**Heteropoly acid catalysts in Prins cyclization for the synthesis of Florol®**

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**Abstract**

H3PW12O40 heteropoly acid supported on SiO2 and its bulk acidic cesium salt Cs2.5H0.5PW12O40 are demonstrated to be highly active and recyclable solid catalysts for for the clean, high-yielding synthesis of Florol® by Prins cyclization of isoprenol and isovaleraldehyde. Florol®, a valuable floral odorant employed in a vast variety of commercial products, was obtained in ca. 80% yield under nearly ambient conditions. Dimethylcarbonate and diethylcarbonate used as green reaction media, low catalyst loadings and mild reaction conditions are important features that contribute to the sustainability of this method.

*Keywords:* Acid catalysis, Prins cyclization, Heteropoly acids, Florol®

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1. **Introduction**

The Prins reaction, involving acid-catalyzed condensation of alkenes with aldehydes, is a powerful tool in organic chemistry for the formation of carbon-carbon bonds. In particular, the reaction of homoallylic alcohols and aldehydes known as the Prins cyclization is one of the most efficient methods for the synthesis of tetrahydropyran derivatives [1,2]. Florol® (tetrahydro-2-isobutyl-4-methyl-2*H*-pyran-4-ol), the compound with a tetrahydropyran backbone,is a floral odorant developed by *Firmenich* and commercialized as a mixture of two racemic diastereoisomers. Florol® is described by *Firmenich* as a fragrance ingredient with “a fresh, soft and natural floral note” which can be applied “in almost all perfume types where it gives elegant floral diffusion without changing the character of the fragrance. It is a very stable and substantive building block that can also be used to replace less stable floral aldehydes” [3]. Florol® is also applied as intermediate to produce Clarycet®, another valuable commercial fragrance compound. Florol® can be extracted from petals of some flowers such as lily flowers; however, the natural sources cannot satisfy a high commercial demand for this compound [4]. Florol® used on the market is produced synthetically from petrochemicals by the intermolecular Prins cyclization of isoprenol (3-methyl-3-buten-1-ol) and isovaleraldehyde (3-methylbutanal) (Scheme 1) [4]. The details of the industrial manufacture of Florol® has not been disclosed, to our knowledge.

We could find several works in the open literature describing the preparation of Florol®. Enantiomerically enriched isomers of Florol® were prepared from hydroxy ketones through a six-step procedure using enzymatic catalysis [5,6]. Another multistep method involving a co-halogenation reaction allowed to obtain Florol® in ca. 45% yield starting from a natural mixture of geraniol and nerol [7]. The preparation of Florol® by the Prins cyclization of isoprenol and isovaleraldehyde was reported using sulfuric or sulfonic acids [8,9], strongly acidic ion-exchange resins such as Amberlyst [9–12], Fe-modified silica [13], MoO3-modified alumosilicates [14] and MoO3/SiO2 [15] as the catalysts.

Heteropoly acids (HPAs) of the Keggin series and their salts, for example H3PW12O40 (HPW) and Cs2.5H0.5PW12O40 (CsPW), constitute an important group of acidic catalysts for the sustainable production of many chemicals [16–18]. These compounds represent valuable substitutes to classical acid catalysts, such as mineral acids and ion-exchange resins, allowing to achieve faster reactions owing to their strong Brønsted acidity and often better reaction selectivity. The substitution of mineral acid catalysts by HPAs usually helps to solve the problems with undesirable side reactions and corrosion. HPA catalysts have been previously applied in Prins cyclization reactions [2,19–22]. In particular, HPW and H3PMo12O40 (HPMo) were used as homogeneous catalysts to synthesize Florol® in aqueous solutions and also anchored on MCM-41 aiming to develop a heterogeneous process [23]. However, because of the high solubility of these HPAs in water, almost complete leaching (98%) of both HPAs from 30 wt% HPA/MCM-41 catalysts to the liquid phase was observed after first catalyst run. The spent HPMo/MCM-41 catalyst containing residual HPMo and the supported catalyst with low HPMo loading (1.5 wt%) were stable to further leaching and promoted the formation of Florol®, albeit at a much lower rate.

