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# Iron(III) Chloride-Catalysed Acetalisation of $\alpha,\beta$ -Unsaturated Carbonyl Compounds Towards Odorant Ketals

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## ABSTRACT

Conjugation of a carbonyl function with a carbon-carbon double bond tends to limit the efficiency of conventional acetalisation procedures. In the present report, we describe our study of acetalisation of  $\alpha,\beta$ -unsaturated carbonyl compounds, either linear, cyclic, aromatic and aliphatic with various 1,2-diols. We found that a simple and sustainable protocol relying on  $\text{FeCl}_3$  as the catalyst could lead to the desired ketals with acceptable yields and excellent selectivities. This approach is presented as a practical alternative to conventional procedures and has been used to generate a series of odorant ketals.

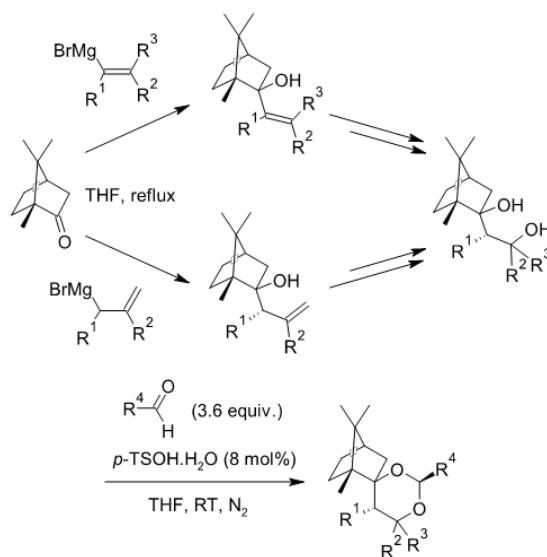
### Keywords:

Acetal  
Synthetic method  
Sustainable chemistry  
Fragrance chemistry

## 1. Introduction

The acetal group is frequently used to protect carbonyl function, and the acetalisation reaction is often a key step in the preparation of cosmetic, food and pharmaceutical products.<sup>1</sup> The most common example is the treatment of a carbonyl compound with ethylene glycol in the presence of *para*-toluene sulfonic acid (*p*-TSA) or other acidic reagents of catalysts to form the corresponding dioxolane.<sup>2,3,4</sup> Besides this simple textbook example, the protocol remains relatively restrictive due to the acid conditions required and the associated risks, such as the formation of by-products, the degradation of reactants and / or products, corrosion of reactors, the difficult recovery of the catalyst, and overall the poor sustainability profile. Chemists in academia and in industry are increasingly striving to move towards milder<sup>5</sup> and more environment friendly conditions.<sup>6</sup>

The synthesis of spiranic heterocycles can be seen as simpler than that of carbocycles due to the heteroatoms' innate nucleophilicity which facilitates the formation of the desired cycles by creating carbon-heteroatom bonds.<sup>7</sup> To design spiranic heterocycles, acetalisation, which makes it possible to form acetals from carbonyl compounds and diols, is thus a method of choice. These approaches have been used in fragrance chemistry, for example using camphor as the starting material and after the formation of vinylisoborneol or allylisoborneol subsequently transformed into corresponding 1,3-diols, spiro[bornyl-2,4'-(1,3-dioxanes)] could be formed by condensation with carbonyl partners of low molecular weight (Figure 1).<sup>8</sup>

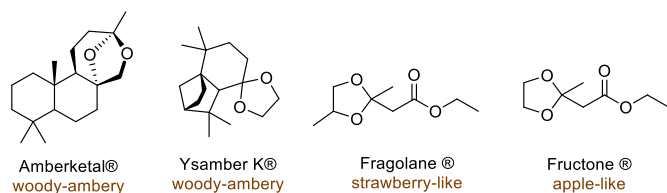


**Figure 1.** Acetals derived from camphor with interesting olfactory properties such as Belambre<sup>®</sup> (R<sup>1</sup>-R<sup>3</sup>=H, R<sup>4</sup>=iPr).

The olfactory properties of these particular spiranic acetals derived from camphor were described as woody, amber, earthy with fruity, balsamic, vetiver, floral, cedarwood, eucalyptus, pine, animal or carrot nuances depending on the substituents.

