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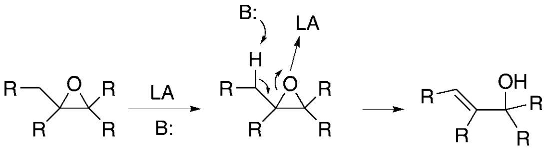
Heterogeneous Catalysis

Selective Isomerization of Epoxides to Allylic Alcohols Catalyzed by TiO_2-Supported Gold Nanoparticles

Christos Raptis, Hermenegildo Garcia, and Manolis Stratakis**

Epoxides play a dominant role as valuable intermediates in organic processes. They provide an array of addition products through either nucleophilic opening or electrophilic activation, or they isomerize to carbonyl compounds or allylic alcohols depending on the reaction conditions (acidic or basic). Regarding their isomerization to allylic alcohols under homogeneous reaction conditions, relatively few procedures are known. The reaction with alkylamide bases[1] or Schlosser's Li/K mixed superbases[2] converts epoxides into allylic alcohols. Sharpless and Lauer[3] presented a method for the isomerization of epoxides to allylic alcohols by using organoselenium chemistry. Under acidic reaction conditions, epoxides primarily isomerize to carbonyl compounds[4] by the Meinwald rearrangement, and allylic alcohols are often formed as by-products. The isomerization of epoxides to allylic alcohols, through a radical pathway ($[Cp_2TiCl]$, $Cp = C_5H_5$) and in moderate yields, is also known.[5]

An alternative unprecedented catalytic mechanism to convert an epoxide into an allylic alcohol would require the development of a mild heterogeneous bifunctional acid/base catalyst. Upon activation of the epoxide moiety by the acidic sites, the basic sites would abstract, in a rather concerted way, a hydrogen atom from the α-carbon atom (with respect to the epoxide functionality) to produce an allylic alcohol (Scheme 1). Our concept is reminiscent of the use of amphoteric aluminum alkoxides or amides[6] under homogeneous reaction conditions. Unfortunately, these reagents act either in stoichiometric or multimolar amounts relative to the epoxide.



Scheme 1. Schematic representation of the isomerization of an epoxide into an allylic alcohol using a bifunctional acid/base catalyst. LA = Lewis acid, B = Lewis base.

There a few examples in the literature concerning the isomerization of epoxides under heterogeneous catalysis. Amphoteric oxides such as Al_2O_3, ZrO_2, TiO_2,[7] or Li_3PO_4 (the last for the industrial production of allyl alcohol from propylene oxide)[8] have been used as catalysts. However, the reactions generally proceed at elevated temperatures to form, apart from allylic alcohols, mixtures of products. Indeed, in tests of the isomerization of a model substrate (6,7-epoxygeranyl acetate (**1**), Table 1) over TiO_2 or SnO_2 in refluxing 1,2-dichloroethane as the solvent (100 mg of TiO_2 or SnO_2 per 0.1 mmol of substrate), the allylic alcohol **1a** was formed; however, several cyclization products,[9] which are typical for an acid-catalyzed pathway, also appear in comparable amounts relative to **1a**. Moreover, the reaction is extremely slow as it proceeds to 15–20 % conversion after 24 hours, and requires a week to reach completion. As a result, new by-products start to form and the reaction mass balance falls to less than 60 %.

To improve the reactivity/selectivity of the isomerization process, we turned our attention to TiO_2 supported on gold nanoparticles, a material that has received tremendous attention in recent years as a catalyst for alcohol[10a–e] and aldehyde[10a–c,d] oxidation wherein O_2 is employed as the oxidant. It has been proposed that the TiO_2 surface stabilizes cationic gold species,[11] such as Au^I, which are detectable by X-ray photoelectron spectroscopy (XPS). We envisioned such species acting as Lewis acid sites to activate the epoxide, whereas the surrounding oxygen atoms from the TiO_2 support could act as basic sites and catalyze the isomerization according to the concept presented in Scheme 1. Gold nanoparticles have demostrated unique activity for promoting chemical transformations of organic compounds which do not occur by using conventional catalysts.[12] We were pleased to find that Au/TiO_2[13] was a perfect catalyst for our purposes. Upon treatment of **1** with Au/TiO_2 suspended in 1,2-dichloroethane the reaction proceeds smoothly and goes to completion within two to three hours at 80 °C. Allylic alcohol **1a** was the only product formed in a yield greater than 90 % after isolation.

