene **21**, the yields were higher than those obtained in β-pinene, except in the case of acetate **33** (only 46%). The nature of the group located in the aromatic ring did not affect the outcome of the reaction. The inertness shown by the exocyclic double bond of valencene under the reaction conditions was also remarkable.

Finally, the benzylic oxidation of indane **22** was studied. The reactions proceeded in a wide range of yields, from moderate in the case of acetate **39** (26%) to good in the case of *p*-methoxybenzoate **37** (88%).

Most reports regarding the Kharasch−Sosnovsky reaction employ an excess of the olefin, with the oxidant being the limiting reagent.[10] This fact restricts the use of this reaction in the case of valuable alkenes. In our case, except when the volatility is an issue, the reactions were carried out employing a 1:1 alkene−oxidant ratio.

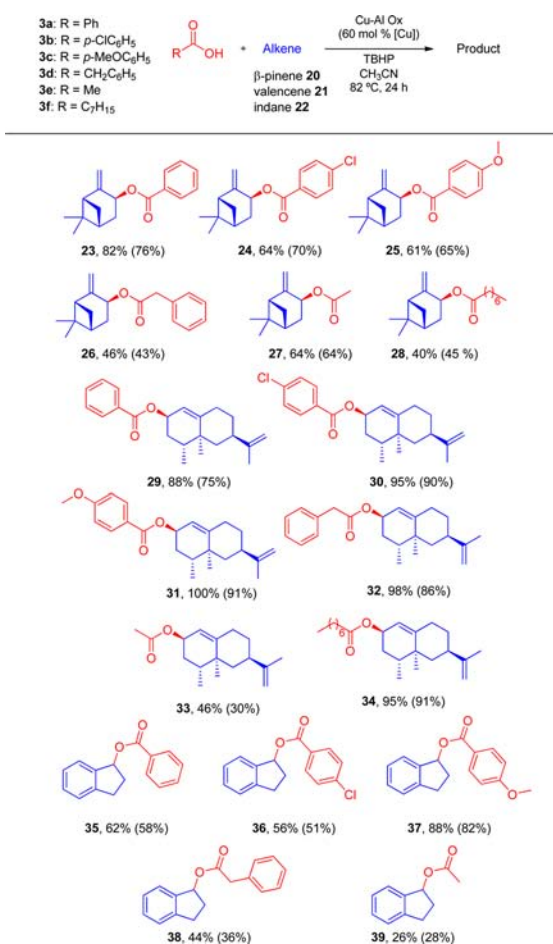**Scheme 1. Oxidation of Simple Cycloalkenes with TBHP in the Presence of Cu−Al Ox[a,b]**
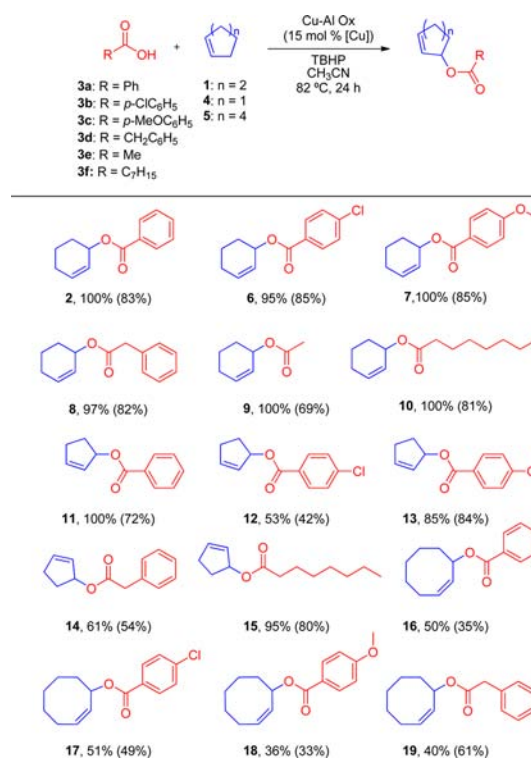
[a]All reactions were carried out using the cycloalkene (4.0 mmol), carboxylic acids **3a−f** (1.0 mmol), TBHP (1.5 mmol), Cu−Al Ox (60 mg), refluxing CH₃CN (4 mL), 24 h. [b]GC yields (isolated yield).

