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Editor's choice paper

Homogeneously catalyzed epoxidation of α,β-unsaturated ketones using simple aluminum salts and aqueous H_2O_2—Is it possible?

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ABSTRACT

Simple aluminum salts activate hydrogen peroxide towards α,β-unsaturated ketones, affording as major products α,β-epoxyketones. The pathway of this reaction involves the interaction between $[Al(H_2O)_6]^{3+}$ and H_2O_2, through hydrogen bonds, in the second-coordination sphere. This interaction enhances the proton exchange between non-coordinated water and hydrogen peroxide, as detected by ^1H NMR experiments. By this means, the hydroperoxide anion, formed as reactive intermediate in the proton exchange between H_2O and H_2O_2, can be trapped by α,β-unsaturated ketones. Surprisingly, this pathway is not followed when diethylmaleate is used as substrate. In this case, the radical addition of THF to the C=C bond of diethylmaleate takes place with high selectivity, affording 2-(THF)-derivatives with high yields.

1. Introduction

At a first glance, aluminium-assisted or -catalyzed oxidations seem to be something far to be possible. Typically, dioxygen and peroxides are activated by transition metals, in which charge transfer between metal and ligands plays a fundamental role to tune the reactivity of the activated oxo- or peroxo-species in the oxyfunctionalization of organic substrates [1]. Although aluminum cannot activate dioxygen or peroxides in the same way as transition metals, this does not mean that aluminum cannot play any role in oxidations at all.

In 1960s Davis and Hall investigated the preparation and properties of various organoaluminum peroxides [2]. These compounds are intermediates formed in the oxidation of alkylaluminum with alkylperoxides. Since R–O–O–Al species are rather unstable, only few examples of well-characterized organoaluminum peroxides are reported [3]. The reactivity of aluminum species/peroxide has been reported by several groups for many types of organic reactions along the last 50 years. Davis and Hall [2a] were the first to show that ketones are obtained in the stoichiometric reaction between aluminum alkoxides and alkylhydroperoxides by a rearrangement of a cyclic transition state involving a four-coordinated aluminum species as shown in Scheme 1.

Oshima et al. [4] reported that the $(t\text{-BuO})_3Al/t\text{-BuOOH}$ system does stereoselective epoxidation of allylic alcohols and also dehydrogenative oxidation of secondary alcohols under mild reaction conditions. The yields reported for epoxides were higher than 70%, and for ketones above 90%. These reactions are proposed to proceed by a three-coordinated aluminum intermediate as shown in Scheme 2 [4]. More recently, Proto and co-workers [5] showed that aluminum alkyls and methylaluminoxane (MAO)/alkylhydroperoxide systems also convert efficiently saturated and unsaturated alcohols to the corresponding ketones and epoxy-alcohols via a four-coordinated intermediate (Scheme 1).

Aluminum alkoxides mediate the transfer of hydride from an alcohol to a ketone. This reaction is known by Meerwein–Pondorff–Verley reduction or by Oppenauer oxidation as this approach can be used either to reduction of ketones or to oxidation of alcohols [6]. The hydride transfer proceeds through a six-member cyclic transition state (Scheme 3), in which both alcohol and ketone O-sites are coordinated to the metal. Hydride donation usually takes place from the less hindered face of the carbonyl group. Al(III) shows slow ligand exchange rate, thus its efficient use in catalytic amounts is not feasible [6]. The utilization of lanthanides catalysts, in which the metal centre shows more favorable ligand

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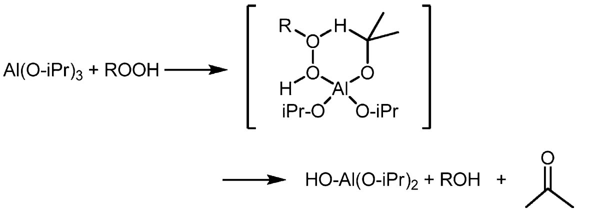
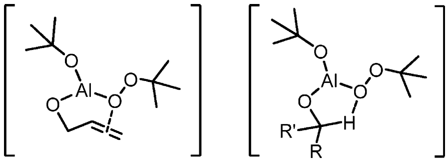


Scheme 1. Stoichiometric reaction between aluminum alkoxides and alkylhydroperoxides [2].



Scheme 2. Intermediates proposed for stereoselective epoxidation of allylic alcohols (left) and dehydrogenative oxidation of secondary alcohols (right) [4,5].

exchange kinetics, expanded the scope of synthetic applications of Meerwein–Pondorff–Verley and Oppenauer reactions [6].

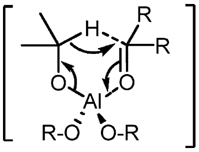
Dodonov and co-workers explored the synthetic possibilities of the (t-BuO$_3$)Al/t-BuOOH system in the oxidation of tri- and tetrasubstituted alkenes [7a], unsaturated ethers [7b,c], and phenylalkenes [7d]. In these reports, radicals are proposed to participate in the oxidation of the substrates.

For organic synthesis, however, the applicability of aluminum alkyls, aluminum alkoxides or MAO/alkylhydroperoxide systems is limited. Firstly, these reagents are expensive and should be used in stoichiometric amounts [4–6]. Additionally, the stability and the safety of these systems are also important issues, since organoaluminum compounds are typically very reactive. Fairly recently, we reported that a simple hexaaquoaluminum salt (2 mol% of $Al(NO_3)_3\cdot 9H_2O$) is able to catalyze the epoxidation of *cis*-cyclooctene at high yield (87% at 12 h) using aqueous 70 wt.% hydrogen peroxide in THF [8]. However $[Al(H_2O)_6]^{3+}$, is quite prone to deactivation under the reaction conditions [8].