Prompted by this result, we examined a series of epoxides and found that the reaction is quite general; the yields are high, and in many cases the product selectivity is remarkable. The results are summarized in Table 1. Apart from **1**, terpenoid epoxides **2**–**4**, which are prone to undergo acid-catalyzed cyclization,[9] exclusively provide their isomeric allylic alcohols **2a**–**4a** in high yields. α-Pinene oxide (**7**), a highly sensitive substrate towards acids,[14] reacts to primarily give *trans*-pinocarveol (**7a**) and a mixture of campholenic

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[*] C. Raptis, Prof. Dr. M. Stratakis
Department of Chemistry, University of Crete
Voutes 71003, Iraklion (Greece)
E-mail: stratakis@chemistry.uoc.gr
Prof. Dr. H. Garcia
Instituto de Tecnologia Quimica
CSIC-UPV Universidad Politecnica de Valencia
46022 Valencia (Spain)
E-mail: hgarcia@qim.upv.es

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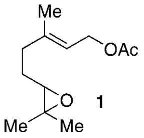
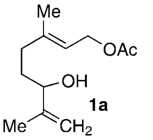
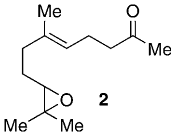
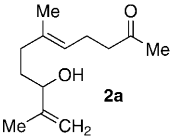
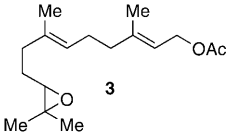
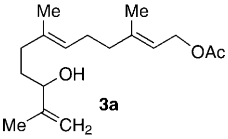
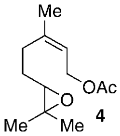
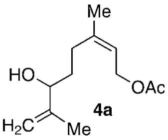
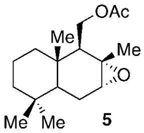
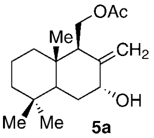
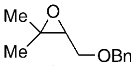
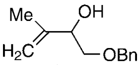
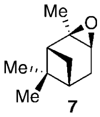
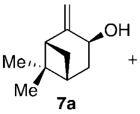
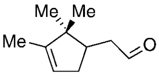
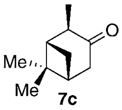
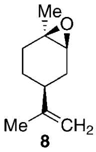
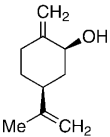
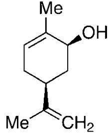
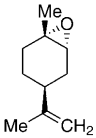
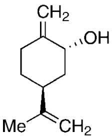
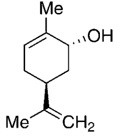
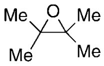
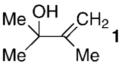
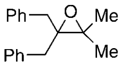
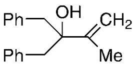
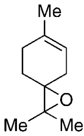
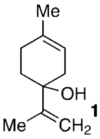
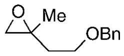
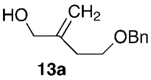
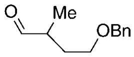
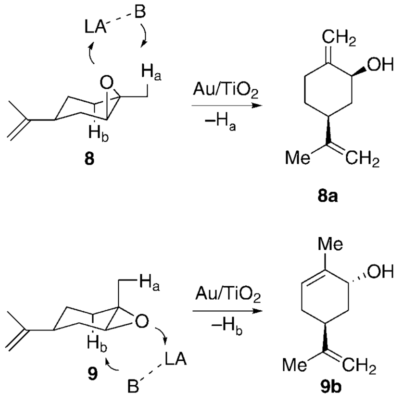
Table 1: Transformation of epoxides into allylic alcohols catalyzed by Au/TiO_2.[a]

Entry	Substrate	*t* [h]	Product(s)	Yield [%]
1	 **1**	3	 **1a**	92
2	 **2**	4	 **2a**	86
3	 **3**	4	 **3a**	88
4	 **4**	4	 **4a**	90
5	 **5**	4	 **5a**	89
6	 **6**	3	 **6a**	88
7	 **7**	5	 **7a** +  **7b** +  **7c** **7a**/**7b**/**7c** = 65:25:10	90
8	 **8**	6	 **8a** +  **8b** **8a**/**8b** = 92:8	86
9	 **9**	10	 **9a** +  **9b** **9a**/**9b** = 55:45	82
10	 **10**	2	 **10a**	98[b]
11	 **11**	2	 **11a**	91
12	 **12**	2	 **12a**	94
13	 **13**	5	 **13a** +  **13b** **13a**/**13b** = 60:40	87

[a] Reaction conditions: the epoxide substrate was added to a suspension of Au/TiO_2 in 1,2-dichloroethane and heated to 80° C for the specified time. [b] Calculated by using GC methods with *n*-nonane as the internal standard. Bn = benzyl.