Our previous works were focused on the use of HPA catalysts mainly for the conversions of terpenes, including the interactions of terpenic olefins with aldehydes [18,24–27]. Now we report that HPW supported on silica and bulk CsPW are highly efficient and recyclable heterogeneous catalysts for the Prins cyclization of isoprenol and isovaleraldehyde to give Florol®. The process works not only in conventional isooctane solvent, but also in “green” solvents such as diethylcarbonate and dimethylcarbonate which are comparable in eco-friendliness to water and ethanol [28,29]. As both CsPW and HPW are insoluble in the solvents used, the catalysts are stable towards leaching and provide fast substrate conversions at low catalyst loadings.

**2. Experimental**

Most of chemical products were from Aldrich. Aerosil 300 silica was from Degussa. The characterization of catalytic materials was performed by 31P MAS NMR (Bruker Avance DSX 400 NMR, spinning rate - 4 kHz, reference - 85% H3PO4), X-ray diffraction (XRD, Rigaku Geigerflex-3034 diffractometer with CuK radiation) and nitrogen physisorption (Micromeritics ASAP 2010 instrument). Contents of W and P in the catalysts were measured by inductively coupled plasma atomic emission spectroscopy (ICP-AES) (Spectro Ciros CCD).

The synthesis of silica-supported H3PW12O40 (HPW/SiO2) was performed by the treatment of Aerosil 300 with an aqueous HPW solution followed by drying at 130oC/0.2-0.3 Torr for 1.5 h, as described in [30]. The content of HPW in HPW/SiO2 was 20 wt%. The surface area of HPW/SiO2 was 200 m2g-1, the volume of pores 0.53 cm3g-1 and the average diameter of pores 14.4 nm. The 31P MAS NMR spectra of HPW/SiO2 exhibited only one signal at ca. –15 ppm, attributed to HPW [31]. XRD analysis revealed that HPW was highly dispersed on silica.

Cs2.5H0.5PW12O40 (CsPW) was synthesized using the previously described method [32] by adding the solution of Cs2CO3 in water (0.47 mol L-1) to the aqueous HPW solution (0.75 mol L-1). The precipitate formed was aged in aqueous mixture for 48 h at room temperature, dried at 45 °C/3 kPa (rotary evaporator) and then at 150 °C/0.1 kPa (oven) for 1.5 h. The surface area of the obtained material was 111 m2g-1, pore volume 0.07 cm3g-1, and average pore diameter 2.4 nm. The content of W and P in CsPW was verified by ICP. 31P MAS NMR spectra of CsPW showed the peak at ca. –15 ppm attributed to the Keggin structure. The acidic properties of the synthesized materials, CsPW and HPW/SiO2,were evaluated calorimetrically by pyridine and ammonia adsorption as reported in previous publications [33–35]. The data on catalyst characterization are given in Supplementary Material (Figures S1–S5).

The catalytic experiments were run in a 10 mL glass vessel using a reflux condenser to prevent evaporation of solvent. Typically, isoprenol (3-methyl-3-buten-1-ol, 0.75–2.25 mmol), isovaleraldehyde (3-methylbutanal, 0.75–7.50 mmol), dodecane (0.30 mmol), HPW/SiO2 (2–5 mg, 0.14 – 0.35 mol of HPW) or CsPW (2–15 mg, 0.60–4.5 mol) and the solvent (total volume of 5.0 mL) were placed into the reactor. The mixture was stirred magnetically at 15–70 oC. The reaction rate was not dependent on the stirring speed, suggesting the absence of mass transfer limitations. Periodically, the stirring was interrupted and after a partial catalyst decantation an aliquot of the reaction solution was taken for the analysis by gas chromatography (GC, Shimadzu 17 chromatograph, Carbowax 20 M, FID, column temperature, 220 °C; detector temperature,250 °C; split ratio, 50:1; carrier gas, H2; oven program: hold at 80 °C for 3 min, increasing the temperature from 80 to 220 ºC by 5 ºC/min, hold at 220 oC for 5 min). The selectivity and conversion were obtained by GC analysis and calculated based on isoprenol (limiting reagent), dodecane was employed as internal standard. Average rates of the isoprenol conversion were determined during the first 30 min and can be used only for rough comparison because the reactions in most cases showed relatively high conversions already at first sampling. To evaluate catalyst stability, leaching experiments were conducted by separating the catalyst by centrifugation (30 min, 6000 rpm) followed by introduction of extra amounts of reagents to the supernatant to continue the process. There was no further reaction observed which indicated that the catalyst was stable towards leaching. The concentration of tungsten in supernatant was verified by atomic absorption spectroscopy on a Hitachi-Z8200 instrument .