Polycyclic compounds with a dioxolane motif generally have ambery-woody odors, and several examples of those are used in perfumery. If combined with an ester function, the resulting odor tends to evolve towards fruity as for Fragolane<sup>®</sup> or Fructone<sup>®</sup>, and the presence of a single methyl substituent can drastically change the odor of the compound. By modulating substituents on this type of structure, olfactory variations can be observed and

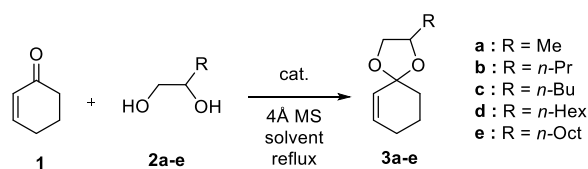
could result in the discovery of new ingredients for perfumery (Figure 2).<sup>7</sup>



**Figure 2.** Examples of acetals used as fragrance ingredients.

Some Brønsted acids as catalysts have shown good yields for this acetalisation reaction<sup>9-11</sup> but not in the case of unsaturated ketones because this type of catalyst represents a risk for these sensitive functions by isomerisation of the double bond. Indeed, the isomerisation of the double bond of unsaturated ketones was studied and it was found in particular that it increased with the decreasing  $pK_a$  of the acid used.<sup>12</sup> Some Lewis acids have also been studied such as  $BF_3 \cdot OEt$ ,<sup>13,14</sup>  $Cu(OTs)_2$ ,<sup>15</sup> or  $ZnCl_2$ <sup>14</sup> but not with  $\alpha,\beta$ -unsaturated substrates or upon the use of toxic reagents.

In this context, we have developed a sustainable methodology based on simple iron salts as catalysts to synthesize substituted acetals using several diols **2a-e** and various  $\alpha,\beta$ -unsaturated carbonyl compounds. As a model substrate, cyclohex-2-en-1-one **1** was used (Figure 3).



**Figure 3.** Acetalisation of cyclohex-2-en-1-one **1** by various diols studied in this work.

Once established, the protocol was applied to other  $\alpha,\beta$ -unsaturated carbonyl compounds in order to evaluate the substrate scope and generate a small library of molecules for olfactory evaluation.

Heterogenous catalysis could be an attractive acetal preparation method. Particularly, in combination with flow chemistry, this may pave a bumpy road to green synthesis in this area. Some of us recently showed how bimetallic nanocatalysis could be an efficient and selective glycerol acetalisation method.<sup>16</sup> At the same time, we engineered such bimetallic material into the 3D-stable easy recyclable catalytic beds ready for flow chemistry applications under standard and induction heating catalysis.<sup>17</sup> Accordingly, we also tested a library of nano-bimetallics as potential catalysts for these  $\alpha,\beta$ -unsaturated carbonyl compounds.

## 2. Results and discussion

Several Brønsted acid catalysts were initially tested on cyclohex-2-en-1-one **1** with various 1,2-diols **2a-d** in the presence of activated molecular sieves (MS) in order to trap the water formed during the reaction and thus shift the equilibrium towards the formation of acetal (Table 1).

**Table 1.** Acetalisation of cyclohex-2-en-1-one **1** with various diols in the presence of Brønsted acids and MS.<sup>a</sup>

Entry	1,2-diol	Catalyst	Time (h)	Conversion <sup>b</sup> Yield (%)
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1	<b>2a</b>	<i>p</i> -TSA	48	-
2	<b>2b</b>	<i>p</i> -TSA	24	-
3	<b>2c</b>	<i>p</i> -TSA	24	-
4	<b>2d</b>	<i>p</i> -TSA	24	67 (50) <sup>c</sup>
5	<b>2e</b>	<i>p</i> -TSA	24	79
6	<b>2e</b>	Amberlyst	48	25

<sup>a</sup>Reaction conditions: 5.0 mmol of cyclohex-2-en-1-one **1**, 5.0 mmol of 1,2-diol, 150 wt% of 4Å MS, 5 mol% of *p*-TSA in anhydrous petroleum ether (10 mL) or 230 mg of Amberlyst in THF (10 mL) at reflux. <sup>b</sup>Determined on unconverted 1,2-diol in <sup>1</sup>H-NMR of crude reaction mixture. <sup>c</sup>Isolated yield.