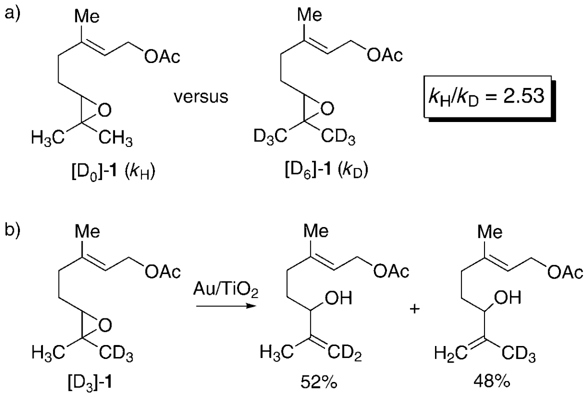
aldehyde (**7b**) and pinanone (**7c**) as by-products (relative ratio **7a**/**7b**/**7c** = 65:25:10). In the case of the diastereomeric limonene epoxides **8** and **9**, *cis*-**8** provides almost exclusively **8a**,[15] whereas *trans*-**9** affords an almost equimolar amount of **9a**[15] and **9b**. This can be rationalized by considering a concerted mechanism (see also Scheme 4b). In the more stable conformation of *trans*-**9**, there is an axially oriented C–H$_b$ bond on the endocyclic geminal carbon atom with respect the epoxide (Scheme 2), which competes for reactivity with the methyl group hydrogen atoms (H$_a$), thereby leading to substantial amounts of *trans*-carveol (**9b**). In contrast, a similar favorable C–H$_b$ conformation is absent on the top face of the most stable conformer of *cis*-**8**; thus *cis*-carveol (**8b**) is formed in a significantly lower yield.



Scheme 2. Rationalization for the product selectivity for the diastereomeric limonene epoxides **8** and **9**.

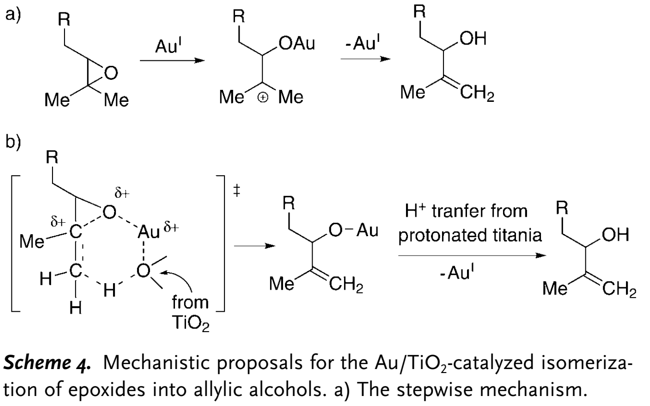
We emphasize that in several cases (products **5a**,[16] **11a**,[17] and **12a**[18]) the regioselectivity for allylic alcohol formation is exceptional. Therefore, the new double bond is always formed with hydrogen atom abstraction from the least hindered position. Even in the case of **11**, the abstraction of the more hindered benzylic hydrogen atom, which forms a thermodynamically more stable conjugated allylic alcohol, does not occur. The same observation holds for terpinolene oxide **12**, which gives exclusively the naturally occurring *p*-mentha-1,8-dien-4-ol (**12a**). By using **10** as a reference substrate, the turnover number of the gold catalyst was calculated to be approximately 950 (see the Supporting Information), which practically means that less than 15 milligrams of the material (Au/TiO$_2$ with 1.5% Au w/w) can catalyze the isomerization of one millimole of the epoxide (144 h, 80°C).

