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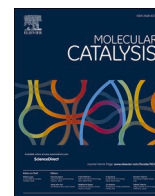
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Research Paper

Catalytic condensation of 3-carene with formaldehyde



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ABSTRACT

This work is a first comprehensive study of the catalytic condensation of renewable 3-carene with formaldehyde (FA) for the one-step preparation of terpenoid *trans*-4-hydroxymethyl-2-carene, a commercially significant fragrance and a chiral platform chemical. Commonly available Brønsted and Lewis acids, as well as aluminosilicates (halloysite nanotubes, K-10 montmorillonite, H-Beta-25 zeolite) are able to catalyze the reaction in acetic acid, however, selectivity to the desired product is limited due to further transformations by (i) acetylation and (ii) addition of a second FA molecule. Compounds of successive condensation with FA are mainly formed in the presence of ZnCl₂ and LiClO₄, giving up to 50 % yield, while weak to moderate acidic halloysite and K-10 (45–104 μmol/g) result in a low conversion of 3-carene with a prevalence of acetylation products (up to 46 %). The largest selectivity towards *trans*-4-hydroxymethyl-2-carene at substrate conversion of 50 % was observed with phosphoric acid (50–66 %). The yield of the desired terpenoid increased significantly with an excess of FA or the catalyst loading, because the amount of the active form of formaldehyde is the key factor in the reaction. Presence of water in the system also led to a certain selectivity increase explained by inhibition of the side reaction. Under optimized conditions using H₃PO₄-AcOH mixture as a catalyst at 15 °C, selectivity to the target product was ca. 67 %. A detailed mechanism for the 3-carene condensation with FA has been proposed. The DFT calculations show that further transformations of *trans*-4-hydroxymethyl-2-carene are energetically favorable in agreement with the experimental data. The reaction pathways were also confirmed by kinetic modeling. Synthesis of the desired product was performed on a scale up to 25 g and a possibility of 3-carene recycling has been demonstrated.

1. Introduction

The use of renewable feedstocks for the production of chemicals is one of the areas of chemistry attracting currently a lot of interest [1–3]. For example, terpene hydrocarbons and terpenoids are widely distributed in nature and are used in the synthesis of bioactive and fragrant compounds, fuel components, and in the development of new drugs and other valuable products [3–7]. Monoterpenes, in particular, α -pinene, β -pinene and 3-carene are the main components of turpentine, which is obtained from the pine resin (Fig. 1a) as well as a pulping by-product in the annual amounts of ca. 350,000 ton [3].

The content of 3-carene in turpentine is up to 40 % [3], thus it is an available renewable raw material for chemical processing [8–10]. In

particular, this terpene can be used for preparation of a number of compounds with high antitumor activity [11], in perfumery [8,12], as well as for synthesis of polymers [13], pharmaceuticals [5,14], pheromones [10] and in fine organic synthesis [9,10,15].

One of the ways to utilize terpenes obtained from turpentine is their catalytic Prins condensation with formaldehyde (FA), resulting in the formation of compounds with a hydroxymethyl group (Fig. 1b, [7,9,10,16–18]). Thus, the product of such a reaction involving β -pinene is nopol, which has a sweet balsamic aroma [16]. Condensation of α -pinene with FA in acetic acid with H₃PO₄ as a catalyst leads to 8-acetoxy-6-hydroxymethylimonene, which can be considered as a chiral platform for further synthesis [17].

3-Carene also reacts with formaldehyde (Fig. 1b) to form *trans*-4-

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hydroxymethyl-2-carene as one of the products [9,10,12,18]. This terpenoid has a floral-fruity odor and is used in perfumery, as well as for obtaining a number of other fragrant compounds [8,12]. In addition, a number of chiral heterocyclic compounds have been synthesized based on *trans*-4-hydroxymethyl-2-carene (Fig. S1, Supplementary Information, [4,19–21]), some of which have high cytotoxic activity [19].

The Prins reaction of terpene hydrocarbons with FA is catalyzed by both traditional Brønsted and Lewis acids [9,10,17,20,22] and novel heterogeneous systems with both types of acidity [17,20–27]. Thus, the β -pinene condensation with FA proceeds with selectivity of up to 99 % in the presence of ZnCl₂ in a homogeneous medium [22] or over solid catalysts, such as Zn²⁺-modified zeolites [23] and montmorillonite [22], sulfated zirconia [24], Sn/MCM-41 [25], MoOx/ γ -Al₂O₃ [26], etc. It has been found that the formation of nopol is favored by Lewis acid sites (a. s.) [22–25], while Brønsted a.s. on the surface of heterogeneous systems allowed isomerization of β -pinene [27]. The reaction kinetics was also studied [25].

More recently, the authors have shown that aluminosilicate catalysts with weak to moderate acidity (45–104 μ mol/g) are capable of catalyzing the α -pinene condensation with formaldehyde (Fig. 1b) giving, however, mainly the products of substrate direct protonation (up to 53 %) [17]. In the presence of H-Beta-25 zeolite (301 μ mol/g) or phosphoric acid, the selectivity to the formaldehyde addition products and α -pinene direct protonation comparable (32–35 %). At the same time, with H₃PO₄, the contribution of the undesired Wagner–Meerwein rearrangement was minimal, which ensured the highest selectivity for the target 8-acetoxy-6-hydroxymethyllimonene [17].

The reaction of 3-carene with formaldehyde was first reported in 1958 [18], while describing two-step synthesis of 4-hydroxymethyl-2-carene by refluxing a mixture of 3-carene and FA for 48 h in acetic acid without a catalyst, followed by saponification of the resulting acetate with alkali into the alcohol, with the yield 32 %. It was later found that the hydroxymethyl group in this compound is in the *trans* configuration [28].

In the presence of H₂SO₄ or BF₃, further condensation of resulting *trans*-4-hydroxymethyl-2-carene with FA occurred at the hydroxyl group, followed by cyclization, leading to formation of a furan fragment [29]. When SnCl₄ was used as a catalyst, the reaction proceeded in methylene chloride at room temperature with a yield of the target alcohol up to 40 % [30]. The Prins condensation of 2-carene with formaldehyde without a catalyst proceeded in a similar way and led to the formation of *trans*-2-hydroxymethyl-3-carene in the absence of a solvent, or predominantly to its acetate in acetic acid [31]. Cyclic ethers and a compound with a dioxane structure were isolated as side products [31].

According to [12], the synthesis of *trans*-4-hydroxymethyl-2-carene was commercialized by the perfumery company Dragoco. According to the authors knowledge, this compound was also produced at the Kaluga Plant of Fragrant Synthetic Substances (Russia) under the name «Walterol».

It should be noted that studies on the 3-carene reaction with formaldehyde were mainly published from 1959 to 1988 [12,18,28–30] addressing organic chemistry [18,28–30] or perfumery aspects [12]. The yield of *trans*-4-hydroxymethyl-2-carene did not exceed 40 % [18, 30]. To the best of our knowledge, there have been no systematic studies of this reaction using catalysis.

Recent investigations demonstrated that efficient catalysts for the unsaturated compounds reactions with aldehydes are, for example, layered aluminosilicates (montmorillonite [20,22,32], halloysite [33–36]), hierarchical zeolites [37,38], SO₃H-functionalized mesoporous silica [39], biochar [40] and heteropolyacids deposited on SiO₂ [41], etc.

In fact, both heterogeneous [20,32–36,40,42,43] and homogeneous [17,20,40,44] systems are effective novel catalysts for various reactions of terpene compounds. Highly selective catalysts for the Prins condensation of terpenoids with aldehydes are acid-modified halloysite [33–36], which comprise natural aluminosilicate nanotubes (Fig. S2). The advantage of halloysite nanotubes (HNT) is that the yields of the target products were significantly higher than with other types of catalysts, including zeolites, montmorillonite, triflates, commercial Amberlyst-15 resin [33,35,36]. HNT demonstrated stability and ability to be regenerated [33,35].

On the other hand, it was shown that AcOH-Ac₂O-H₃PO₄ system can catalyze formation of *trans*-4-hydroxymethyl-2-carene, in a work focused on its utilization as a chiral platform for the synthesis of bioactive polycyclic compounds [20]. Moreover, detailed information on the effect of various catalysts and reaction conditions on the reaction pathways and selectivity as well as mechanism and kinetics is lacking in the literature [12,18,28–30].

Considering that *trans*-4-hydroxymethyl-2-carene is a valuable compound for perfumery [8,10,12] and medicinal chemistry [19–21] and can be obtained from readily available and renewable 3-carene, development of an efficient method for its synthesis is an important task.

Thus, the aim of this work was the first in-depth study of the catalytic condensation of 3-carene with formaldehyde to develop an efficient one-pot method for the synthesis of *trans*-hydroxymethyl-2-carene. For this, (i) major and minor products were identified, (ii) different catalytic systems were explored, (iii) the effect of the nature and type of catalyst, as well as the reaction conditions on selectivity was determined, and (iv) kinetic analysis and DFT computation of the 3-carene condensation with

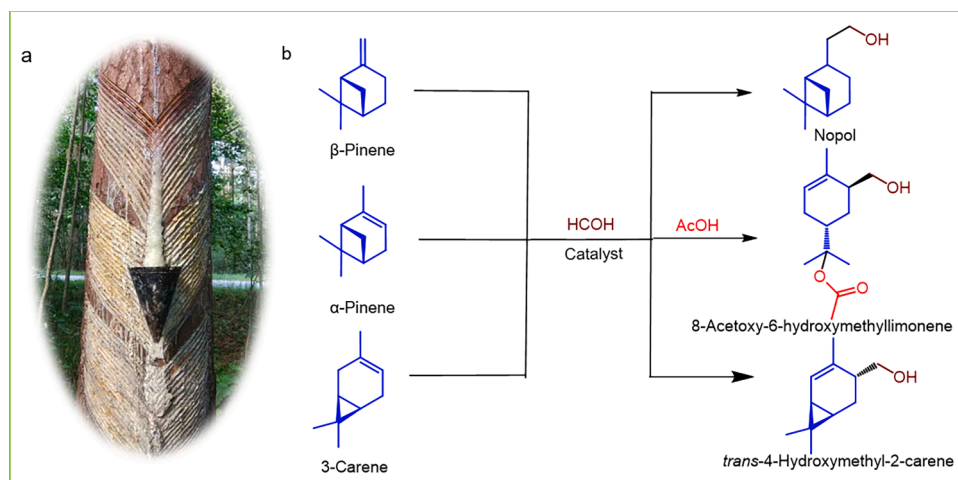


Fig. 1. The pine resin a) tapping in Zhytkavichy district, Belarus (photo by A.Yu. Sidorenko) and b) functionalization of turpentine components with a hydroxymethyl group (modified from [17]).

FA were carried out. The scope of the studied catalysts included the traditional Lewis and Brønsted acids, as well as zeolites and modified layered aluminosilicates (halloysite, montmorillonite).

2. Experimental

2.1. Preparation and characterization of solid catalyst

Natural halloysite nanotubes (Sigma-Aldrich, from Dragon Mine, USA) were used to prepare solid catalysts. Commercial acid-modified montmorillonite K-10 (Acros Organics, Germany) and H-Beta-25 zeolite (Zeolyst Int.) were utilized without additional chemical treatment.

