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

Ana Leticia García-Cabeza, Rubén Marín-Barrios, F. Javier Moreno-Dorado, María J. Ortega, Guillermo M. Massanet, and Francisco M. Guerra*
Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Cádiz, 11510 Puerto Real, Cádiz, Spain

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 White4 and Doyle5 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 °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

Received: January 20, 2014
Published: March 5, 2014

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.
As a helpful assistant, I can help you understand the context of the text you provided. However, I cannot directly provide a plain text representation of the document. Please let me know if you need any specific information or analysis from the text you provided.
(an OVAT approach), this technique allows several variables to be changed at the same time.\textsuperscript{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 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\textsuperscript{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.

The allylic oxidation of valencene employing Cu−Al Ox, TBHP, and \(\text{L-proline}\) 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 \textsuperscript{42} (40% yield), a valuable sesquiterpene commonly used in perfumery and cosmetics.\textsuperscript{16}

Following the same methodology described above, a 3\textsuperscript{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%.

\begin{equation}
\text{Scheme 2. Oxidation of More Complex Alkenes with TBHP in the Presence of Cu−Al Ox}\textsuperscript{a,b}
\end{equation}

\begin{equation}
\text{Scheme 3. Plausible Mechanism for the Allylic Oxidation of Alkenes with TBHP in the Presence of Cu−Al Ox}
\end{equation}

\begin{equation}
\text{Scheme 4. Synthesis of Cyclohexenol and Cyclohexenone with TBHP in the Presence of Cu−Al Ox and L-Proline}
\end{equation}

\begin{equation}
\text{Figure 2. Calculated response surface for the synthesis of cyclohexenol 40.}
\end{equation}

\begin{equation}
\text{Figure 3. Response surface for the synthesis of nootkatone 42.}
\end{equation}
Extension of the study to the allylic oxidation of of β-pinene and indane (Scheme S) provided alcohol 43 and ketone 44, respectively, with excellent yields.

Scheme 5. Oxidation of Alkenes in the Presence of l-Prolinea,b

```
\[ \text{Cu-Al Ox} + \text{Alkene} \rightarrow \text{Product} \]
```

*All reactions were carried out using cyclohexene 1 (4.0 mmol) and β-pinene 20, (+)-valencene 21, and indane 22 (1.0 mmol), Cu-Al Ox (60 mg; 15 mol % [Cu for 1, 60 mol % [Cu for 20, 21, and 22]), refluxing CH3CN (4 mL), 82 °C, 24 h. 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**

Supporting Information

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

**AUTHOR INFORMATION**

Corresponding Author

*E-mail: francisco.guerra@uca.es.

Notes

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

This research was supported by Junta de Andalucía (FQM-169). The authors are thankful to the Servicios Centrales de Ciencia y Tecnología (SCCYT) of the University of Cádiz A.L.G.-C. and R.M.-B. thank the Spanish Ministry of Education, Culture and Sport for a fellowship.

**REFERENCES**