The products were separated after reaction by a column chromatography (silica gel 60, hexane/chloroform eluent) and identified by GC-MS (Shimadzu QP2010-PLUS, 70 eV), 1H and 13C-NMR (Bruker 400 MHz, CDCl3, TMS). Product characterization is given in the Supplementary Material.

1. **Results and discussion**

Two types of major products were observed after Prins reaction of isoprenol (**1**) with isovaleraldehyde (**2**) over the HPA catalysts (20%HPW/SiO2 or bulk CsPW): tetrahydropyran and dihydropyran derivatives (Scheme 2). The reaction did not proceed without catalysts. The products were separated by column chromatographyand identified by GC-MS and NMR.

Florol® (**3**) was formed as a mixture of two diastereoisomers, *syn* and *anti*, in the ratio of 2:1. The isomers differ from each other by the relative position of the hydroxy and isopropyl groups with respect to the tetrahydropyran ring as depicted in Scheme 2. The major differences in the chemical shifts in the NMR spectra of *syn* and *anti* Florol® were observed for carbons C-1 and C-6 and their hydrogens (Supplementary Material). Among the four enantiomers of the Florol® molecule, which possesses two asymmetric carbon atoms C-1 and C-3 (Scheme 2), two enantiomers of the *syn* diastereoisomer have much more intense odor and are mostly responsible for the flavor of commercial Florol® [6]. The Prins cyclization of isoprenol and isovaleraldehyde catalyzed by CsPW and HPW results preferentially (probably for steric reason) in the most valuable isomers of Florol®(ca. 70% *syn*)in which methyl and isopropyl groups are in *trans* positions. This isomer distribution is consistent with the literature [23].

Dihydropyran products were formed as a mixture of three isomers **4a**, **4b** and **4c** with different position of the C=C bond (Scheme 2). Judging from the structure, compounds **4a**, **4b** and **4c** can formally be seen as the products of dehydration of the Florol® molecule with hydrogen abstraction from one of three carbon atoms adjacent to carbon C-3, which is bound to the hydroxy group. However, the dehydration of the Florol® was not observed in our experiments. Under the conditions applied, the **4a**/**4b**/**4c** ratio was ca. 1:1:3, with isomer **4c** always predominant. Noteworthy, diacetal, which could be formed from isovaleraldehyde and isoprenol, was not observed among the products in appreciable amounts.

The relative amounts of tetrahydropyran and dihydropyran derivatives among the reaction products strongly depended on reaction variables; therefore, our efforts were focused on the maximization of the reaction selectivity for Florol®.

* 1. *Reactions in isooctane solutions*

The results on the reaction of isoprenol with isovaleraldehyde in isooctane catalyzed by HPW/SiO2 are summarized in Table 1. The reaction of isoprenol with 1 equivalent of isovaleraldehyde in the presence of only 0.04 wt% of HPW/SiO2 (per total reaction mixture) resulted in 80% isoprenol conversion in 4 h at 50 oC. The total selectivity for both isomers of Florol® was ca. 70%, the other products being dihydropyran derivatives **4** (Table 1, run 1). At a higher reaction temperature or with a higher catalyst loading, the reaction proceeded faster but without improving Florol® selectively (Table 1, runs 2 and 3). High substrate conversions were registered already at first GC sampling; the reaction rates given in Table 1 and 2 are only rough estimates.