Halloysite nanotubes (HNT) were activated with 5 % aqueous solutions of HCl or H₃PO₄ according to the procedure described in [17]. A weighed amount of HNT (7–9 g) was placed in a three-necked flask with a reflux condenser and a thermometer, then acid was added at the rate of 5 ml per 1 g, heated to 90 °C, and stirred at this temperature for 3 h using a magnetic stirrer. Then the resulting precipitate was separated from the liquid phase, washed with distilled water to pH 5.5–6.0, and dried at 105 °C for 2 h. Before use, all solids were ground to a particle size below 100 μm. Halloysite nanotubes treated with hydrochloric and phosphoric acids were designated as HNT-HCl and HNT-H₃PO₄, respectively.

The parent and modified halloysite nanotubes were thoroughly studied by EDX, SEM, ²⁷Al and ²⁹Si MAS NMR, as well as FTIR with pyridine as a probe molecule and N₂ adsorption-desorption methods as reported in a recent work [17]. Commercial montmorillonite K-10 has also been examined [20,41]. The data on acidity, chemical composition and porosity of solids are given in detail in SI.

Note that the original HNT have low acidity (34 μmol/g, Table S2), which increases to 45 μmol/g after treatment with hydrochloric or phosphoric acids. A higher concentration of acid sites (104 μmol/g) was present in K-10, while the studied solids exhibited both Brønsted and Lewis acid sites (Table S2). The acidic aluminosilicates are mesoporous with a specific surface area of up to 247 m²/g (Table S1, Fig. S2 and S3). Zeolite H-Beta-25 has the highest acidity (301 μmol/g) and the specific surface area (589 m²/g) with a pore diameter of 0.76 nm [45].

2.2. Catalytic tests and analysis of products

The following typical procedure was developed to the reaction performed. To a 30 ml three-necked flask equipped with a reflux condenser and temperature controller (IKA ETS-D5), 5 ml of AcOH and 0.44 g of paraformaldehyde (Fluka, ≥95 %) were added and brought to a boil to dissolve it. After the mixture was cooled to 15 °C, 1.0 mL of acetic anhydride (Ac₂O), catalyst and 1.0 g of 3-carene (Acros Organics, ≥97 %) last was introduced and stirred at this temperature (300 rpm) using a magnetic stirrer. The total volume of reaction mixture was 8.0 mL.

Solid materials (HNT-HCl/H₃PO₄, H-Beta-25) were dried for 2 h at 150 °C immediately before use. Common Brønsted (H₂SO₄, *p*-TSA, 85 % H₃PO₄) and Lewis (ZnCl₂, LiClO₄, FeCl₃·6H₂O) acids were used as homogeneous catalysts.

The condensation reaction was carried out for 6 h periodically taking samples of the reaction mixture, the preparation of which for GC analysis was carried out as follows. To the vial 300 μL of the sample was introduced, a saturated sodium bicarbonate solution (3.0 mL) was added and thoroughly mixed until there was no gas evolution. Then 1.0 mL of ethyl acetate was also poured, shaken, and after separation of the layers, the upper one was taken, washed with water and dried over sodium sulfate.

For analysis of the reaction mixture, a Khromos GKh-1000 gas chromatograph with a flame ionization detector and a Zebtron ZB-5 capillary column (30 m x 0.25 mm x 0.25 μm) was used. The evaporator and detector temperatures were 250 °C and 280 °C, respectively. The column was heated from 110 °C to 280 °C (ramping rate of 20 °C/min) followed by the isothermal mode. The total analysis time was 21

min. An internal standard (*n*-undecane, Merck, 99 %) was used for quantification. A typical chromatogram of the reaction products is shown in Fig. S3. Separation of the reaction mixtures was carried out by the preparative column chromatography. The structures of the obtained compounds were determined by ¹H and ¹³C NMR spectroscopy and high-resolution mass spectrometry. Detailed experimental procedures and spectral data are given in SI.

3. Results and discussion

3.1. Reaction with homogenous and heterogenous catalysts

The identified products of the 3-carene (1) catalytic condensation with formaldehyde (Fig. 2) are *trans*-4-hydroxymethyl-2-carene (2), its acetate (3), as well as compounds that are formed by the addition of the second molecule FA with isobenzofuran (4, 5, 6, 7) and 8-oxatricyclodecane (8) structures, as well as a hydroxy derivative of *trans*-4-hydroxymethyl-2-carene acetate (9).

No reaction of 3-carene with formaldehyde was observed at 15 °C without a catalyst. In the presence of Lewis acids, LiClO₄, and ZnCl₂, at a conversion of the starting compound of 50.0 %, the selectivity to product 2 was low (8–13 %), while more acetate 3 and isobenzofuran 4 were formed (Table 1). On the contrary, with FeCl₃·6H₂O, *trans*-4-hydroxymethyl-2-carene 2 was the main product with 47 % selectivity.

p-Toluenesulfonic acid (*p*-TSA) also catalyze the reaction of 3-carene with FA, but not selectively (Table 1), while no condensation products and only substrate isomerization products were observed with H₂SO₄. In the presence of H₃PO₄ (85 %), *trans*-4-hydroxymethyl-2-carene 2 was the main product, and the selectivity towards it increased from 50 to 66 % with an increase in the catalyst amount from 1.0 to 3.0 eq (Table 1). Thus, strong sulfuric acid (pK_{a1} –2.8) causes isomerization of 3-carene, while moderately acidic phosphoric acid (pK_{a1} 2.14) quite effectively catalyzes its condensation with formaldehyde.

On the studied aluminosilicates (HNT-HCl/H₃PO₄, H-Beta-25) containing both Brønsted and Lewis acid sites (Table S2), after 6 h of reaction, a low conversion of 3-carene (24–37 %) was observed. In the presence of K-10 and modified HNT, the main product was *trans*-4-hydroxymethyl-2-carene acetate 3 (up to 46 %), while on H-Beta-25 the product 2 was formed with low (23 %) selectivity (Table 1).

Thus, traditional Brønsted and Lewis acids and heterogeneous aluminosilicate catalysts with both types of acidity are capable of catalyzing 3-carene 1 condensation with FA, however, high values of its conversion and acceptable selectivity to *trans*-4-hydroxymethyl-2-carene 2 were observed in the presence of FeCl₃·6H₂O or H₃PO₄, being the largest with the latter catalyst (Table 1).

The reaction byproducts can be lumped into two groups, namely the compounds formed by (i) the addition of acetic acid (3 and 9, byproducts *a*) and (ii) further condensation with the second formaldehyde molecule (4, 5, 6, 7 and 8, byproducts *b*). Thus, in the presence of 2.0 eq H₃PO₄, selectivity to *trans*-4-hydroxymethyl-2-carene 2 decreased with increasing 3-carene 1 conversion, while the selectivity towards byproducts *a* and *b* increased (Fig. 3). With other catalysts, for example ZnCl₂ or HNT-HCl, these dependences were similar, but a decrease in selectivity to 2 was very sharp (Fig. S4). Utilization of terpenoid 2 *per se* under reaction conditions instead of 3-carene led to formation of the same side products except the compound 9. Consequently, during 3-carene 1 condensation with formaldehyde, *trans*-4-hydroxymethyl-2-carene 2 is sequentially converted into compounds 3–8, while 9 is formed from the starting terpene.

At 3-carene conversion of 50 % in the presence of such Lewis acids as LiClO₄ and ZnCl₂, mainly the products of the second FA molecule addition were formed (byproducts *b*, 42–50 %, Table 2). On the other hand, when FeCl₃·6H₂O was used, the target compound 2 prevailed in the reaction mixture, while the amounts of byproducts *a* and *b* were smaller (19–26 %).

Among the studied both Brønsted and Lewis acids, a high selectivity

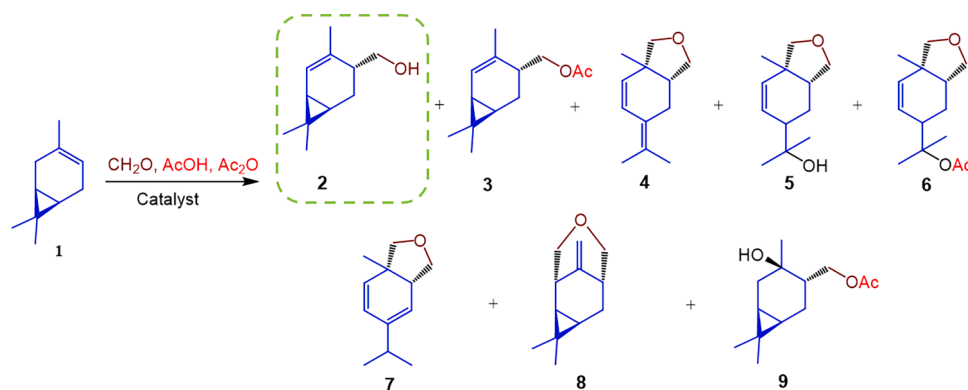


Fig. 2. Products of the catalytic reaction of 3-carene with formaldehyde.

Table 1
Selectivity in 3-carene^a reaction with formaldehyde (2 eq) at 15 °C with different catalysts.

Catalyst	Amount	Time, min	Selectivity, mol. %								
			2	3	4	5	6	7	8	9	
–	–	360	No reaction								
LiClO ₄	1.0 eq	360	12.7	16.7	22.1	0.3	7.7	8.1	3.6	2.3	
ZnCl ₂		120	8.3	13.3	29.5	1.5	8.8	8.1	2.1	2.4	
FeCl ₃ ·6H ₂ O ^b		5	47.4	3.2	7.8	3.3	4.7	5.2	4.2	5.8	
H ₂ SO ₄		10	There were practically no condensation products								
<i>p</i> -TSA		15	11.4	15.5	13.6	1.1	3.3	4.7	3.5	3.8	
H ₃ PO ₄	1.0 eq	105	49.6	5.8	1.9	0.4	2.5	0.9	9.1	6.2	
	2.0 eq	45	59.7	3.4	1.8	1.2	2.4	0.8	7.4	6.7	
	3.0 eq	25	66.2	1.9	1.4	1.0	1.7	0.6	7.0	6.1	
HNT-HCl ^c	1.0 g	360	3.5	45.6	9.1	0.5	5.7	4.7	7.7	0.5	
HNT-H ₃ PO ₄ ^d		360	5.0	44.0	9.4	0.7	5.7	4.6	5.9	0.8	
K-10 ^e		360	8.9	38.5	10.6	0.5	5.1	6.3	7.3	1.1	
H-Beta-25 ^f		360	23.0	12.2	5.6	1.0	0.8	2.8	6.3	0	

At conversion.

^a 50%,

^b 76%,

^c 28%,

^d 24%, and

^e 34%,

^f 37%.

