



## Prins cyclization: Synthesis of compounds with tetrahydropyran moiety over heterogeneous catalysts



Martina Stekrova<sup>a</sup>, Päivi Mäki-Arvela<sup>a</sup>, Narendra Kumar<sup>a</sup>, Erfan Behravesht<sup>a</sup>, Atte Aho<sup>a</sup>, Quentin Balme<sup>a</sup>, Konstantin P. Volcho<sup>b,c</sup>, Nariman F. Salakhutdinov<sup>b,c</sup>, Dmitry Yu. Murzin<sup>a,\*</sup>

<sup>a</sup> Laboratory of Industrial Chemistry and Reaction Engineering, Åbo Akademi University, FI-20500 Turku, Finland

<sup>b</sup> N. N. Vorozhtsov Institute of Organic Chemistry, Russian Academy of Sciences, Novosibirsk 630090, Russia

<sup>c</sup> Novosibirsk State University, Novosibirsk 630090, Russia

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### ABSTRACT

Tetrahydropyrans, compounds with 6-membered oxygen-containing heterocycles, are widely used for the synthesis of biologically active compounds with analgesic, anti-inflammatory or cytotoxic activity. Synthesis of compounds with the desired structure can be realized by several methods, including the acidic catalyzed Prins cyclization of homoallylic alcohol with simple aldehydes. In the current study, synthesis of compounds with the desired tetrahydropyran framework by Prins cyclization of benzaldehyde and alcohols with different structure, namely isopulegol and 3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol, was investigated. Different parent zeolites as well as their metal modified forms and mesoporous materials were employed in the comparative investigation. Activity and selectivity of the tested catalysts were correlated with their physico-chemical properties. The highest conversion and selectivity toward the product with the tetrahydropyran structure was achieved using Ce-MCM-41 in the interactions of isopulegol and benzaldehyde.

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## 1. Introduction

New biologically active substances are often synthesized from a variety of compounds isolated from natural sources. It has been discovered that compounds with 6-membered oxygen-containing heterocycles with tetrahydropyran moiety are widely used for the synthesis of biologically active compounds with a potential for use in medicine [1]. These compounds can exhibit analgesic, anti-inflammatory or cytotoxic activity [1–4]. Synthesis of compounds with the desired tetrahydropyran structure can be realized by several important methods, including Prins cyclization onto oxocarbenium ions, oxy-Michael reactions, transition metal catalyzed cyclizations, reduction of cyclic hemi ketals and hetero-Diels-Alder cycloaddition [1]. Recently an in-depth review on the synthesis of tetrahydropyrans and related heterocycles via Prins cyclization has been reported by Olier et al. [5].

Preparation of compounds with the desired tetrahydropyran structure can be performed by the acidic catalyzed ene-Prins cyclization of homoallylic alcohol with simple aldehydes [1,2,6]. It is known that Brønsted as well as Lewis acids can catalyze Prins cyclization reactions. Reaction mechanism of Prins cyclization over various heterogeneous solid acid catalysts such as sulfated zirconia and cellulose-SO<sub>3</sub>H has been proposed [7,8]. The influence of types and strength of acid sites on the formation of tetrahydropyrans was described by Breugst et al. [9]. Synergic effects between weak Brønsted and Lewis acids were analyzed by Density Functional Theory in Prins cyclization of but-3-en-1-ol and 2-methoxybenzaldehyde [8]. Yadav et al. reported synthesis of octahydro-2H-chromen-4-ol from (*R*)-citronellal and aldehydes using scandium triflate at ambient temperature in dichloromethane [6]. Synthesis of the same product, octahydro-2H-chromen-4-ol, from isopulegol and vanillin over acid modified montmorillonite clays at 35 °C was described by Timofeeva et al. [2]. Synthesis of 4-OH-tetrahydropyrans over Ni(II)-*N,N*-dioxide complex and FeCl<sub>3</sub> as catalysts was described by Zheng et al. [10]. A broad range of substrates was tested in the reaction under

\* Corresponding author.

E-mail address: [dmurzin@abo.fi](mailto:dmurzin@abo.fi) (D.Yu. Murzin).

mild reaction conditions [10]. Synthesis of 8-oxabicyclo [3.2.1] oct-2-enes and 9-oxabicyclo [3.3.1] nona-2, 6-dienes from enynol via oxonium/Prins-type cyclization using Au(I) catalyst has been reported by Vandavasi et al. [11].

In the current study, synthesis of compounds with the desired tetrahydropyran framework was investigated (Fig. 1a and b). Two alcohols with a different structure, namely isopulegol (Fig. 1a) and 3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol (Fig. 1b), were tested in the Prins cyclization reaction with benzaldehyde.

Isopulegol (Fig. 1a), a monoterpene alcohol, belongs to natural compounds and can be isolated from a variety of essential oils (e.g., from *Eucalyptus citriodora*) [12]. It can be synthetically prepared by the catalytic cyclization of citronellal [13]. Isopulegol is widely used in flavor and perfume industry for the production of fragrances and is an important intermediate for the synthesis of menthol, a fine chemical widely used in pharmaceuticals, agrochemicals and various cosmetics.

Diol (3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol) (Fig. 1b) is product of verbenol oxide isomerization. It has been discovered that this diol possesses potent activity against Parkinson disease [14] which is one of the most common neurological diseases. Decisive influence of absolute configuration of *diol* on its biological activity was shown in ref. [14]. (1*R*,2*R*,6*S*)-*Diol* can be synthesized from carvone [15], but the most effective way leading to this compound with high stereoselectivity starts from (–)-verbenone and includes three stages: epoxidation of verbenone to verbenone oxide with hydrogen peroxide in alkali/methanol solution, reduction of verbenone oxide using  $\text{LiAlH}_4$  and subsequent isomerisation of obtained verbenol oxide [16,17]. Verbenone is a natural organic compound which can be found in a variety of plants or synthesized by allylic oxidation of  $\alpha$ -pinene [18].