The selectivity was significantly improved by increasing the concentration of isovaleraldehyde. The reaction of isoprenol with 5 equivalents of isovaleraldehyde gave 84% selectivity for Florol® (Table 1, run 4). The process could be performed at nearly ambient temperature without a decrease in selectivity (Table 1, run 5, 6 and 7). Varying the temperature and catalyst loading allowed to attain high reaction rates maintaining 82–85% selectivity for Florol® (isoprenol conversions were nearly complete in 0.5–1 h, Table 1, runs 8 and 9). As expected, the reactions occurred faster at higher temperatures (Table 1, cf. runs 1 and 2, runs 4, 5 and 6, runs 8 and 9). With the doubled initial concentration of isoprenol, Florol® could be synthesized in ca. 75% yield with only 0.04 wt% of the catalyst, which corresponds to 0.01 mol% of HPW. Isovaleraldehyde should be used in excess to ensure high reaction selectivity for Florol®. Non-reacted isovaleraldehyde can be recycled.

HPW is not soluble in isooctane; therefore, leaching problems were not expected. Nevertheless, such a possibility was checked. After run 4 (Table 1), the mixture was centrifuged to remove the catalyst. The remaining solution was not active for the conversion of isoprenol. The separated spent catalyst was washed with chloroform and employed in two sequential recycling runs (Table 1, runs 4a and 4b) showing approximately the same performance. Extra amounts of reactants were added to the filtrate, with no further reaction being observed.

*3.2. Reactions in dimethylcarbonate (DMC) and diethylcarbonate (DEC) solutions*

Further important advances in terms of sustainability were achieved by performing the process in diethylcarbonate and dimethylcarbonate solutions. Biodegradable and non-toxic DMC and DEC have been increasingly used as “green” solvents in many organic reactions [25,27,36–38]. These compounds possess prestigious sustainability rankings in the modern guides for solvent selection, next to water and ethanol [28,29]. It is worthwhile to note that boiling points of DMC (90 oC) and DEC (126 oC) are not high in comparison with other organic carbonatesto allow easy distillation from reaction products. The reactions catalyzed by heteropoly acid are often strongly dependent on the solvent [25]. Finding a green solvent, in which the reaction is fast and selective towards the desired product and, moreover, in which HPA will not leach from support, is a challenge. CsPW, which is insoluble in DMC and DEC, was used in our work to catalyze the process in these media. CsPW has high thermal stability, a large surface area (hence a large density of surface acid sites, much larger than in the bulk H3PW12O40), and its acid sites are almost as strong as those in the bulk H3PW12O40 [34]. Recently, we have successfully applied CsPW in related reactions of aldehydes with olefins in DEC and DMC, without having any leaching or recovery problems [24,25,27].

Examples for the Prins cyclization of isoprenol and isovaleraldehyde in DMC and DEC catalyzed by CsPW are given in Table 2. The reaction of isoprenol with 1 equivalent of isovaleraldehyde at a very low catalyst loading(0.04 wt%, 2 mg of the catalyst in 5.0 mL) showed a fast substrate conversion at nearly ambient temperature (88% conversion in 0.5 h at 30 oC, Table 2, run 1). However, Florol® was formed in only 42% yield, with main reaction products being dihydropyran derivatives **4**. With higher catalyst loading, the selectivity to Florol® did not change significantly (Table 2, run 2); whereas a 5-fold increase in isovaleraldehyde concentration increased the Florol® yield to 63% (Table 2, run 3; Fig. 1).

Attempts to optimize the reaction by varying the temperature and catalyst amounts did not result in better selectivity (Table 2, runs 4, 5, 6 and 7 vs. run 3). Increasing the reaction temperature to 70 oC resulted in a decrease in the Florol® selectivity (Table 2, run 7). However, increasing the concentration of isovaleraldehyde allowed to obtain Florol® in a higher yield (72%, Table 2, run 8; Fig. 1). In contrast, an increase in the concentration of isoprenol had no effect on the selectivity for Florol® (Table 2, runs 9 and 10 vs. run 8). In these reactions up to ca. 4000 mol of isoprenol per mole of CsPW was converted with ca. 75% selectivity for Florol® at nearly total conversion of the alcohol.