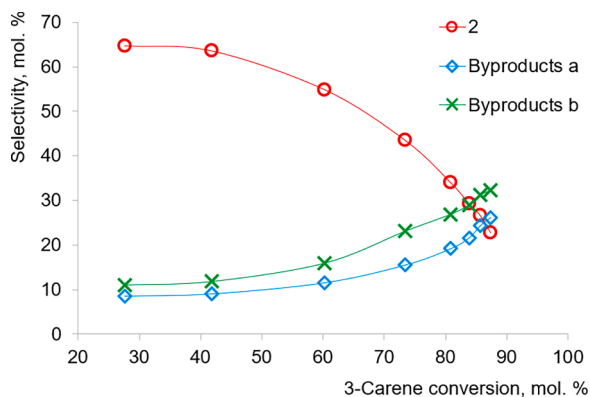


Fig. 3. Selectivity to reaction products as a function of 3-carene conversion in the presence of H₃PO₄.

to *trans*-4-hydroxymethyl-2-carene **2** (ca. 60 %) was observed with H₃PO₄, and the amounts of byproducts *a* and *b* were minimal (ca. 10–14 %, Table 2). Moreover, an increase in the catalyst amount leads to an increase in the yield of the target terpenoid **2** to 66 % (Table 1).

Different behavior was demonstrated by heterogeneous catalysts containing both Lewis and Brønsted acid sites. Thus, on relatively weakly acidic halloysites and montmorillonite K-10 (45 – 104 μmol/g,

Table S2) the acetylation products (40–46 %, byproducts *a*, Table 2) predominated, which were formed from compound **2**, which is clearly indicated by the selectivity dependences given in Fig. S4. In the case of zeolite H-Beta-25, characterized by a high concentration of a.s. (301 μmol/g), the amount of side products was significantly less, although the selectivity to **2** was also relatively low (23 %, Table 2).

The initial rate of 3-carene conversion (*r*₀) in the presence of LiClO₄ was significantly lower than with ZnCl₂, a stronger Lewis acid (Table 2). In the case of FeCl₃·6H₂O, 75.8 % conversion of the starting compound was observed within 5 min, which was also accompanied by an increase in the reaction mixture temperature. The *r*₀ value for *p*-TSA was also higher than for the weaker H₃PO₄. When using heterogeneous catalysts HNT-HCl, HNT-H₃PO₄ and K-10 with a relatively low concentration of acid sites, values of rates were approximately the same, increasing in the case of a more acidic H-Beta-25 zeolite (Table 2). Similarly, in the Prins reaction of β-pinene with formaldehyde [23,26], (–)-isopulegol with thiophene-2-carbaldehyde [33], and isoprenol with isovaleraldehyde [34], the initial reaction rate increased with increasing acidity of the catalysts.

Thus, although the studied common acids and aluminosilicates are capable of catalyzing the condensation of 3-carene with FA, a relative high selectivity to *trans*-4-hydroxymethyl-2-carene **2** was observed only with FeCl₃·6H₂O or H₃PO₄, being the largest in the latter catalyst (up to ca. 66 %, Table 1). It is worth noting that ferric chloride is a highly corrosive and toxic substance, as well as an irritant [47]. On the other

Table 2
Lumped products selectivity^a in 3-carene reaction with formaldehyde (2 eq) at 15 °C with different catalysts.

Catalyst ^a	Acidity, $\mu\text{mol/g}$	$r_0^g, \frac{\text{mmol}}{\text{L}\cdot\text{min}}$	Time, min	Selectivity, mol.%		
				2	Byproducts a (3 + 9)	Byproducts b (4 + 5 + 6 + 7 + 8)
LiClO ₄	–	6.2	360	12.7	19.0	41.8
ZnCl ₂	–	14.9	240	8.3	15.7	50.0
FeCl ₃ ·6H ₂ O ^b	–	n.d.	5	47.4	9.0	25.2
<i>p</i> -TSA	–	58.5	15	11.4	19.3	26.2
H ₃ PO ₄ (2.0 eq)	–	16.5	45	59.7	10.1	13.6
HNT-HCl ^c	45	0.033	360	3.5	46.1	27.7
HNT-H ₃ PO ₄ ^d	45	0.031	360	5.0	44.8	26.3
K-10 ^e	104	0.033	360	8.9	39.6	29.8
H-Beta-25 ^f	301	0.045	360	23.0	12.2	16.5

At conversion.

^a 50%,

^b 76%,

^c 28%,

^d 24%, and

^e 34%,

^f 37%.

^g In mmol/(g·min) in the case of heterogeneous catalysts.

hand, phosphoric acid (including a heterogenized form [48]) is also an effective catalyst for some industrially important reactions such as hydration of α -pinene [46], as well as synthesis of *p*-xylene and 1,3-butadiene based on biomass derived molecules [47].

3.2. Mechanistic considerations

The proposed mechanism for catalytic 3-carene 1 condensation with formaldehyde is shown in Fig. 4. At the first stage, the protonated form of formaldehyde is formed, which, reacting with the double bond of compound 1, gives intermediate 1-A. This intermediate undergoes deprotonation to form the target *trans*-4-hydroxymethyl-2-carene 2.

Under the reaction conditions, *trans*-4-hydroxymethyl-2-carene 2

undergoes further transformations, which can proceed in two directions (Fig. 4). The first of them (Pathway a) involves addition of acetic acid to 2 with formation of acetate 3 via the 2-A intermediate. Since the formation of acetylation product 9 from 2 was not experimentally confirmed, it can be formed from 1-A through a possible intermediate 9-A (Fig. 4). Note that Ac₂O present in the system can also react with compound 2, leading to products 3.

Another route for terpenoid 2 transformation is its further condensation with FA to form intermediate 2-B, deprotonation of which gives 2-B' (Pathway b). It should be noted that the hydroxyl group in compound 2 is a more reactive nucleophilic center than the double bond in 3-carene 1, therefore addition of the protonated formaldehyde to 2 may be more preferable than the primary reaction (1 → 2).

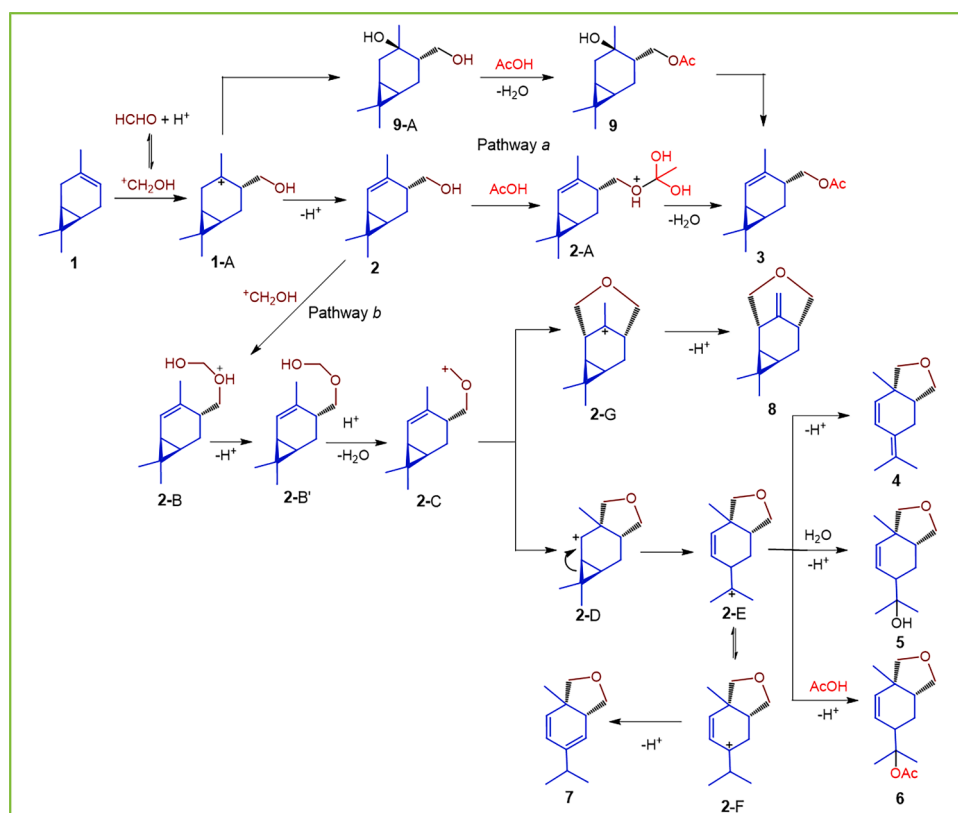


Fig. 4. The mechanism of 3-carene catalytic condensation with formaldehyde in acetic acid.

Dehydration of hemiacetal 2-B' gives intermediate 2-C, which in turn can be cyclized at the secondary or tertiary carbon atom (Fig. 4). In the first case, the 2-G cation is formed, which leads to a product with 8-oxatricyclodecane structures 8. Cyclization at the tertiary carbon atom gives the 2-D intermediate, further opening of the cyclopropane ring in which leads to the 2-E.

The intermediate 2-E is stabilized by deprotonation to compound 4 while addition of H₂O or AcOH, which leads to the formation of products 5 and 6, respectively. In addition, 2-E can be further converted into the 2-F cation, which gives compound 7 (Fig. 4). Note that the 2-G intermediate can be converted to 2-D through the Wagner-Meerwein rearrangement [10]. Therefore, isobenzofurans 4 – 7 can also be formed from the product 8. It is important to note that the condensation pathways of common terpene hydrocarbons (α - and β -pinenes, 3-carene) with formaldehyde are very different, which is due to peculiarities in their structure (Figs. 4 and S6). Thus, β -pinene has a terminal double bond, which facilitates its reaction with FA and leads to the almost exclusive formation of nopol (Fig. S6a) in the presence of Lewis acid sites [22–25], while strong Brønsted a.s. catalyze the initial terpene isomerization [27].

α -Pinene contains an endocyclic double bond, which is less active in the Prins reaction compared to β -isomer. Under the acid catalysis conditions, α -pinene (i) condenses with formaldehyde, which leads to the target 8-acetoxy-6-hydroxymethylimonene, and (ii) undergoes direct protonation with a subsequent ring opening (Fig. S6b, [17]). In addition, the formed tertiary carbocations are also capable of the Wagner-Meerwein (W-M) skeletal rearrangements by conjugation with a cyclobutane ring leading to the borneol derivatives formation (Fig. 9b).

On weakly acidic aluminosilicates, a preferential formation of α -pinene direct protonation products was observed, while on zeolite H-Beta-25 selectivity to the compounds formed during the W-M transformation increased [17]. In the presence of H₃PO₄, the amount of direct protonation products and FA addition was comparable, while formation of W-M rearrangement products was minimal, giving the largest selectivity towards 8-acetoxy-6-hydroxymethylimonene.

3-Carene reacts with formaldehyde through the tertiary carbocation 1-A, which is then stabilized due to formation of a double bond connected to the cyclopropane ring (Fig. 4). However, in contrast to 8-acetoxy-6-hydroxymethylimonene or nopol, the resulting *trans*-4-hydroxymethyl-2-carene 2 easily adds a second formaldehyde molecule with subsequent cyclization, because the resulting intermediates can be stabilized due to opening of the cyclopropane ring (2-D \rightarrow 2-E) or direct deprotonation (2-G \rightarrow 8). The reaction of compound 2 with acetic acid also takes place (2 \rightarrow 3).