Baeyer-Villiger oxidation of ketones using $AlCl_3$ dissolved in ethanol and 30 wt.% H_2O_2 was recently reported by Lei et al. [9] The authors showed that cyclic ketones and acyclic ketones are transformed almost quantitatively into the corresponding lactones or esters with very high selectivity (99%). However, the reaction mechanism involving the oxygen transfer from H_2O_2 to ketones needs elucidation [9].

Mandelli et al. [10] reported that aluminum nitrate in acetonitrile can catalyze the hydroperoxidation of alkanes. The authors reported that a yield of 31% cyclooctane hydroperoxide could be attained at 70 °C after 32 h. The oxidation is proposed to occur with the participation of hydroxyl radicals, as suggested by the parameters of selectivity for the oxidation of linear and branched alkanes.

Nowadays there are some hypotheses that aluminum could also take place in oxidative processes in biological systems. Exley [11] has revised the pro-oxidant activity of aluminum in biological systems, showing that there are provoking evidences for a “pro-oxidant” role of aluminum both in vitro and in vivo preparations. Aluminum seems to facilitate both superoxide- and iron-driven biological oxidation by mechanisms that remain to be resolved [11].



Scheme 3. Proposed transition-state of the Meerwein–Pondorff–Verley–Oppenauer reactions [6].

In this report, we show that catalytic amounts of $[Al(H_2O)_6]^{3+}$ strongly enhance the nucleophilicity of H_2O_2, activating it towards epoxidation of α,β-unsaturated ketones. The previous problems related to catalyst deactivation [8] are not observed in the reactions with α,β-unsaturated ketones or with α,β-unsaturated diesters. The mechanism for the activation of H_2O_2 by $[Al(H_2O)_6]^{3+}$ was studied by ^1H NMR experiments. Herein we show that $[Al(H_2O)_6]^{3+}$ act catalyzing the exchange of protons between H_2O_2 and H_2O. In this process the reactive intermediate HOO^- is formed, which is then easily trapped by electrophilic substrates. Although the ionic pathway involving HOO^- species is prevailing in the epoxidation of α,β-unsaturated ketones, the radical pathway is revealed as the exclusive route followed in the reaction with diethylmaleate.

2. Experimental

Warning: the concentration of hydrogen peroxide in organic solvents should not be higher than to 25 wt.%. Mixtures of peroxides and THF can be explosive by shock or friction!

2.1. Epoxidation of (R)-carvone

A solution containing (R)-carvone (25 mmol, Merck) and di-n-butylether (12.5 mmol, internal standard (IS), Fluka) in THF (p.a., Merck) was prepared to give a total volume of 25 mL. The reaction was started adding 2 mL of a fresh solution of $Al(ClO_4)_3\cdot 9H_2O$ (0.50 mmol, Fluka) dissolved in 70 wt.% H_2O_2 (56 mmol, Peroxidos do Brasil, Solvay) into the solution of (R)-carvone at 80 °C under reflux. For the reactions using 30 wt.% H_2O_2, 5 mL of oxidant were used. Samples were taken at different reaction times and analyzed by GC using a HP 6890 gas chromatograph, equipped with a Zorbax 1 column (28 m). The temperature program used in all analyses was: 40 °C (6 min), 180 °C (18 min), 280 °C (5 min) and 350 °C (isothermal, 5 min). The retention times (min) were: IS 5.3, (**1**) 13.5, (**1a**) 14.2, and (**1b**) 13.93. The epoxide was quantified using a calibration curve obtained with standard solutions of **1a**. An authentic sample of **1a** was prepared as described in Ref. [23]. Products were identified by GC–MS using EI and CI modes. The amount of byproducts was estimated considering that their FID responses are the same as that of epoxide **1a**. Selectivity is always given with respect to converted substrate. MS Spectrum: **1a** (CI, $M^{+\bullet}$ 166), EI m/z 166 (1), 123 (39), 85 (50), 67 (55), 55 (29), 43 (100); **1b** (CI, $M^{+\bullet}$ 168), EI m/z 150 (2), 108 (68), 95 (26), 82 (66), 67 (55), 54 (34), 43 (100).

2.2. Epoxidation of isophorone

The reaction using isophorone (25 mmol, Acros) was carried out at 60 °C following the procedure described for (R)-carvone. The epoxide **2a** was quantified by GC using a calibration curve obtained with standard solutions. The retention times (min) of the components were: (**2**) 10.4, (**2a**) 9.8, (**2b**) 12.2, (**2c**) 12.9, (**2d**) 13.6, (**2e**) 12.6. An authentic sample of **2a** was prepared using an alkaline H_2O_2 solution as described in Ref. [24]. Mass spectrum: **2a** (CI, $M^{+\bullet}$ 154), EI m/z, 154 (6), 139 (20), 126 (11), 97 (21), 83 (100), 69 (48), 55 (44); **2b** (CI, $M^{+\bullet}$ 154), EI m/z, 154 (3), 136 (3), 125 (6), 111 (16), 82 (100), 72 (30); **2c** (CI, $M^{+\bullet}$ 172), EI m/z, 158 (1), 140 (5), 125 (5), 112 (10), 101 (13), 83 (27), 70 (10), 58 (40); **2d** (CI, $M^{+\bullet}$ 172), EI m/z, 172 (7), 154 (10), 139 (6), 114 (23), 99 (100), 83 (23), 71 (13), 57 (23); **2e** (CI, $M^{+\bullet}$ 156), EI m/z, 156 (1), 138 (13), 123 (1), 100 (43), 82 (90), 70 (100), 58 (33).