Considering that compounds **4a**, **4b** and **4c** can formally be seen as the products of the dehydration of the Florol® molecule, it could be suggested that the concentration of water would affect the distribution between the tetrahydropyran and dihydropyran products. Indeed, with 1 equivalent of added water (with respect to isoprenol), the process occurred much more selectively to Florol® giving less dihydropyrans **4** (Table 2, cf. runs 11 and 1; runs 12 and 3; runs 13 and 8, Fig. 1). In all these cases, the reaction proceeded slightly slower in the presence of water. The best result was obtained in run 13 (Table 2), which gave 80% yield of Florol® in 1 h at 30 oC, using a 10-fold excess of isovaleraldehyde and 1 equivalent of added water. Further addition of water (5 equivalents) strongly impeded the reaction and lead to a drastic drop in the Florol®selectivity (Table 2, run 14).

DEC, the compound with even higher sustainability ranking than DMC [29], was also found to be an appropriate solvent for the Prins cyclization of isoprenol and isovaleraldehyde (Table 2, runs 15–17). In DMC and DEC, the reactions were equaly facile (Table 2, cf. runs 3 and 15; runs 8 and 16; runs 13 and 17), allowing for 80% yield of Florol® under optimized conditions.

Although CsPW is insoluble in both polar and non-polar media, including low-polar DMC and DEC, we have tested possible leaching of active ingredients. After run 2 (Table 2), the mixture was centrifuged to remove the catalyst then extra amounts of the reactants were added to the filtrate and the process was continued. Further conversion did not occur in this run, thus affirming that the catalyst operated truly heterogeneously. The tungsten concentration in the filtrate was verified by atomic absorption spectroscopy, which indicated less than 1.5% leaching of CsPW. The separated catalyst was washed with chloroform and employed in two sequential recycling runs (Table 2, runs 2a and 2b) showing approximately the same performance.

*3.3. Reaction mechanism*

The generally accepted mechanism for Prins cyclization reactions can be applied to the condensation of isoprenol and isovaleraldehyde as depicted in Scheme 3 [1,9,23]. This mechanism involves protonation of aldehyde **2** by HPW or CsPW which possess strong Brønsted acidity. The protonated aldehyde reacts with the hydroxy group of homoallylic alcohol **1** to generate protonated hemiacetal **A**. Elimination of water from hemiacetalic intermediate **A** originates oxocarbenium ion **B**, which undergoes rearrangement via the interaction of the C=C bond with the oxocarbenium ion resulting in intermediate **C** (the Prins type cyclization). The interaction of the tertiary carbocation **C** with water gives the desired Florol® (**3**)and regenerates the catalyst. Alternatively, the intermediate carbocation **C** can undergo proton elimination from one of the adjacent positions to give three isomers of dihydropyran **4**, which differ from each other by the position of the double bond. Introducing extra amounts of water can help to decrease the contribution of dihydropyran derivatives **4** and increase the selectivity to Florol®. The explanation for the lower yield of Florol with CsPW could be the hydrophobicity of this catalyst. It is well documented that CsPW has a rather hydrophobic surface, whereas HPW is hydrophilic [16]. Hydrophilic silica support in HPW/SiO2 can also play a role as it can store water and provide it for the reaction with cation **C** to form **3**. It was found that a high excess of isovaleraldehyde is needed to attain a better Florol® selectivity. We suggest that the increase in Florol® selectivity with increasing aldehyde concentration (up to about 20 vol%) could be due to the change in the polarity of solution, which may affect the competition between deprotonation and hydration of carbocation **C** in favour of the hydration.

1. **Conclusions**

We have demonstrated that H3PW12O40 (HPW) supported on silica and its bulk acidic cesium salt Cs2.5H0.5PW12O40 (CsPW) are highly active and recyclable heterogeneous catalysts for the Prins condensation of isoprenol and isovaleraldehyde allowing for the clean, high-yielding synthesis of Florol®. Florol® is a floral odorant used in a vast variety of commercial products. The yields and selectivities obtained for Florol® as well as stereoselectivities for the most valuable syn isomer are among the best reported so far to our knowledge [8,10,11,23]. The reactions occur in green media, dimethylcarbonate or diethylcarbonate (both having high rankings in modern guides for solvent selection), which is an important advantage for sustainability of the method. Both CsPW and HPW are insoluble in the solvents employed. This allowed for the development of truly heterogeneous catalysts stable towards leaching at a high content of active ingredients in the solid. For this reason, the catalysts successfully operate at low loadings (0.04 wt%, 0.02–0.03 mol%) providing fast substrate conversions (0.5–1 h) under nearly ambient conditions. In contrast, most of the methods reported previously (cited in Introduction) require elevated temperatures (usually 70–90oC), long reaction times (usually several hours, up to 24 h) and high catalyst loadings.