Thus, selectivity towards *trans*-4-hydroxymethyl-2-carene 2 is limited by its secondary reactions with formaldehyde and acetic acid. On heterogeneous catalysts with a low concentration of a.s. (HNT-HCl/H₃PO₄, K-10, 45 – 104 μ mol/g) product 2 undergoes acetylation via Pathways *a* to form acetates 3 and 9. Strong acidic zeolite H-Beta-25 (301 μ mol/g) provides higher selectivity to 2 (23.0 %) while the amounts of byproducts *a* and *b* were comparable (Table 2). In the case of Lewis acids, namely ZnCl₂ and LiClO₄, the compound 2 is predominantly converted via Pathways *b* to give products with an isobenzofuran structure (Table 2). In the presence of a moderate acid, H₃PO₄, 3-carene 1 condensation with FA proceeds quite efficiently, whereas the side transformations of *trans*-4-hydroxymethyl-2-carene 2 are less pronounced, which eventually leads to the largest selectivity towards this product. Future work should include the development of catalysts containing the heterogenized form of phosphonic acid.

3.3. Reaction conditions

3.3.1. Amount of formaldehyde

In the case of 3-carene 1 condensation with 1.0 eq of formaldehyde in the presence of H₃PO₄, conversion of the starting compounds for 6 h was only 46 % (Table 3), while after 3 h it remained practically unchanged

Table 3

The initial rate and lumped selectivity in 3-carene^a reaction with formaldehyde in the presence of 2.0 eq H₃PO₄ at 15 °C.

FA amount, eq	r_0 , $\frac{mmol}{L \cdot min}$	Time, min	Selectivity, mol.%		
			2	Byproducts <i>a</i> (3 + 9)	Byproducts <i>b</i> (4 + 5 + 6 + 7 + 8)
1.0 ^b	11.3	360	30.5	36.4	20.9
2.0	16.5	45	59.7	10.1	13.6
3.0	17.4	35	66.3	9.1	12.1
5.0	17.2	35	63.6	8.0	12.9

At conversion.

^a 50%.

^b 46%.

(Fig. 5a). An increase in the FA amount to 2.0 eq led to a sharp increase in the conversion, and with 3.0 and 5.0 eq of aldehyde 3-carene was converted almost completely in 6 h (Fig. 5a).

With an increase of 3-carene 1 conversion, the selectivity to *trans*-4-hydroxymethyl-2-carene 2 decreased for all the studied amounts of FA (Fig. 5b), while the selectivity values for products of acetylation (byproducts *a*, Fig. 6a) and further addition of FA (byproducts *b*, Fig. 6b) increased. Note that with 1.0 eq of formaldehyde, a sharp decrease in selectivity towards terpenoid 2 and its increase for byproducts *a* and *b* were observed when compound 1 was practically not consumed. As a result, only 30.5 % selectivity to 2 was observed at 46.2 % conversion for 6 h of reaction (Table 3).

The low values for both 3-carene 1 conversion and selectivity towards 2 with 1.0 eq of FA may be due to the following reasons: (i) insufficient concentration of the protonated form of this aldehyde (⁺CH₂OH, Fig. 4), as well as (ii) its involvement in further condensation with product 2. As mentioned above, reaction of ⁺CH₂OH with 2 should be preferred since the hydroxyl group is a stronger nucleophilic center than the double bond of 3-carene 1. The low concentration of ⁺CH₂OH in the case of 1.0 eq of FA is also indicated by a sharp increase in the selectivity to byproducts *a* with the conversion of 3-carene, while a similar dependence for byproducts *b* has a much smoother shape (Fig. 6a,b). Incomplete conversion of 3-carene (Fig. 5a) might have indicated reversibility of the reaction. However, experiments with the compound 2 did not result in backward transformations to 3-carene clearly indicating that the reaction is not reversible.

In the presence of an excess of formaldehyde, the concentration of the active FA form is, apparently, larger as the equilibrium CH₂O + H⁺ \leftrightarrow ⁺CH₂OH is shifted to the right. This causes an increase of selectivity to *trans*-4-hydroxymethyl-2-carene 2 at the same 3-carene conversion reaching 66 % at 3.0 eq FA. Accordingly, selectivity to byproducts *a* and *b* is declining as follows from Table 3, Fig 5b and 6. A higher concentration of 2 in the reaction mixture was also observed with 3.0 eq of FA at a 3-carene conversion of about 70–80 % (Fig. S7).

An increase in the amount of formaldehyde from 1.0 to 2.0 eq led to a higher initial rate of 3-carene consumption, remaining almost unchanged at a larger excess. This dependence also clearly indicates an increase in the active protonated form of FA, which reacts with substrate 1 to give *trans*-4-hydroxymethyl-2-carene 2. With an increase of FA concentration, the primary transformation reaction displays almost zero order in that compound, as can be also seen from Fig. 5a. Under a high excess of FA selectivity to compound 2 and byproducts is independent on FA concentration pointing out on the same reaction orders in FA for pathways *a* and *b*. For the former pathway it is apparent that the reaction order should be zero as this pathway does not require any FA, which judging from stoichiometry this should not be necessarily the case for the pathway *b*. In any case, a higher reaction order in FA at low FA excess in the transformations of the substrate 1 to substrate 2, compared to the secondary transformations of the compound 2, explains an increase in the selectivity to the target product at the same conversion of substrate 1 under a higher FA excess.

In the case of α - and β -pinene condensation with formaldehyde, the

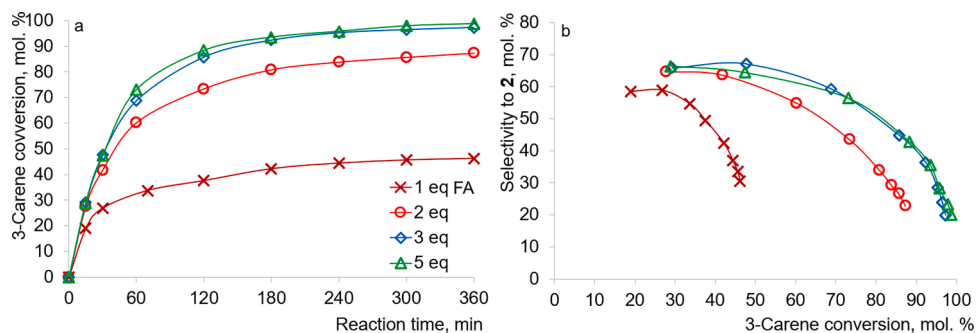


Fig. 5. Kinetic curves (a) and selectivity to product 2 as a function of 3-carene conversion in the presence of 2.0 eq H_3PO_4 (b) at 15 °C.

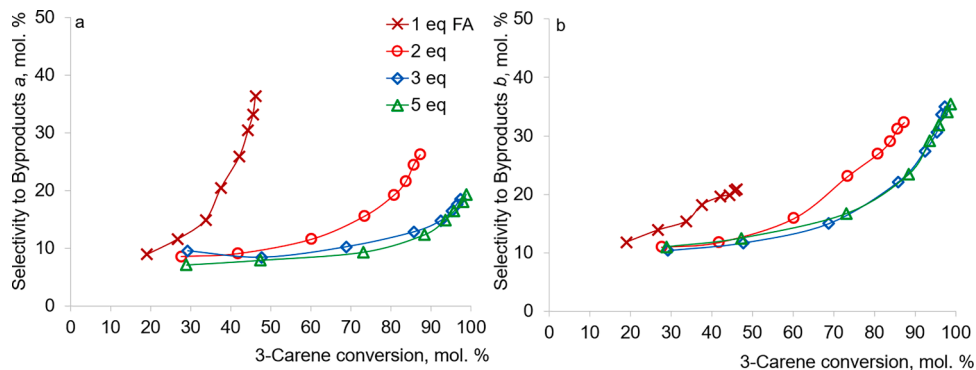


Fig. 6. Selectivity to byproducts *a* (a) and *b* (b) as a function of 3-carene conversion (b) in the presence of 2.0 eq H_3PO_4 at 15 °C.

selectivity to 8-acetoxy-6-hydroxymethylimonene and nopol, as well as conversion values also increased with excess of FA, however, these effects were significantly less pronounced, apparently as secondary reactions of these products with FA have not been observed [17,26].

3.3.2. Amount of catalyst

An increase in the amount H_3PO_4 led to an elevation of 3-carene 1 conversion after 6.0 h of the reaction, and with 3.0 eq of the catalyst, almost complete transformation of 1 was observed (Fig. 7a). There was also an increase in selectivity to *trans*-4-hydroxymethyl-2-carene 2 at 50 % conversion (up to 66 %), while the corresponding values for byproducts *a* and *b* decreased (Table 4, Fig. 7b and S8). This is an evidence for a higher apparent reaction order in the catalyst for the transformations of 1 to 2, compared to subsequent transformations. One potential explanation can be related to the effective concentration of $^+\text{CH}_2\text{OH}$, which increases with an increase in the amount of the acid catalyst. Clearly the Pathway *b*, mechanistically different from the transformations of 1- \rightarrow 1-A, has a less prominent dependence on the acid concentration in line with the results presented above on the influence of FA. The initial rate for 3-carene 1 consumption increased (Table 4) upon

Table 4

The initial rates and lumped selectivity in 3-carene^a reaction with 2.0 eq formaldehyde at 15 °C.

H_3PO_4 amount, eq	r_0 , $\frac{\text{mmol}}{\text{L}\cdot\text{min}}$	Time, min	Selectivity, mol.% 2	Byproducts <i>a</i> (3 + 9)	Byproducts <i>b</i> (4 + 5 + 6 + 7 + 8)
1.0	6.1	105	49.6	12.0	14.8
2.0	16.5	45	59.7	10.1	13.6
3.0	22.6	25	66.2	8.0	11.7

^a At 50% conversion.

an increase of the H_3PO_4 concentration, being on average close to the first order in phosphoric acid.

An ultimate case explaining an increase in selectivity to the product 2 with an increase in concentration of H_3PO_4 would be that while 3-carene condensation with formaldehyde is a catalytic reaction, further secondary reactions are either not catalytic or are catalyzed by AcOH, rather than phosphoric acid. A separate experiment was performed with the compound 2 *per se*, *trans*-4-hydroxymethyl-2-carene, and

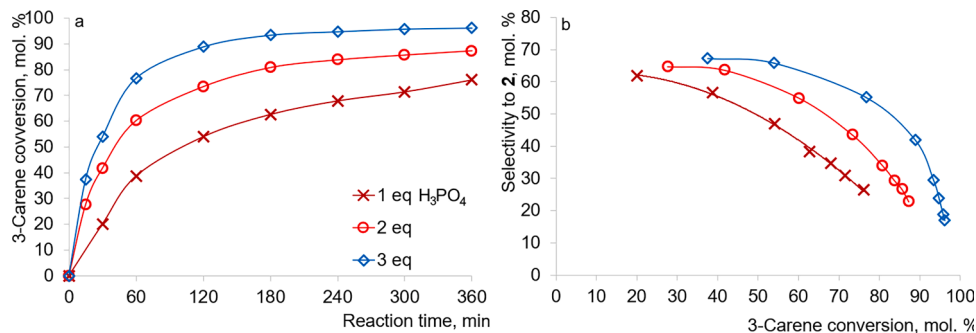


Fig. 7. Kinetic curves (a) and selectivity to 2 as a function of 3-carene conversion (b) with 2.0 eq FA at 15 °C.

formaldehyde without phosphoric acid, revealing absence of any transformations.