According to the mechanisms proposed by Beckwith and Savitzas[11] and Mayoral et al.[12] for the Kharasch−Sosnovsky reaction, a plausible mechanism for the present allylic oxidation is outlined in Scheme 3. In this mechanism, the solid Cu−Al Ox provides a surface in which coordination with the Cu or Al atoms may diminish the activation energy needed for the homolytic cleavage of the O−O or the C−H bonds of the TBHP or the cyclohexene, respectively. The presence of a second metallic atom in the close vicinity to the Cu atom would help to lock the reacting species. After formation of the cyclohexenyl radical, the carboxylic acid would be locked by the Cu or Al atoms. Finally, a pericyclic rearrangement would take place, providing the corresponding ester.

The use of amino acids as the carboxylic acid partner was also investigated. When we employed L-proline and cyclohexene as the olefin (Scheme 4), it was found that, contrary to the expected esterification process described above, only cyclohexenol **40** and cyclohexenone **41** were detected, although in low yield (12% and 11%, respectively).

Given that the reaction led to the formation of a free hydroxyl group or a ketone, a different mechanism should be considered. A possible explanation would involve the formation of a complex between the L-proline ligand and the copper atom of Cu−Al Ox as reported by the Ding[13] and Stahl[14] groups.

Since the mechanism of the latter transformation was unclear, its optimization was troublesome. This fact and the low yields obtained prompted us to employ a statistical approach, the design of experiments (DoE), to increase the yield. DoE is a statistical method that defines a domain for every variable involved in a reaction. Instead of changing one variable at a time

Scheme 2. Oxidation of More Complex Alkenes with TBHP in the Presence of Cu−Al Ox[a,b]

3a: R = Ph
3b: R = p-ClC₆H₅
3c: R = p-MeOC₆H₅
3d: R = CH₂C₆H₅
3e: R = Me
3f: R = C₇H₁₅

β-pinene 20
valencene 21
indane 22

23, 82% (76%) 24, 64% (70%) 25, 61% (65%)
26, 46% (43%) 27, 64% (64%) 28, 40% (45%)
29, 88% (75%) 30, 95% (90%)
31, 100% (91%) 32, 98% (86%)
33, 46% (30%) 34, 95% (91%)
35, 62% (58%) 36, 56% (51%) 37, 88% (82%)
38, 44% (36%) 39, 26% (28%)

[a]All reactions were carried out using alkene (1.0 mmol), carboxylic acids **3a−f** (1.0 mmol), TBHP (1.5 mmol for valencene **21**, 3.0 mmol for β-pinene **20**, and indane **22**), Cu−Al Ox (60 mg), refluxing CH₃CN (4 mL), 24 h. [b]GC yields (isolated yield).

Scheme 3. Plausible Mechanism for the Allylic Oxidation of Alkenes with TBHP in the Presence of Cu−Al Ox
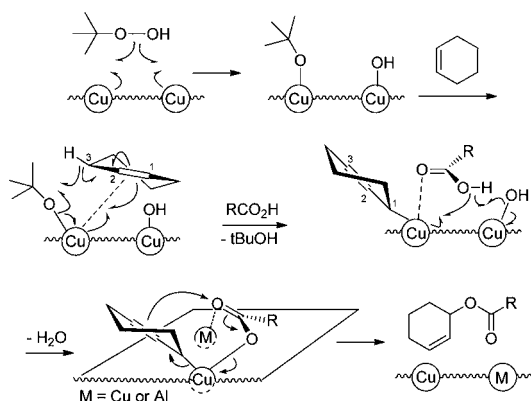
(an OVAT approach), this technique allows several variables to be changed at the same time.[15] The experiments are run under the conditions determined by a chosen algorithm, and different yields are obtained. With these data in hand, a model that accounts for the dependence of the yield with regard to every variable studied can be calculated. It is then possible to predict

Scheme 4. Synthesis of Cyclohexenol and Cyclohexenone with TBHP in the Presence of Cu−Al Ox and L-Proline
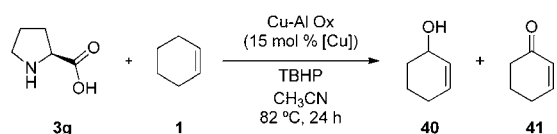
the yield of a given reaction under certain conditions or to optimize the conditions in order to obtain the highest possible yield.