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**Table 1**

Prins cyclization of isoprenol (**1**) and isovaleraldehyde (**2**) in isooctane solutions.a

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Run | Aldehyde **2** | HPW/SiO2 | *T* | Time | Conversion | Selectivity (%) | Ratec | TOFc |
|  | (mmol) | (µmol) | (°C) | (h) | (%) | **3** | **4**b | mmol L-1 h-1 | s-1 |
| 1 | 0.75 | 0.14 | 50 | 0.54 |  64 80 | 7273 | 2626 | 192 | 1.90 |
| 2 | 0.75 | 0.14 | 60 | 0.52 |  85 96 | 6562 | 3437 | 255 | 2.53 |
| 3 | 0.75 | 0.35 | 50 | 0.52 |  90 97 | 7070 | 2928 | 270 | 1.07 |
| 4d,e | 3.75 | 0.35 | 50 | 0.51 |  97100 | 8484 | 15 15 | 291 | 1.15 |
| 4ad | 3.75 | 0.35 | 50 | 0.51 |  95100 | 8383 | 15 15 | 285 | 1.13 |
| 4bd | 3.75 | 0.35 | 50 | 0.51 |  98100 | 8585 | 14 14 | 294 | 1.17 |
| 5 | 3.75 | 0.35 | 40 | 0.51 |  91 97 | 8285 | 1614 | 273 | 1.08 |
| 6 | 3.75 | 0.35 | 30 | 0.5 |  75 | 83 | 16 | 225 | 0.89 |
|  |  |  |  | 3 |  92 | 83 | 16 |  |  |
| 7 | 3.75 | 0.14 | 30 | 0.5 |  60 | 80 | 18 | 180 | 1.79 |
|  |  |  |  | 6 |  93 | 84 | 15 |  |  |
| 8 | 3.75 | 0.14 | 40 | 0.52 |  80 97 | 8585 | 1414 | 240 | 2.38 |
| 9 | 3.75 | 0.14 | 50 | 0.51 |  86100 | 8182 | 1717 | 258 | 2.56 |
| 10f | 3.75 | 0.14 | 70 | 0.5 |  96 | 75 | 24 | 576 | 5.71 |

a Isoprenol 0.75 mmol; HPW/SiO2 2–5 mg (0.14–0.35 µmol); solvent isooctane; total - 5.0 mL. The values for selectivity and conversion were based on isoprenol reacted. b **4a**+**4b**+**4c**. c Average rate of isoprenol conversion and average turnover frequency (mol of isoprenol converted per mol of a total amount of HPW in the catalyst per second) during the first 30 min, can be used only for rough comparison because the reactions in most cases showed relatively high conversions already at first sampling. d After run 4, the spent catalyst was re-used in runs 4a and 4b. e The filtrate was charged with additional amounts of the reactants, no further conversion occurred for 1 h. f Isoprenol 1.50 mmol.

**Table 2**

Prins cyclization of isoprenol (**1**) and isovaleraldehyde (**2**) in green solventsa