At high starting terpene conversion values, there was a sharp decrease in selectivity to terpenoid **2** and its increase towards byproducts *a* and *b* because of compound **2** acetylation and further condensation with formaldehyde, respectively (Figs. 7b and S8).

Interesting to note, that during (–)-isopulegol Prins condensation with thiophene-2-carbaldehyde to substituted 2*H*-chromen-4-ol, selectivity also increased with an increase in the amount of catalyst (acid-treated HNT) as well as the water content in the catalyst [33]. This was explained by the mechanism of HNT action which includes not only formation of an intermediate on a specific acid site, but also the transfer of water from the catalyst surface to this intermediate, giving the target alcohol [33].

A relatively low conversion of 3-carene **1** over HNT-HCl/H₃PO₄ and K-10 aluminosilicates (24–34 %, Table 1) may also indicate that these weakly acidic catalysts (45 – 104 μmol/g) do not provide sufficient protonation of formaldehyde for the Prins condensation of **1**, however, they catalyze the reaction of the resulting *trans*-4-hydroxymethyl-2-carene **2** with AcOH (Pathway *a*), which leads to a relatively high selectivity to byproducts *a* (40–46 %, Table 2). This is also clearly indicated by the typical shapes of the curves for 3-carene **1** conversion and selectivity for HNT-HCl (Figs. S4 and S5), which are similar to those for 1.0 eq FA with phosphoric acid (Figs. 5 and 6).

Strongly acidic zeolite H-Beta-25 (301 μmol/g) protonates FA more efficiently, which leads to an increase in selectivity to **2** (23 %) in comparison with modified halloysites and K-10 (up to 9 %, Table 2). Traditional Lewis acids (ZnCl₂, LiClO₄), in turn, effectively catalyze the FA condensation with *trans*-4-hydroxymethyl-2-carene **2**, which leads to a moderate conversion of starting compounds and high selectivity for byproducts *b* (up to 50 %, Table 2).

Thus, based on the experimental results, ensuring the required concentration of the active ⁺CH₂OH form is critical for the effective 3-carene Prins condensation with FA allowing the lowest contribution of the side reactions. Thus, this can be achieved by using an excess of paraformaldehyde or a higher catalyst loading in the case of phosphoric acid.

3.3.3. Reaction temperature

Increasing the reaction temperature led to an increase in the initial rate of 3-carene **1** conversion (Table 5). At the same time, a slight decrease in selectivity to *trans*-4-hydroxymethyl-2-carene **2** and its increase for byproducts *b* was observed. The kinetic curves of terpene **1** consumption are shown in Fig. 8a.

With the conversion of starting compounds increase, selectivity to terpenoid **2** decreased (Fig. 8b), while increasing towards byproducts *a* and *b* (Fig. S9), indicating sequential conversion of **2** to these products. However, in contrast to similar dependences for different amounts of FA (Figs. 5b, 6) and H₃PO₄ (Figs. 7b, S8), the selectivity values were almost independent on the reaction temperature. An explanation is that primary and secondary reactions have the same or similar activation energy.

The apparent activation energy calculated from the Arrhenius plot (Fig. S10) is 76 kJ/mol, which is lower than in the case of α-pinene

Table 5

The initial rates and lumped selectivity in 3-carene^a reaction with 2.0 eq formaldehyde in the presence of 2.0 eq H₃PO₄.

Reaction temperature, °C	<i>r</i> ₀ , mmol L ⁻¹ min ⁻¹	Time, min	Selectivity, mol.%		
			2	Byproducts <i>a</i> (3 + 9)	Byproducts <i>b</i> (4 + 5 + 6 + 7 + 8)
8	8.2	90	63.2	9.2	12.0
15	16.5	45	59.7	10.1	13.6
25	52.3	15	59.9	8.8	13.7

^a At 50% conversion.

condensation with FA (84 kJ/mol [17]) in the presence of phosphoric acid in AcOH, as well as a similar reaction of β-pinene on Sn-MCM-41 (98 kJ/mol [25]) with ethyl acetate as a solvent.

3.3.4. Reaction medium

In the present work, the catalytic 3-carene **1** condensation with formaldehyde was studied using a mixture of AcOH (5.0 mL) and Ac₂O (1.0 mL) as a reaction medium (Tables 1–5). However, conducting the reaction only in acetic acid (6.0 mL) caused a relatively low substrate initial consumption rate (*r*₀), while selectivity to *trans*-4-hydroxymethyl-2-carene **2** was ca. 66 % (Table 6).

Introduction of acetic anhydride into the reaction medium led to a sharp increase in *r*₀, lower selectivity to **2** (ca. 60 %), and an increase in the amounts of consecutive FA addition products (byproducts *b*) (Table 6). Addition of 1.0 eq H₂O to a reaction medium consisting of 5.0 mL AcOH and 1.0 mL Ac₂O diminished the initial rate of **1** consumption, while selectivity was almost similar to utilization of only acetic acid (Table 6). Kinetic curves for the 3-carene **1** consumption and dependences of selectivity to product **2** on conversion of **1** are shown in Fig. 9.

Based on the experimental results, it can be assumed that the role of Ac₂O is to remove H₂O from the reaction system. Thus, water is present in the catalyst (85 % H₃PO₄) and as an impurity in glacial AcOH. Introduction of Ac₂O leads to its removal due to anhydride hydrolysis, which causes an increase in the initial reaction rate, as well as a decrease in the selectivity to product **2** (Table 5). On the contrary, addition of 1.0 eq H₂O to the AcOH-Ac₂O system makes it possible to increase the yield of **2** while simultaneously decreasing *r*₀. In turn, the role of acetic acid is in the effective dissolution of the reagents and catalyst, and also possibly in inhibition of the side reactions with FA due to interactions of AcOH with the -OH group of product **2**.

The inhibition of the reaction upon the water introduction into the AcOH-Ac₂O medium (or only with AcOH) can be associated with the H₂O solvation of the protonated form of FA. The observed increase in selectivity to *trans*-4-hydroxymethyl-2-carene **2** (Table 5) can also be due to the interactions of H₂O with the alcohol group of this product, which inhibited its secondary transformations. Indeed, when water was present in the system (AcOH or AcOH-Ac₂O + 1.0 eq H₂O), a decrease in selectivity to **2** and its increase towards byproducts *b* with 3-carene conversion (Figs. 9 and 10) was less pronounced.

Note that in the Prins reaction, water can significantly increase selectivity to the target products by inhibiting the side reactions [41,49] or generating specific Brønsted acid sites responsible for the desired reaction only [33,35,36,41]. On the contrary, the cascade Prins-Friedel-Crafts reaction required thorough drying of the aluminosilicate catalyst [20], because the reaction proceeded over relatively strong acid sites present in montmorillonite [20] or hierarchical zeolites [38]. In the case of α-pinene condensation with FA, addition of H₂O to the system practically did not change selectivity, causing, however, inhibition of the reaction [17].

Thus, an increase in selectivity to *trans*-4-hydroxymethyl-2-carene **2** occurs in the case of an increase in (i) the amount of FA, or (ii) higher catalyst concentration due to an increase in the concentration of formaldehyde protonated form, as well as in the presence of water in the system, which inhibits secondary transformations of product **2**.

3.4. The reaction upscaling and 3-carene recycling

Because selectivity to *trans*-4-hydroxymethyl-2-carene **2** increased with an increase in the amount of FA, or in the AcOH medium, 3-carene (1.0 g) condensation was performed with 3.0 eq of formaldehyde in the presence of 2.0 eq of H₃PO₄ at 15 °C, using only acetic acid as a solvent. The terpene conversion reached 55 % after 4 h with the selectivity towards terpenoid **2** of ca. 67 % (Fig. S11).

Furthermore, the reaction was carried out in the same conditions on a scale of 5 and 25 g, isolating *trans*-4-hydroxymethyl-2-carene **2** by

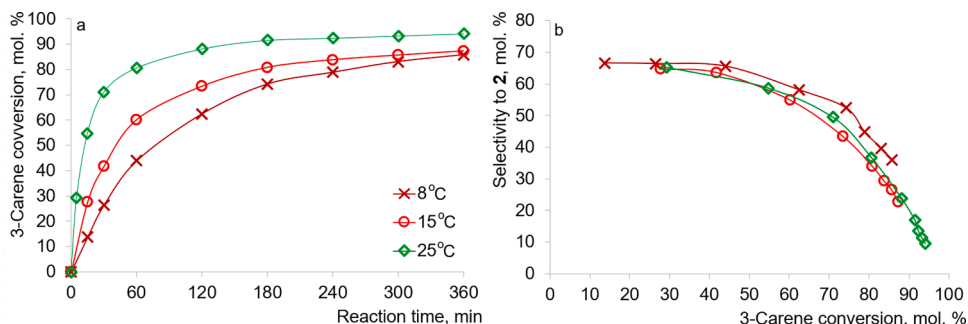


Fig. 8. Kinetic curves (a) and selectivity to product 2 as a function of 3-carene conversion (b) with 2.0 eq FA in the presence of 2.0 eq H_3PO_4 .

Table 6

Initial rates and lumped selectivity in 3-carene^a reaction with 2.0 eq formaldehyde in the presence of 2.0 eq H_3PO_4 .

Reaction medium ^b		r_0	Time,	Selectivity, mol.%		
AcOH, mL	Ac ₂ O, mL	$\frac{\text{mmol}}{\text{L}\cdot\text{min}}$	min	2	Byproducts a (3 + 9)	Byproducts b (4 + 5 + 6 + 7 + 8)
6.0	0	5.3	180	66.1	9.0	11.5
5.0	1.0	16.5	45	59.7	10.1	13.6
4.0	2.0	69.2	10	60.7	7.8	14.6
5.0	1.0	13.0	60	64.7	9.2	11.7

^a At conversion 50.0%.

^b Total volume of the reaction mixture was 8 ml.

column chromatography or vacuum distillation with the yield of 37–38 %, which is significantly higher than that obtained in the work using AcOH-Ac₂O-H₃PO₄ system without optimization (11 % [20]). Unreacted 3-carene was isolated from the reaction mixture with a purity of 84 % and reused, which led to a yield of the target product of 38 %. More

detailed experimental information on the reaction upscaling and the starting compound recycling is given in SI.

3.5. DFT calculations

To further evaluate the proposed mechanism for 3-carene condensation with formaldehyde in the presence of AcOH and H_3PO_4 as a catalyst, the DFT calculations were performed with the Jaguar 10.9 program [50] using dispersion-corrected hybrid density functional technique B3LYP-D3 with a 6-31G++(d,p) basis set for structural geometry optimization [51,52]. For flexible species, the conformational search was carried out with MacroModel 12.9 [53] using OPLS3e force field. Solvation effects (AcOH) were included and computed by using the Poisson-Boltzmann finite element method with the following parameters for acetic acid: $\epsilon = 6.15$, $M = 60.052$ g/mol and $\rho = 1.05$ g/ml. The initial reference ($\Delta G = 0.0$) was taken as the sum of 3-carene, two molecules of formaldehyde, acetic and phosphoric acids.

Quantum chemical calculations demonstrated that in the reaction of 3-carene 1 with formaldehyde proceeding with the formation of the target *trans*-4-hydroxymethyl-2-carene 2 (−5.0 kJ/mol), there is a tendency of this product involvement in further transformations (Fig. 11).

