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Scope and limitations of one-pot multistep reactions with heterogeneous catalysts: The case of alkene epoxidation coupled to epoxide ring-opening

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ABSTRACT

The combination of two reactions in one-pot multistep system requires the compatibility not only between the catalysts of both reactions, but also between all the reaction components and conditions. In the case of the coupling of alkene epoxidation and epoxide ring opening, it has been possible to synthesize cyanohydrin and azidohydrin derivatives through a simple process that involves a one-pot multistep process by using a mixture of two heterogeneous catalysts, a silica-grafted Ti catalyst and ytterbium chloride, whose efficiency depends on the reactivity of the starting alkene. In addition, in some cases the mixture of catalysts can be recovered and reused in several one-pot multistep cycles. However, this system is not possible with electron-deficient alkenes, as the basic catalyst required for epoxidation has shown to be incompatible with the ring-opening process.

1. Introduction

The substitution of conventional stoichiometric methodologies by catalytic processes, combined with the possibility of process intensification by combining several catalytic steps into a one-pot catalytic system, provides a means to improve the economical and environmental aspects of the chemical processes by minimizing the use of chemicals, the waste production and the processing time.

Soluble chemical catalysts can interact, even with mutual destruction in case of incompatible species. For example, acidic catalysts are incompatible with basic catalysts in solution. In this case, heterogeneous catalysis would allow the isolation of the catalytic sites, avoiding their destructive interaction in the so-called “*wolf-and-lamb*” reactions [1]. Furthermore, the use of heterogeneous catalysts allows the easy separation and reuse in other reactions, with the additional advantages that isolation and purification of intermediates are not required. This methodology should constitute a powerful tool in applied chemistry, allowing extremely complex chemical transformations taking place in a one-pot cleaner and more efficient process.

In spite of the interest of this strategy, applications have been scarcely described in the literature. Some examples of use of this methodology are: the sequence of dehydrohalogenation–hydrogenation reactions promoted by modified sol–gel materials [2], acid–base tandem reactions catalyzed by isolated active centers on clay materials [3], base-functionalized magnetically recoverable nanoparticles together with catalytic solids for different tandem reactions [4], a one-pot tandem deacetalization and enantioselective aldol reaction using resin-supported acidic and basic catalysts [5], a sequence of a Michael addition followed by a *N*-acyl iminium cyclization catalyzed by resin supports base and acid catalysts [6], a dehydration–hydrogenation sequence promoted by a supported palladium catalyst on a magnetically separable composite and a cross-linked sulfonic acid polystyrene [7], a condensation–dehydration–reduction reactions using a multifunctional base–acid–metal catalyst [8], or the shift of the coupling of the base-catalyzed transesterification of oil and the acid-catalyzed acetalization of glycerol by use of a zeolitic membrane [9]. One probable reason for the small number of examples might be the need for compatibility between catalysts, solvents, reagents, concomitant products and general conditions of both reactions.

Epoxides are versatile intermediates in organic synthesis because the ring can be easily opened with a large variety of reagents. This reaction is very important in organic synthesis because it leads to the preparation of 1,2-difunctionalized compounds in one step with stereochemical control. In consequence one interesting couple of reactions would be the epoxidation of an alkene and the ring opening of the formed epoxide with a nucleophile (Scheme 1).

Due to environmental considerations, organic hydroperoxides and hydrogen peroxide would be good oxidants for this type of

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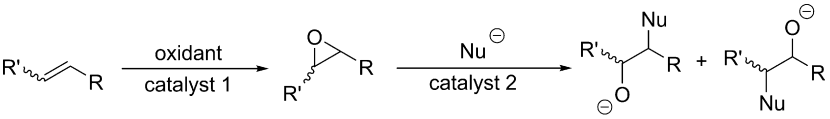

Scheme 1.

reactions [10]. However hydrogen peroxide and concomitant water are good nucleophiles that may open the epoxide in the presence of the second catalyst. Organic hydroperoxides would be then more suitable for one-pot sequential reactions. According to the electronic properties of the substrate different heterogeneous catalysts have to be used. For electron-rich alkenes, metal catalysts (Ti, W, Mo...) are more suitable [11]. One simple and efficient catalyst for this type of reaction would be silica modified with Ti(O^{i}Pr) groups [12,13]. In the case of electron-deficient alkenes a basic catalyst would be necessary, and KF/Al_2O_3 has proven to be the most efficient [14].

Many different nucleophiles have been used for epoxide ring-opening, most of them containing heteroatoms, which allows obtaining compounds such as 1,2-azido alcohols [15], 1,2-halohydrins [16], 1,2-hydroxy sulfides [17], or 1,2-diols [18]. Among them α-azido alcohols are important precursors for alternative syntheses of β-aminoalcohols [19]; some of them are part of the structures of pharmaceutical compounds, useful chiral auxiliaries, or intermediates for the synthesis of amino sugars. On the other hand, cyanide is a particularly interesting carbon-based nucleophile for epoxide ring-opening because of its low cost and the synthetic versatility of the nitrile ring-opened products. In view of this, trimethylsilyl azide [20–22] and trimethylsilyl cyanide [23–26] were selected for this study as examples for heteroatom and carbon nucleophiles respectively. Ytterbium derivatives were considered as catalysts for both reactions [27].