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Run | Alcohol **1** | Aldehyde **2** | CsPW | *T* | Time | Conversion | Selectivity (%) | Ratec | TOFc |
|  | (mmol) | (mmol) | (µmol) | (°C) | (h) | (%) | **3** | **4**b | mmol L-1 h-1 | s-1 |
| Solvent: dimethylcarbonate |  |
| 1 | 0.75 | 0.75 | 0.60 | 30 | 0.53 |  88100 | 4242 | 5757 | 264 | 0.61 |
| 2d,e | 0.75 | 0.75 | 4.50 | 30 | 0.5 | 100 | 36 | 63 | 300 | 0.09 |
| 2ad | 0.75 | 0.75 | 4.50 | 30 | 0.5 | 100 | 34 | 64 | 300 | 0.09 |
| 2bd | 0.75 | 0.75 | 4.50 | 30 | 0.5 | 100 | 35 | 65 | 300 | 0.09 |
| 3 | 0.75 | 3.75 | 0.60 | 30 | 0.5 | 100 | 63 | 36 | 300 | 0.69 |
| 4 | 0.75 | 3.75 | 1.50 | 30 | 0.5 | 100 | 62 | 37 | 300 | 0.28 |
| 5 | 0.75 | 3.75 | 0.60 | 15 | 0.5 |  95 | 65 | 33 | 285 | 0.66 |
| 6 | 0.75 | 3.75 | 0.60 | 50 | 0.5 | 100 | 62 | 37 | 300 | 0.69 |
| 7 | 0.75 | 3.75 | 0.60 | 70 | 0.5 | 100 | 49 | 45 | 300 | 0.69 |
| 8 | 0.75 | 7.50 | 0.60 | 30 | 0.5 | 100 | 72 | 26 | 300 | 0.69 |
| 9 | 1.50 | 7.50 | 0.60 | 30 | 0.5 |  99 | 76 | 23 | 594 | 1.38 |
| 10 | 2.25 | 7.50 | 0.60 | 30 | 2 |  97 | 72 | 26 | 720 | 1.67 |
| 11f | 0.75 | 0.75 | 0.60 | 30 | 0.54 |  50 84 | 6060 | 3938 | 150 | 0.48 |
| 12f | 0.75 | 3.75 | 0.60 | 30 | 0.52 |  78 97 | 7070 | 2929 | 234 | 0.54 |
| 13f | 0.75 | 7.50 | 0.60 | 30 | 0.51 |  90100 | 8080 | 1919 | 270 | 0.63 |
| 14g | 0.75 | 0.75 | 0.60 | 30 | 1 |  36 | - | - | 108 | 0.25 |
| Solvent: diethylcarbonate |  |
| 15 | 0.75 | 3.75 | 0.60 | 30 | 0.5 |  97 | 59 | 40 | 291 | 0.67 |
| 16 | 0.75 | 7.50 | 0.60 | 30 | 0.5 | 100 | 70 | 28 | 300 | 0.69 |
| 17f | 0.75 | 7.50 | 0.60 | 30 | 0.51 |  90100 | 8080 | 1818 | 270 | 0.63 |

a CsPW 2–15 mg (0.60–4.50 µmol); total - 5.0 mL. The values for selectivity and conversion were based on isoprenol reacted. b **4a**+**4b**+**4c**. c Average rate of isoprenol conversion and average turnover frequency (mol of isoprenol converted per mol of CsPW per second) during the first 30 min, can be used only for rough comparison because the reactions in most cases showed relatively high conversions already at first sampling. d After run 2, the spent catalyst was re-used in runs 2a and 2b. e The filtrate was charged with additional amounts of the reactants, no further conversion occurred for 1 h. f 0.75 mmol of H2O was added. g 3.75 mmol of H2O was added.



**Scheme 1.** Synthesis of Florol® by Prins cyclization of isoprenol (**1**) and isovaleraldehyde (**2**).



**Scheme 2.** The products of the Prins cyclization of isoprenol and isovaleraldehyde: Florol® (**3**) and dihydropyran derivatives **4a**, **4b** and **4c**.



**Scheme 3.** Mechanism suggested for the Prins cyclization of isoprenol (**1**) and isovaleraldehyde (**2**).



**Figure 1.** Prins cyclization of isoprenol (**1**) and isovaleraldehyde (**2**) to give Florol® (**3**): effect of added water and concentration of **2**. Conditions: **1** - 0.75 mmol; CsPW - 2 mg (0.60 µmol); solvent dimethylcarbonate; 30 oC; reaction mixture volume 5.0 mL; amounts of water and aldehyde **2** are given with respect to isoprenol **1**. The data correspond to runs 1, 3, 8, 11, 12 and 13 from Table 2. Selectivity for **3** is given for nearly complete conversions.