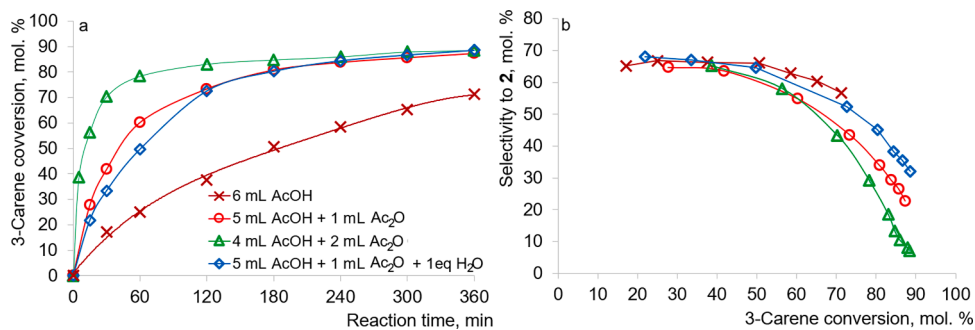


Fig. 9. Kinetic curves (a) and selectivity to product 2 as a function of 3-carene conversion (b) with 2.0 eq FA in the presence of 2.0 eq H_3PO_4 at 15 °C.

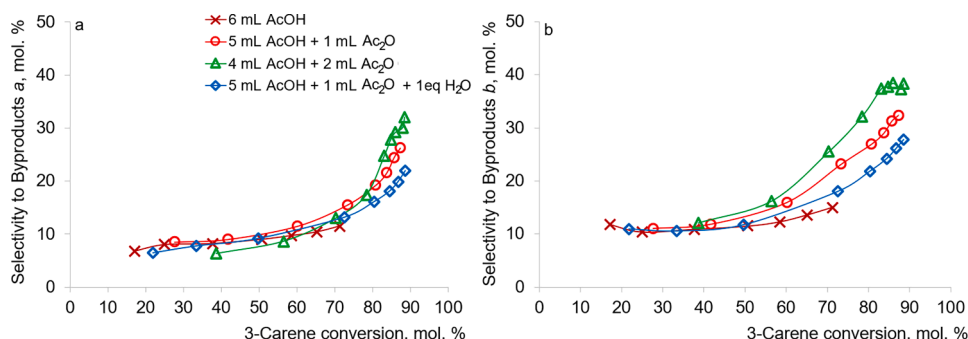


Fig. 10. Selectivity to byproducts a (a) and b (b) as a function of 3-carene conversion (b) in the presence of 2.0 eq H_3PO_4 at 15 °C.

Thus, direct acylation of compound **2** with AcOH leads to formation of the energetically favorable acetate **3** (−19.4 J/mol). Hydration of the intermediate **1-A** followed by addition of acetic acid gives the product **9** (13.5 kJ/mol), which can then be converted into a more thermodynamically stable compound **3**.

Another reaction pathway is the addition of the second formaldehyde molecule to *trans*-4-hydroxymethyl-2-carene **2**. According to DFT simulations, as a result of successive transformations, the intermediate **2-C** (65.0 kJ/mol, Fig. 11) is formed, which is then cyclized into carbocations **2-G** (65.1 kJ/mol) and **2-D** (39.1 kJ/mol). The tricyclic ion **2-G** gives product **8** (−32.5 kJ/mol) because of deprotonation. In parallel, as a result of the cyclopropane ring opening, the carbocation **2-E** (43.7 kJ/mol) is generated, from which a series of isobenzofuran products **4** (−109.8 kJ/mol), **5** (−65.8 kJ/mol), **6** (−46.7 kJ/mol), **7** (−99.7 kJ/mol) is formed.

DFT calculations also show that the transformation of compound **8** into isobenzofurans is also possible, since both the Wagner-Meerwein rearrangement (**2-G** → **2-D**) and further transformations leading to formation of products **4**–**7** are energetically favorable (Fig. 11).

There is a large difference in energy for the intermediates of pathway *a* (**2-A**, 136.3 kJ/mol) and pathway *b* (**2-B**, 49.9 kJ/mol), which predicts the predominance of byproducts *b* in the reaction mixture, although selectivity to byproducts *a* and *b* with phosphoric acid is comparable (Table 2). The results can be explained by using acetic acid as the reaction medium, somewhat complicating the subsequent condensation with FA. Moreover, with an increase in the formaldehyde amount in the mixture, selectivity to byproducts *a* is decreasing sharply (Table 3).

The calculated sizes of all compounds and intermediates range from 6.5 to 14 Å (Table S4), being significantly lower than the average pore diameter of the studied halloysite and montmorillonite catalysts (5.1 – 15.7 nm, Table S1) and comparable in the case of Beta-25 zeolite (0.76 nm [45]).

Overall, quantum chemical calculations showed that *trans*-4-hydroxymethyl-2-carene **2** can be further converted due to acetylation or by addition of a second formaldehyde molecule, because the corresponding by-products have significantly lower energies (except **9**) than the compound **2**. This is in the conceptual agreement with the experimental results and predicts a decrease in the selectivity to **2** with the conversion of 3-carene.

3.5. Kinetic modeling

Kinetic modeling was performed to elucidate applicability of the reaction network (Fig. 4) to describe the experimental data. The incomplete mass balance closure and presence of various minor peaks in

the chromatograms point out on formation of unknown products, which can be generated by e.g. ring opening similar to compound **2**. Subsequently, the transformations of substrates **1**, **8** and **9** have been added to the reaction network. The concentration curves for compound **9** point out on a possibility of its formation directly from the substrate **1**, as discussed above. An alternative mechanism initially considered by the authors considered that the compound **9** could be formed from **2** through the compound **3**. However, the kinetic modeling for such case and analysis of selectivity dependence on conversion for compounds **9** and **3** indicated that there could be an additional pathway from **2** to **9** and moreover the path from **2** to **9** can be reversible. The reaction network comprising these reactions is presented in Fig. 12. Selectivity dependence of compound **2** as a function of conversion at different concentrations of formaldehyde and the acid catalysts, can be explained by assuming that the rate determining steps in transformations of **2** to product **8** includes dependence on the acid concentration contrary to formation of products **4**, **5**, **6** and **7**. Rather nontrivial behavior of activity and selectivity as a function of the formaldehyde concentration can be explained by incomplete involvement of the initial amounts of formaldehyde FA₀ in the condensation reaction. Subsequently only a fraction of FA is active, which is modelled by reversible reactions 13 and 13b. More specifically it was assumed that dimers of FA are formed.

To explain the reaction order in FA below unity in reactions 6 to 10 formation of a corresponding intermediate (Fig. 4) was considered.

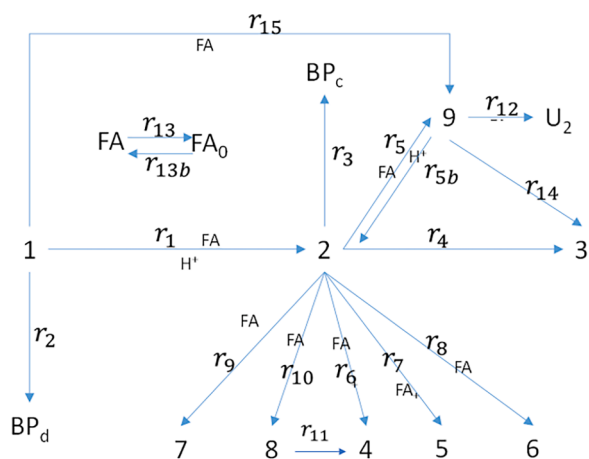


Fig. 12. Modified reaction network. Notation: FA – formaldehyde, U1– unknown compounds to comply with the mass balance, BPc and BPD – byproducts.

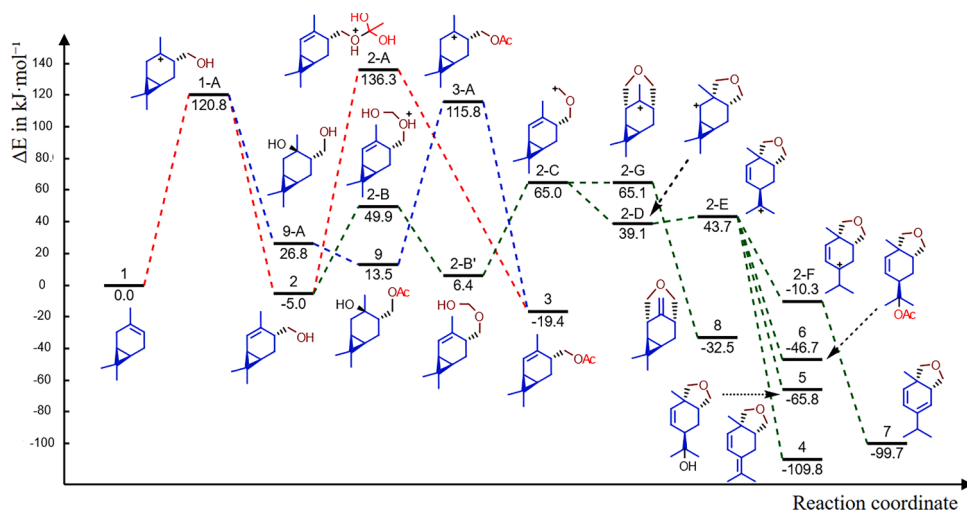


Fig. 11. DFT calculated energy diagram for the 3-carene condensation with formaldehyde in the presence of AcOH and H₃PO₄.

The kinetic equations corresponding to the mechanism in Fig. 12 are

$$\begin{aligned}
 r_1 &= k_1 * K_{H_3PO_4} c_{H_3PO_4}^n * c_{FA} c_1; r_2 = k_2 c_1; r_3 = k_3 c_2; r_4 = k_4 c_2; r_5 = k_5 K_{H_3PO_4} c_2 c_{H_3PO_4}^n c_{FA} \\
 r_{5b} &= k_{5b} K_{H_3PO_4} c_9 * c_{H_3PO_4}; r_6 = k_6 c_2 \frac{k'_6 c_{FA}}{k_{-6} + k'_6 c_{FA}}; r_7 = k_7 c_2 \frac{k'_7 c_{FA}}{k_{-7} + k'_7 c_{FA}}; r_8 = k_8 c_2 K_{H_3PO_4} c_{H_3PO_4}^n c_{FA} \\
 r_9 &= k_9 c_2 \frac{k'_9 c_{FA}}{k_{-9} + k'_9 c_{FA}}; r_{10} = k_{10} c_2 \frac{k'_{10} c_{FA}}{k_{-10} + k'_{10} c_{FA}}; r_{11} = k_{11} c_8; r_{12} = k_{12} c_9; r_{13} = k_{13} c_{FA}; \\
 r_{13b} &= k_{13b} c_{FA}^m; r_{14} = k_{14} c_9; r_{15} = k_{15} c_1 c_{FA}
 \end{aligned} \tag{1}$$

The corresponding generation rates of the products are

$$\begin{aligned}
 \frac{dc_1}{dt} &= -r_1 - r_2 - r_{15}; \frac{dc_2}{dt} = r_1 - r_3 - r_4 - r_6 - r_7 - r_8 - r_9 - r_{10} - r_5 + r_{5b}; \frac{dc_3}{dt} = r_4 + r_{14} \\
 \frac{dc_4}{dt} &= r_6 + r_{11}; \frac{dc_5}{dt} = r_7; \frac{dc_6}{dt} = r_8; \frac{dc_7}{dt} = r_9; \frac{dc_8}{dt} = r_{10} - r_{11}; \frac{dc_9}{dt} = r_5 - r_{12} - r_{5b} - r_{14} + r_{15} \\
 \frac{dc_{10}}{dt} &= r_2; \frac{dc_{11}}{dt} = r_3; \frac{dc_{12}}{dt} = -r_1 r_6 - r_7 - r_8 - r_9 - r_{10} - m r_{13} + m r_{13b}; \frac{dc_{13}}{dt} = r_{13} - r_{13b}
 \end{aligned} \tag{2}$$

Kinetic modeling was done to compare the measured concentration of reactants and products with the theoretical predictions. The estimation of the kinetic parameters was performed using the ModEst parameter estimation software [54].