The ultimate aim of this work is the combination of the epoxidation-ring opening reactions in the same reaction flask but, as previous step, the conditions for each individual reaction and the compatibility between the different components of both reactions will be studied.

2. Experimental

Reagents were purchased from Aldrich and used as received without further purification. KF/Al_2O_3 catalyst was purchased from Fluka and it was dried at 140 °C under vacuum for 12 h prior to use.

2.1. Catalysts preparation and characterization

SiO_2–Ti(O^{i}Pr)$_2$: This catalyst was prepared by treatment of Merck 60 silica with Ti(O^{i}Pr)$_4$ (2.5 mmol/g) following a procedure reported in the literature [13]. The catalyst was dried at 140 °C under vacuum for 12 h prior to use.

Ytterbium-exchanged laponite: To a solution of $YbCl_3$ (121.6 mg, 0.4 mmol) in methanol (6 mL), laponite (1 g) was slowly added and the suspension was stirred at room temperature for 24 h under argon. The solid was filtered off, thoroughly washed with methanol (10 mL) and then with dichloromethane (20 mL) and dried under vacuum.

Characterization: The surface areas were determined BET nitrogen isotherms at 77 K: SiO_2–Ti(O^{i}Pr)$_2$ 448 m^2/g, Yb-laponite 203 m^2/g. The metal content was determined by ICP: SiO_2–Ti(O^{i}Pr)$_2$ 1.07 mmol Ti/g, Yb-laponite 0.38 mmol Yb/g. SiO_2–Ti(O^{i}Pr)$_2$ was also analyzed after six consecutive cyclohexene epoxidations: 0.95 mmol Ti/g. After the first cyclohexene oxide trimethylsilylcyanation run, the Yb content of Yb-laponite was only 0.12 mmol/g.

2.2. Catalytic test

2.2.1. Epoxidation of alkenes with SiO_2–Ti(O^{i}Pr)$_2$

To a mixture of alkene (2 mmol) and hydroperoxide (1 mmol) in 1.5 mL of solvent under argon, 27.8 mg of dried titanium-silica catalyst were added. In the case of *tert*-butyl hydroperoxide, the anhydrous hydroperoxide form (4 Å MS in decane) was used. The mixture was stirred at 65 °C (at 25 °C in the case of cyclohexene). The reaction was monitored by GC (FID from Hewlett–Packard 5890 II), using a cross-linked methyl silicone column (30 m × 0.25 mm × 0.35 pm), helium as carrier gas (20 psi), injector temperature 230 °C, detector temperature 250 °C and oven temperature program: 45 °C (4 min)–25 °C/min–200 °C (0 min)–40 °C/min–250 °C (5 min). At the end of reaction, the catalyst was removed by filtration and washed with dry dichloromethane.

2.2.2. Epoxidation of α,β-unsaturated ketones

To a mixture of TBHP (178 μL, 5.5 M in decane, 1 mmol) and α,β-unsaturated ketone (2 mmol) in toluene (1.5 mL), dried KF/Al_2O_3 (0.1 mmol) was added. The mixture was stirred at room temperature under argon for 24 h. Yield was determined by ^{1}H-NMR in the crude after filtration of the catalyst.

2.2.3. Epoxide ring-opening with TMSCN/$TMSN_3$

Caution!: TMSCN liberates toxic gas in contact with water. Although the used amounts of TMSCN were very small reactions were carried out under a safety hood, wearing gloves, safety glasses and lab coat, and at the end, all residues were treated with bleach. To a mixture of epoxide (1 mmol) and TMSNu (1.2 mmol), ytterbium catalyst ($YbCl_3$ or ytterbium-exchanged laponite, 0.1 mmol) was added under argon. The mixture was stirred at the corresponding temperature (see Table 3) and the reaction monitored by GC with the method described above. The catalyst was removed by filtration and washed with dry dichloromethane.

2.2.4. One-pot reactions

Titanium and ytterbium catalysts were added to a mixture of alkene and hydroperoxide in toluene under conditions described above. The reaction was monitored by GC and at the end of the epoxidation reaction TMSNu (2.4 mmol) was added. The mixture of catalysts was filtered and washed with dry dichloromethane and reactivated under vacuum for 12 h prior to reuse.

3. Results and discussion

3.1. Epoxidation

First, the catalyst for epoxidation of electron-rich alkenes was prepared by treatment of dried silica with Ti(O^{i}Pr)$_4$ in anhydrous toluene under reflux [13,28]. The different commercially available organic hydroperoxides were tested in the epoxidation of several alkenes (Scheme 2).

The results (Table 1) show that the currently available anhydrous *tert*-butyl hydroperoxide (Table 1, entry 1) was less efficient than that the previously available solution in isooctane (87% yield) [13] and the best result (89% yield) was obtained with cumene hydroperoxide (CHP) (Table 1, entry 2). No by-products (diol or 2-alkoxycyclohexanol, allylic oxidation products) were detected,