The aim was to prepare compounds with the desired tetrahydropyran moiety (product 4 in Fig. 1a and product 8 in Fig. 1b) using solid acid and metal (Fe, Ce, Au) modified heterogeneous catalysts. The criteria for the selection of catalysts were based on the assumptions of an important role of the type of acid sites (Brønsted and Lewis), their amount and strength and the structure of catalytic materials in Prins cyclization reaction. A further aim was to study the function of metals such as Au, Ce and Fe in the synthesis of compounds with tetrahydropyran moiety via Prins cyclization, as their catalytic behavior was described in the literature for similar substrates. Detail catalyst characterization was carried out using various techniques in order to study the physico-chemical properties of catalysts and explain the catalytic results. It should also be pointed out that despite of the fact that (–)-isopulegol was used as one of the reagents, the emphasis was not put into stereoselectivity and only racemic products were analyzed.

## 2. Experimental methods

Metal-modified zeolites (Beta-25 and Beta-150) and mesoporous MCM-41 were prepared, characterized and tested in the present study. As a comparison proton forms of zeolites were tested in Prins cyclization reactions. Furthermore, one commercial gold catalyst was tested in the same reaction. Zeolites and other support materials were modified by iron, gold and cerium and tested in Prins cyclization reaction of two different monoterpene alcohols with benzaldehyde.

### 2.1. Materials

$\text{NH}_4$ -Beta-25 (25 =  $\text{SiO}_2/\text{Al}_2\text{O}_3$  molar ratio),  $\text{NH}_4$ -Beta-150 and  $\text{NH}_4$ -Beta-300 zeolites were purchased from Zeolyst International. Aluminum oxide used as another support was obtained from UOP Inc.

Ferric nitrate and cerium nitrate used as the metal precursors were purchased from Fluka. The gold precursor, in the form of hydrogen tetrachloroaurate(III) hydrate, 99.9% (metals basis), was supplied by Alfa Aesar.

(–)-Isopulegol (SAFC, 98.9%), benzaldehyde (Fluka, 99.0%) and toluene (99.8%) were supplied by Sigma–Aldrich (Germany) and used as received. Diol (3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol) was synthesized at the Vorozhtsov Novosibirsk Institute of Organic Chemistry, with a purity of 98.5%.

### 2.2. Catalysts preparation

$\text{NH}_4^+$  form of zeolites were transformed to proton forms at  $500^\circ\text{C}$  in a muffle oven using a step calcination procedure.

MCM-41 was synthesized in the sodium form (Na-MCM-41) using a Parr autoclave (300 mL) as mentioned in Ref. [19] with few modifications [20]. After synthesis of MCM-41, it was filtered, washed with distilled water, dried overnight at  $100^\circ\text{C}$  and calcined at  $450^\circ\text{C}$ .

Iron and cerium modified catalysts were prepared using conventional evaporation impregnation (IMP) method. Ferric nitrate ( $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ ) and cerium nitrate ( $\text{Ce}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ ) were used as iron and cerium precursors, respectively, in all cases. In the evaporation impregnation method aqueous solutions of metal nitrates were applied. The mixtures were stirred for 24 h at  $60^\circ\text{C}$ . The other steps of the synthesis were evaporation, drying at  $100^\circ\text{C}$  overnight and calcination at  $450^\circ\text{C}$  for 4 h.

Au-Beta-25 was prepared by the deposition-precipitation method. The proton form of zeolite Beta-25 was dispersed in an aqueous solution of the gold precursor. In the next step, aqueous ammonium hydroxide was added into the suspension in order to increase pH to 10.5. The suspension was stirred for 3 h at  $50^\circ\text{C}$ . The final catalyst was filtered, washed by deionized water, dried overnight at  $100^\circ\text{C}$  and calcined at  $300^\circ\text{C}$  for 3 h.

### 2.3. Catalysts characterization

The characterization of catalysts was carried out using nitrogen adsorption and FTIR spectroscopy with pyridine as a probe molecule. For selected catalysts also transmission electron microscopy was applied.

The specific surface area of supports and metal modified catalysts was determined by nitrogen adsorption using Sorptometer 1900 (Carlo Erba instruments). The samples were outgassed at  $150^\circ\text{C}$  for 3 h before each measurement. The BET equation was used for calculation of the specific surface area of mesoporous materials, silica and alumina and the Dubinin equation was used for calculation of the specific surface area of microporous zeolites.

The acidity of the proton and metal modified catalyst was measured by infrared spectroscopy (ATI Mattson FTIR) using pyridine ( $\geq 99.5\%$ ) as a probe molecule for qualitative and quantitative determination of both Brønsted and Lewis acid sites. The samples were pressed into thin pellets (10–25 mg), which were pretreated at  $450^\circ\text{C}$  before the measurements. Pyridine was first adsorbed for 30 min at  $100^\circ\text{C}$  and then desorbed by evacuation at different temperatures. Three different temperatures were used for desorption of pyridine, namely at  $250$ – $350^\circ\text{C}$ , which corresponds to all (weak, medium and strong) sites,  $350$ – $450^\circ\text{C}$ , reflecting medium and strong sites and  $450^\circ\text{C}$ , which is related only to strong sites [21]. The amount of Brønsted and Lewis acid sites was calculated from the intensities of the corresponding spectral bands,  $1545\text{ cm}^{-1}$  and  $1450\text{ cm}^{-1}$ , respectively, using the molar extinction parameters reported by Emeis [22].

The textural properties and metal particle size of the catalysts were also characterized using transmission electron microscope,

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