To shed light on the isomerization mechanism, we performed a kinetic competition between 6,7-epoxygeranyl acetate ([D$_0$]-**1**) and deuterium-labeled [D$_6$]-**1**[19] (Scheme 3a). Their relative reactivity ratio, which corresponds to the intermolecular isotope effect, k_H/k_D, was 2.53 ± 0.03. The isotope effect was calculated by using GC analysis of the reaction mixture at 15–35% conversion (see the Supporting Information). This result indicates that the hydrogen atom abstraction occurs in the rate-determining step. Additionally, the stereoselectively labeled epoxide [D$_3$]-**1**[19] gave a slight preference (52%) for deuterium, relative to hydrogen (48%) atom abstraction (Scheme 3b).



Scheme 3. Stereoisotopic studies for the isomerization of the deuterium-labeled epoxy geranyl acetates [D$_3$]-**1** and [D$_6$]-**1**.

In combination, these results rule out a stepwise mechanism (acid-catalyzed opening of the epoxide to form an intermediate carbocation) and provide clear evidence for a concerted mechanism. Taking into account a stepwise mechanism (Scheme 4a) with a rate-determining step for the formation of the intermediate carbocation, an intermolecular isotope effect k_H/k_D greater than one would expect for the competition of [D$_0$]-**1** versus [D$_6$]-**1** because of a β-secondary isotope effect. Yet, its magnitude would not be expected in any case to reach or exceed the value of two. Furthermore, considering the above-mentioned possible reaction energy profile in the case of [D$_3$]-**1**, an intermediate carbocation would exhibit, in a second fast product-forming step, a higher reactivity of the CH$_3$ group relative to the CD$_3$ group because of a primary isotope effect; however, this is not the case. If we consider a reaction energy profile in which the fast formation of the intermediate is followed by a product-forming rate-determining step, the intermolecular competition of [D$_0$]-**1** versus [D$_6$]-**1** would provide a significant value for a primary isotope, which does occur; however, [D$_3$]-**1** should exhibit higher reactivity for the CH$_3$ group relative to the CD$_3$ for the reasons we analyzed above. Therefore, both energy reaction profiles of a stepwise mechanism are ruled out. We propose



Scheme 4. Mechanistic proposals for the Au/TiO$_2$-catalyzed isomerization of epoxides into allylic alcohols. a) The stepwise mechanism. b) The concerted mechanism.

that the reaction occurs through a concerted mechanism (Scheme 4b). Coordination to the epoxide functionality to the Au^I species on the TiO_2 surface results to the simultaneous hydrogen atom abstraction from one of the *gem* carbon atoms by the oxygen atoms of TiO_2. For [D_3]-**1**, making a rough deconvolution, we estimate the reactivity of the less hindered *gem*-methyl to be approximately three times higher than that of the more hindered one. Through labeling of the less hindered methyl as CD_3, its reactivity drops and becomes almost similar to that of the more hindered *gem*-CH_3 group, because of the primary isotope effect of k_H/k_D being approximately 2.5. This extrapolated site selectivity is in agreement with the remarkable regioselectivity for allylic alcohol formation in the case of epoxides **5**, **10**, and **11** (Table 1), where hydrogen atom abstraction occurs from the less hindered position.

In conclusion, we have presented a novel and practical application of gold nanoparticles supported on TiO_2 as a heterogeneous catalyst for the isomerization of epoxides to allylic alcohols. The reaction proceeds in high yields and the product selectivity is often remarkable. Taking into account recent reports[20] that gold nanoparticles catalyze the epoxidation of alkenes in the presence of molecular oxygen, our finding would open the way to develop an efficient system for the one-pot gold-catalyzed transformation of alkenes into allylic alcohols or enones. Additional research on the improvement of this process using other metal nanoparticles supported on TiO_2 is in progress, as well as the exploration of Au/TiO_2 as a catalyst for other organic transformations.

Experimental Section

Typical procedure: The epoxide (0.2 mmol) was added to a suspension of Au/TiO_2 (20 mg) in 1,2-dichloroethane and the mixture was then heated to 80 °C (normally within a few hours, see Table 1) until the starting material was consumed (determined by TLC or GC analysis). The reaction mixture was filtered through a short pad of silica gel or Celite, and the solvent was removed under vacuum to yield the reaction product(s).

^1H and ^{13}C NMR spectra for all products, as well as procedures for the preparation of labeled epoxides [D_3]-**1** and [D_6]-**1**, and for the measurement of the intermolecular kinetic isotope effect can be found in the Supporting Information.

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Keywords: nanoparticles · epoxides · heterogeneous catalysis · isomerization · reaction mechanisms

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