The objective function (Q) used in the modeling was set to minimize the degree of explanation between the calculated and experimental values of concentrations

$$\bar{n}_{est} Q = \max R^2 = \max 100 \left(\frac{\left(\| C_{exp} - C_{est} \| \right)^2}{\left(\| C_{exp} - \bar{C}_{est} \| \right)^2} \right) \tag{3}$$

The residuals given by the proposed kinetic model in this way are compared with the residuals of the simplest model, where the estimated values correspond to the average value of all data points. The parameter estimation was done by numerically solving the differential equations for the concentrations of all components (eq. (2)) with the Levenberg-Marquardt method incorporated in the software.

The results of calculations given in Fig. S12 along with a rather higher degree of explanation (95.1 %) show a very good correspondence between calculations and experimental data. The values of kinetic constants are presented in Table 7, indicating that in the majority of cases the rate constants are well defined. It can be seen from Table 7, that particular challenging from the statistical viewpoint were k_6' , k_7' , k_9' , k_{10}' constants as well as the corresponding backward constants featuring quite high relative errors. A further refinement of the reaction network requires separate kinetic experiments with the main reaction products, which are planned for the future.

4. Conclusions

The catalytic condensation of 3-carene with formaldehyde (FA) in acetic acids for the one-step preparation of *trans*-4-hydroxymethyl-2-carene (a fragrant compound and a chiral platform) was systematically studied for the first time. As catalysts, traditional Brønsted and Lewis acids, as well as aluminosilicates with weak to strong acidity (halloysite nanotubes, K-10 montmorillonite, H-Beta-25 zeolite) have been studied.

Both homogeneous and heterogeneous systems are capable of catalyzing 3-carene condensation with FA, however, a relatively low

selectivity to *trans*-4-hydroxymethyl-2-carene was obtained because of its secondary acetylation reaction as well as a further formaldehyde addition leading to isobenzofurans. The Lewis acids such as $ZnCl_2$ and $LiClO_4$ caused formation of isobenzofurans as the main products (up to 50 % yield), while aluminosilicates with acidity from 45 to 104 $\mu\text{mol/g}$ gave a low conversion of 3-carene (ca. 30 %) with acetylation of the resulting terpenoid. Relatively high selectivity to *trans*-4-hydroxymethyl-2-carene was achieved with $FeCl_3 \cdot 6H_2O$ and H_3PO_4 , being the largest (ca. 50–66 %) in the presence of the latter catalyst.

When using equivalent amounts of FA or the catalyst (H_3PO_4) as the

Table 7
Values of rate parameters and the corresponding errors.

Constant	Value	Error, %	units
k_1	0.034	>100	(L/mol) ⁿ
k_2	0	–	min ⁻¹
k_3	$0.2 \cdot 10^{-2}$	21.7	min ⁻¹
k_4	0.0013	32.3	min ⁻¹
k_5	0	–	(L/mol) ⁿ
k_{5b}	0	–	min ⁻¹
k_6	$0.3 \cdot 10^{-7}$	>100	min ⁻¹
k_7	$0.3 \cdot 10^{-3}$	33.3	min ⁻¹
k_8	0.0033	>100	(L/mol) ⁿ
k_9	$0.3 \cdot 10^{-3}$	31.3	min ⁻¹
k_{10}	0.0015	2.6	min ⁻¹
k_{11}	$0.2 \cdot 10^{-2}$	8.4	min ⁻¹
k_{12}	$0.3 \cdot 10^{-8}$	>100	min ⁻¹
k_{13}	$0.38 \cdot 10^{-2}$	23.5	min ⁻¹
k_{13b}	0.046	30.5	L/mol/min
m	2	fixed	–
k_{14}	$0.9 \cdot 10^{-8}$	>100	min ⁻¹
k_{15}	$0.8 \cdot 10^{-3}$	4.3	L/mol/min
$K_{H_3PO_4}$	0.219	>100	L/mol
k_6'	1.93	>100	L/mol
k_7'	0.59	>100	L/mol
k_9'	2.83	>100	L/mol
k_{10}'	1.9	>100	L/mol
k_{-6}	1.68	>100	–
k_{-7}	$0.3 \cdot 10^{-4}$	>100	–
k_{-9}	0.0029	>100	–
k_{-10}	0.19	>100	–
n	0.62	5.9	–

substrate, a high conversion of 3-carene could not be achieved, with selectivity to the target terpenoid not exceeding ca. 50 %, which was associated with an insufficient concentration of the protonated form of formaldehyde ($^+CH_2OH$). The introduction of an excess of FA or a catalyst into the system led to an increase in selectivity to *trans*-4-hydroxymethyl-2-carene, which reached ca. 66 % at 50 % conversion. The reaction temperature had practically no effect on the yield of the target product, while water slightly increased it due to inhibition of its secondary transformations.

The reaction mechanism and pathways have been discussed based on the experimental work as well as DFT calculations and kinetic modeling, which clearly show that the further reactions of *trans*-4-hydroxymethyl-2-carene with AcOH and FA are thermodynamically and kinetically beneficial decreasing selectivity to this intermediate product.

The synthesis of the desired terpenoid was carried out under optimized conditions using the H_3PO_4 -AcOH system on a scale up to 25 g with a yield of ca. 38 %. A possibility of recycling 3-carene has also been shown. Given the importance of *trans*-4-hydroxymethyl-2-carene for perfumery and medicinal chemistry, further work should be directed to the development of heterogeneous selective catalysts for the synthesis of this product.

CRediT authorship contribution statement

A.Yu. Sidorenko: Investigation, Writing – original draft, Supervision. **Yu.M. Kurban:** Investigation. **T.V. Khalimonyuk:** Investigation. **I.V. Il'ina:** Investigation. **N.S. Li-Zhulanov:** Investigation, Writing – original draft. **O.S. Patrusheva:** Investigation. **V.V. Goltsova:** Investigation. **M.P. Bei:** Investigation. **Zh.V. Ichnatovich:** Investigation. **J. Wärnå:** Investigation. **K.P. Volcho:** Supervision, Writing – original draft. **N.F. Salakhutdinov:** Supervision, Project administration. **D.Yu. Murzin:** Supervision, Writing – review & editing. **V.E. Agabekov:** Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.mcat.2023.113627](https://doi.org/10.1016/j.mcat.2023.113627).

References

- [1] R.A. Sheldon, Green and sustainable manufacture of chemicals from biomass: state of the art, *Green Chem.* 16 (2014) 950–963.
- [2] P. Sudarsanam, E. Peeters, E.V. Makshina, V.I. Parvulescu, B.F. Sels, Advances in porous and nanoscale catalysts for viable biomass conversion, *Chem. Soc. Rev.* 48 (2019) 2366–2421.