Three variables were considered for the study: (i) the amount of Cu−Al Ox, (ii) the equivalents of TBHP, and (iii) the temperature. The election of acetonitrile as the solvent set the temperature at 82 °C, enabling the cleavage of the O−O bond of the TBHP. With only two variables, it was possible to perform a 3^2 full-factorial design with two central points, which resulted in 11 experiments (see the Supporting Information for the experimental matrix).

This design increased the yield to 40% for cyclohexenol and 48% for cyclohexenone, which represents a 88% of overall oxidation yield, employing 15 mg/mmol of Cu−Al Ox and 6.0 equiv of TBHP at 82 °C. The curved shape of the attained response surface (Figure 2) revealed that higher amounts of Cu−Al Ox and TBHP would not result in significant higher yields.
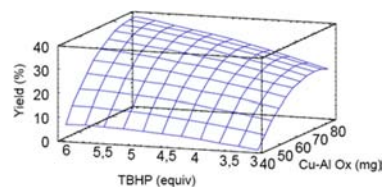

Figure 2. Calculated response surface for the synthesis of cyclohexenol **40**.

The allylic oxidation of valencene employing Cu−Al Ox, TBHP, and L-proline was studied next. We first carried out an experiment employing 1.5 equiv of TBHP and 60 mg/mmol of Cu−Al Ox. In contrast to the results of cyclohexene, the reaction produced only nootkatone **42** (40% yield), a valuable sesquiterpene commonly used in perfumery and cosmetics.[16]

Following the same methodology described above, a 3^2 full-factorial design, with 9 experiments and 2 extra central points, was conducted. The statistical analysis of the model thus obtained (see the Supporting Information) displayed that the main factor involved was the amount of Cu−Al Ox employed in the reaction. The amount of oxidant resulted irrelevant in the experimental domain. The response surface is displayed in Figure 3.

The best result corresponded to 60 mg/mmol substrate of Cu−Al Ox and 4.5 equiv of TBHP, which proceeded in 64% yield. The reaction yield was thus improved from 40 to 64%.
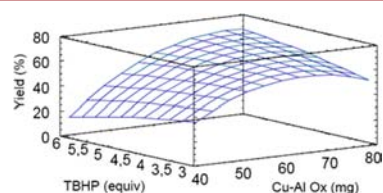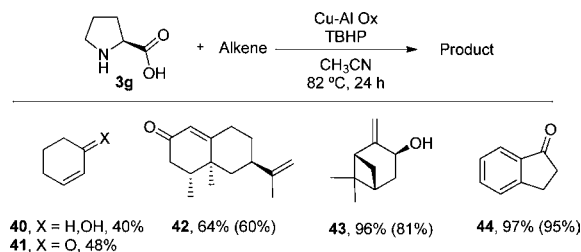

Figure 3. Response surface for the synthesis of nootkatone **42**.

Extension of the study to the allylic oxidation of of β-pinene and indane (Scheme 5) provided alcohol **43** and ketone **44**, respectively, with excellent yields.

Scheme 5. Oxidation of Alkenes in the Presence of L-Proline[a,b]

40, X = H,OH, 40%   **42**, 64% (60%)   **43**, 96% (81%)   **44**, 97% (95%)
41, X = O, 48%

[a]All reactions were carried out using cyclohexene **1** (4.0 mmol) and β-pinene **20**, (+)-valencene **21**, and indane **22** (1.0 mmol), L-proline **3g** (1.0 mmol), TBHP (6.0 mmol for **1** and **20** and 4.5 mmol for **21** and **22**), Cu−Al Ox (60 mg; 15 mol % [Cu] for **1**, 60 mol % [Cu] for **20**, **21**, and **22**), refluxing CH$_3$CN (4 mL), 82 °C, 24 h. [b]GC yields (isolated yield).

To verify the uniqueness of L-proline in this context, an amino acid and amine series were also tested, leading to poorer results compared to L-proline (see the Supporting Information).

In summary, we have demonstrated the capacity of Cu−Al Ox to catalyze the allylic oxidation of cyclic alkenes. The reactions are technically easy to perform and provide synthetically useful yields. In addition, DoE has revealed itself as a valuable tool for the optimization of these processes. The use of Cu−Al Ox discloses a promising route to the allylic oxidation of valuable alkenes. Its preparation is amenable to fine-tuning, and its chemical properties can thus be modulated. Its catalytic behavior in other reactions is currently under study.

■ ASSOCIATED CONTENT

S Supporting Information

Experimental procedures, DoE optimization details, compound characterization, and ^{1}H/^{13}C NMR reprints. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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