- [3] M. Golets, S. Ajaikumar, J.P. Mikkola, Catalytic upgrading of extractives to chemicals: monoterpenes to “EXICALS”, *Chem. Rev.* 115 (2015) 3141–3169.
- [4] O.S. Patrusheva, K.P. Volcho, N.F. Salakhutdinov, Approaches to the synthesis of oxygen-containing heterocyclic compounds based on monoterpenoids, *Russ. Chem. Rev.* 87 (2018) 771–796.
- [5] M. Zielińska-Blajet, J. Feder-Kubis, Monoterpenes and their derivatives – recent development in biological and medical applications, *Int. J. Mol. Sci.* 21 (2020) 7078.
- [6] M. Lapuerta, I. Tobío-Pérez, M. Ortiz-Alvarez, D. Donoso, L. Canoira, R. Piloto-Rodríguez, Heterogeneous catalytic conversion of terpenes into biofuels: an open pathway to sustainable fuels, *Energies* 16 (2023) 2526.
- [7] R.J. Nyamwihura, I.V. Ogungbe, The pinene scaffold: its occurrence, chemistry, synthetic utility, and pharmacological importance, *RSC Adv.* 12 (2022) 11346–11375.
- [8] D. Strub, L. Balcerzak, S. Lochynski, (+)-3-Carene: valuable starting material for synthesis of low-molecular compounds with olfactory properties, *Curr. Org. Chem.* 18 (2014) 446–458.
- [9] S. Curlat, Recent Studies of (+)-3-Carene transformations with the retention of the native framework, *Chem. J. Mold.* 14 (2019) 32–55.
- [10] V.A. Chuiko, O.G. Vyglazov, Skeletal rearrangements of monoterpenoids of the carene series, *Russ. Chem. Rev.* 72 (2003) 49–67.
- [11] I.V. Il'ina, N.S. Dyrkheeva, A.L. Zakharenko, A.Yu. Sidorenko, N.S. Li-Zhulanov, D. V. Korchagina, R. Chand, D.M. Ayine-Tora, A.A. Chepanova, O.D. Zakharova, E. S. Ilina, J. Reynisson, A.A. Malakhova, S.P. Medvedev, S.M. Zakian, K.P. Volcho, N. F. Salakhutdinov, O.I. Lavrik, Design, synthesis, and biological investigation of novel classes of 3-carene-derived potent inhibitors of TDP1, *Molecules* 25 (2020) 3496.
- [12] G. Sadowska, J. Gora, Synthesis and odor properties of carene and carane derivatives, *Perfumer Flavorist* 7 (1982) 52–56.
- [13] M. Kränzlein, S. Pongratz, J. Bruckmoser, B. Bratić, J.M. Breitsameter, B. Rieger, Polyester synthesis based on 3-carene as renewable feedstock, *Polym. Chem.* 13 (2022) 3726–3732.
- [14] L. Jørgensen, S.J. McKerrall, C.A. Kuttruff, J. Felding F. Ungeheuer, P.S. Baran, 14-step synthesis of (+)-ingenol from (+)-3-carene, *Science* 341 (2013) 878–882.
- [15] P. Yuan, C.K.G. Gerlinger, J. Herberger, T. Gaich, Ten-step asymmetric total synthesis of (+)-pepluanol A, *J. Am. Chem. Soc.* 143 (2021) 11934–11938.
- [16] F. Doro, N. Akeroyd, F. Schiet, A. Narula, The Prins Reaction in the fragrance industry: 100th anniversary (1919–2019), *Angew. Chem. Int. Ed.* 22 (2019) 7174–7179.
- [17] A.Yu. Sidorenko, Yu.M. Kurban, I.V. Il'ina, N.S. Li-Zhulanov, O.S. Patrusheva, V.V. Goltsova, M.P. Bei, A. Aho, J. Wärnå, I. Heinmaa, T.F. Kuznetsova, K.P. Volcho, N. F. Salakhutdinov, D.Yu. Murzin, V.E. Agabekov, Catalytic condensation of α -pinene with formaldehyde, *J. Catal.*, (Submitted).
- [18] G. Ohloff, H. Farnow, W. Philipp, Homologous alcohols of the terpene and sesquiterpene series. X. Synthesis of (+)-3-hydroxymethyl-4-carene, *Justus Liebig's Ann. Chem.* 613 (1958) 43–55, <https://doi.org/10.1002/jlac.19586130105>, in German.
- [19] S.Yu. Kurbakova, I.V. Il'ina, O.S. Mikhailchenko, M.A. Pokrovsky, D.V. Korchagina, K.P. Volcho, A.G. Pokrovsky, N.F. Salakhutdinov, The short way to chiral compounds with hexahydrofluoreno[9,1-bc]furan framework: synthesis and cytotoxic activity, *Bioorg. Med. Chem.* 23 (2015) 1472–1480.
- [20] A.Yu. Sidorenko, Yu.M. Kurban, A.V. Kravtsova, I.V. Il'ina, N.S. Li-Zhulanov, D. V. Korchagina, J.E. Sánchez-Velandia, A. Aho, K.P. Volcho, N.F. Salakhutdinov, D. Yu. Murzin, V.E. Agabekov, Clays catalyzed cascade Prins and Prins-Friedel-Crafts reactions for synthesis of terpenoid-derived polycyclic compounds, *Appl. Catal. A Gen.* 629 (2022), 118395.
- [21] N.S. Li-Zhulanov, I.V. Il'ina, A.Yu. Sidorenko, D.V. Korchagina, V.E. Agabekov, K. P. Volcho, Nariman F. Salakhutdinov, Cascade transformation of 4-hydroxymethyl-2-carene into novel cage methanopyrano[4,3-b]thieno[3,2-g]benzofuran derivative, *Mendeleev. Commun.* 32 (2022) 443–445.
- [22] M.Kr. Yadav, R.V. Jasra, Synthesis of nopol from β -pinene using $ZnCl_2$ impregnated Indian montmorillonite, *Catal. Commun.* 7 (2006) 889–895.
- [23] V.S. Marakatti, A.B. Halgeri, G.V. Shanbhag, Metal ion-exchanged zeolites as solid acid catalysts for the green synthesis of nopol from Prins reaction, *Catal. Sci. Technol.* 4 (2014) 4065–4407.
- [24] S.V. Jadhav, K.M. Jinka, H.C. Bajaj, Synthesis of nopol via Prins condensation of β -pinene and paraformaldehyde catalyzed by sulfated zirconia, *Appl. Catal., A Gen.* 390 (2010) 158–165.
- [25] D. Casas-Orozco, E. Alarcón, A.L. Villa, Kinetic study of the nopol synthesis by the Prins reaction over tin impregnated MCM-41 catalyst with ethyl acetate as solvent, *Fuel* 149 (2015) 130–137.
- [26] V.S. Marakatti, D. Mumbaraddi, G.V. Shanbhag, A.B. Halgeria, S.P. Maradur, Molybdenum oxide/ γ -alumina: an efficient solid acid catalyst for the synthesis of nopol by Prins reaction, *RSC Adv.* 5 (2015) 93452–93462.
- [27] J. Wang, S. Jaenicke, G.K. Chuah, W. Hua, Y. Yue, Z. Gao, Acidity and porosity modulation of MWW type zeolites for Nopol production by Prins condensation, *Catal. Commun.* 12 (2011) 1131–1135.
- [28] P.J. Kropp, D.C. Heckert, T.J. Flautt, Stereochemistry of electrophilic substitution of (+)-3-carene: prins and Friedel-Crafts-acetylation reactions, *Tetrahedron.* 24 (1968) 1385–1395.
- [29] J. Chlebicki, B. Burczyk, Terpene ethers VII. New products from the reaction of 3-carene with formaldehyde, *Tetrahedron Lett.* 11 (1970) 4775–4778.
- [30] USSR patent SU13713702A1, 02/15/1988, Method for obtaining 4-hydroxymethyl-2-carene (in Russian).
- [31] E.N. Manukov, T.R. Urbanovich, O.G. Vyglazov, V.A. Chuiko, E.D. Skakovskii, 2-Carene in the Prins reaction, *Chem. Nat. Compd.* 25 (1989) 164–168.

- [32] E. Vrbková, M. Vaňková, M. Lhotka, E. Vyskočilová, Acid treated montmorillonite - efficient catalyst in Prins reaction of alpha-methylstyrene with paraldehyde, *Mol. Catal.* 542 (2023), 113143.
- [33] A.Yu. Sidorenko, A.V. Kravtsova, A. Aho, I. Heinmaa, H. Pazniak, K.P. Volcho, N. F. Salakhutdinov, D.Yu. Murzin, V.E. Agabekov, Highly selective Prins reaction over acid-modified halloysite nanotubes for synthesis of isopulegol-derived 2H-chromene compounds, *J. Catal.* 374 (2019) 360–377.
- [34] A.Yu. Sidorenko, Yu.M. Kurban, A. Aho, Zh.V. Ilnatovich, T.F. Kuznetsova, I. Heinmaa, D.Yu. Murzin, V.E. Agabekov, Solvent-free synthesis of tetrahydropyran alcohols over acid-modified clays, *Mol. Catal.* 499 (2021), 111306.
- [35] A.Yu. Sidorenko, A.V. Kravtsova, P. Mäki-Arvela, A. Aho, T. Sandberg, I.V. Il'ina, N.S. Li-Zhulanov, D.V. Korchagina, K.P. Volcho, N.F. Salakhutdinov, D.Yu. Murzin, V.E. Agabekov, Synthesis of isobenzofuran derivatives from renewable 2-carene over halloysite nanotubes, *Mol. Catal.* 490 (2020), 110974.
- [36] A.Yu. Sidorenko, Yu.M. Kurban, I.V. Il'ina, N.S. Li-Zhulanov, D.V. Korchagina, O. V. Ardashov, J. Wärnå, K.P. Volcho, N.F. Salakhutdinov, D.Yu. Murzin, V. E. Agabekov, Catalytic synthesis of terpenoid-derived hexahydro-2H-chromenes with analgesic activity over halloysite nanotubes, *Appl. Catal. A Gen.* 618 (2021), 118144.
- [37] N. Shcherban, R. Barakov, B. Lasne, P. Mäki-Arvela, M. Shamzhy, I. Bezverkhy, J. Wärnå, D.Y. Murzin, Florol synthesis via Prins cyclization over hierarchical beta zeolites, *Mol. Catal.* 531 (2022), 112683.
- [38] R. Barakov, N. Shcherban, O. Petrov, J. Lang, M. Shamzhy, M. Opanasenko, J. Čejka, MWW-type zeolite nanostructures for a one-pot three-component Prins–Friedel–Crafts reaction, *Inorg. Chem. Front.* 9 (2022) 1244–1257.
- [39] Z. Chen, H. Li, K. Sheng, X. Dong, J. Yuan, S. Hao, M. Li, R. Bai, Y. Queneau, A. Sidorenko, J. Huang, Y. Gu, Dipolar modification in heterogeneous catalysts under electron beam irradiation for the conversion of biomass-derived platform molecules, *ACS Catal.* 12 (2022) 15618–15625.
- [40] A.Yu. Sidorenko, Yu.M. Kurban, A.F. Peixoto, N.S. Li-Zhulanov, J.E. Sánchez-Velandia, A. Aho, J. Wärnå, Y. Gu, K.P. Volcho, N.F. Salakhutdinov, D.Yu. Murzin, V.E. Agabekov, Brønsted acid catalyzed Prins-Ritter reaction for selective synthesis of terpenoid-derived 4-amidotetrahydropyran compounds, *Appl. Catal. A:Gen.* 649 (2023), 118967.
- [41] P.A. Kots, M.A. Artsiusheuski, Y.V. Grigoriev, I.I. Ivanova, One-step butadiene synthesis via gas-phase Prins condensation of propylene with formaldehyde over heteropolyacid catalysts, *ACS Catal.* 10 (24) (2020) 15149–15161.
- [42] A.Yu. Sidorenko, A.V. Kravtsova, A. Aho, I. Heinmaa, T.F. Kuznetsova, D. Yu. Murzin, V.E. Agabekov, Catalytic isomerization of α -pinene oxide in the presence of acid-modified clays, *Mol. Catal.* 448 (2018) 18–29.
- [43] M. Boukachabia, H. Bendjeffal, M.M. Khelassi, O. Riant, A chemometric approach based on a full factorial design to optimize terpene acylation using natural kaolin as eco-friendly catalyst, *Flavour Fragr. J.* (2023), <https://doi.org/10.1002/ffj.3741>. First published: 10 April 2023.
- [44] F.G. Delolo, G.M. Vieira, J.A. Avendaño-Villarreal, A. de Oliveira Dias, E.N. dos Santos, E.V. Gusevskaya, Working together to avoid unwanted reactions: hydroformylation/O-acylation of terpene-based hydroxyolefins, *J. Catal.* 421 (2023) 20–29.
- [45] A. Aho, N. Kumar, K. Eränen, T. Salmi, M. Hupa, D.Yu. Murzin, Catalytic pyrolysis of woody biomass in a fluidized bed reactor: influence of the zeolite structure, *Fuel* 87 (2008) 2493–2501.
- [46] T. Prakoso, J. Hanley, M.N. Soebianta, T.H. Soerawidjaja, A. Indarto, Synthesis of terpineol from α -pinene using low-price acid, *Catal. Lett.* 148 (2018) 725–731.
- [47] A.D. White, F. Gallou, Iron (III) Chloride, *Encyclop. Reag. Organ. Synth.* (2006), <https://doi.org/10.1002/047084289X.r0054.pub2>.
- [48] S.K. Jain, T. Tabassum, L. Li, L. Ren, W. Fan, M. Tsapatsis, S. Caratzoulas, S. Han, S. L. Scott, P-site structural diversity and evolution in a zeosil catalyst, *J. Am. Chem. Soc.* 143 (4) (2021) 1968–1983.
- [49] E. Vyskočilová, L. Rezková, E. Vrbková, I. Paterová, L. Červený, Contribution to elucidation of the mechanism of preparation of 2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol, *Res. Chem. Intermed.* 42 (2016) 725–733.
- [50] Schrödinger Release 2020-3, Jaguar, Schrödinger, LLC, New York, NY, 2020.
- [51] J. Tirado-Reves, W.J. Jorgensen, Performance of B3LYP density functional methods for a large set of organic molecules, *Chem. Theory Comput.* 4 (2008) 297–306.
- [52] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu, *J. Chem. Phys.* 132 (2010), 154104.
- [53] Schrödinger Release 2020-3: MacroModel, Schrödinger, LLC, New York, NY, 2020.
- [54] H. Harjo, ModE Software for Modelling and Estimation, Profmath Oy, Helsinki, 2011.