In the presence of *p*-TSA, with diols **2a-c** presenting rather short side chains (Me, *n*-Bu, *n*-Pr respectively) and thus of higher relative polarity, solubility issues were observed in petroleum ether and no reaction occurred (Table 1, entries 1-3). Better results were obtained with diols with a longer carbon chain such as *n*-hexyl **2d** and *n*-octyl **2e**, respectively (Table 1, entries 4, 5). In addition, the Amberlyst/THF system made it possible to observe the desired product only in the case of diol **2e**, but the reaction remained poorly effective (Table 1, entry 6).

Next, a solvent screening was carried out in order to solve the solubility issues and to improve conversions and yields (Table 2).

**Table 2.** Solvent screening in the acetalisation of cyclohex-2-en-1-one **1** with various diols in the presence *p*-TSA and 4Å MS.<sup>a</sup>

Entry	1,2-diol	solvent	Time (h)	Conversion <sup>b</sup> Yield (%)
1	<b>2c</b>	Et <sub>2</sub> O	48	-
2	<b>2e</b>	Et <sub>2</sub> O	48	-
3	<b>2c</b>	DCM	48	-
4	<b>2e</b>	DCM	48	-
5	<b>2c</b>	THF	48	-
6	<b>2e</b>	THF	24	16
7	<b>2c</b>	Toluene	48	-
8	<b>2e</b>	Toluene	24	32
9	<b>2c</b>	Cyclohexane	6	73 (16) <sup>c</sup>
10	<b>2e</b>	Cyclohexane	6	74 (37) <sup>c</sup>

<sup>a</sup>Reaction conditions: 2.5 mmol of cyclohex-2-en-1-one **1**, 2.5 mmol of 1,2-diol, 150 wt% of 4Å MS, 5 mol% *p*-TSA in 5 mL of refluxing solvent. <sup>b</sup>Determined on unconverted 1,2-diol in <sup>1</sup>H-NMR of crude reaction mixture. <sup>c</sup>Isolated yield.

In the case of Et<sub>2</sub>O and DCM, the expected acetal was not formed neither with hexane-1,2-diol **2c** or decane-1,2-diol **2e** due to solubility issues resulting in a heterogeneous reaction mixture in these solvents (Table 2, entries 1-4). In THF and toluene, diol **2c** was found unreactive and diol **2e** was found slightly reactive (Table 2, entries 5-8). On the other hand, the conversion of diol **2e** in these two solvents was significantly slower than in petroleum ether (see Table 1, entry 4). In cyclohexane though, excellent conversions up to 74% were obtained after only 6 hours of the reaction, either with **2c** or **2e** (Table 2, entries 9, 10), while side chain length was a limitation in petroleum ether.

Using of new solvent conditions, a screening of conventional catalysts used in the literature was then performed and compared to *p*-TSA in cyclohexane (Table 3). Procedures describing the use of Lewis acids such as  $ZnCl_2$  **Reference source not found**,<sup>2</sup> and  $BF_3 \cdot OEt_2$ ,<sup>13,15</sup> were adapted to cyclohex-1-en-2-one

**1** and pentane-1,2-diol **2c**. *p*-TSA remained still more effective than Lewis acids ZnCl<sub>2</sub> and BF<sub>3</sub>·OEt<sub>2</sub>. To this list, FeCl<sub>3</sub> **Reference source not found.**<sup>3</sup> was added, which has shown an excellent result with cyclohexanone<sup>18</sup> and decane-1,2-diol **2e**.<sup>19</sup>

**Table 3.** Screening of catalysts in the acetalisation of cyclohex-1-en-2-one **1** with **2c**.<sup>a</sup>

Entry	Solvent	T (°C)	Catalyst (equiv.)	Time (h)	Conversion <sup>b</sup> Yield (%)
1	Cyclohexane	reflux	<i>p</i> -TSA (0.1)	24	73 (16) <sup>c</sup>
2	Cyclohexane	reflux	ZnCl <sub>2</sub> (0.1)	5	57 (9) <sup>c</sup>
3	CHCl <sub>3</sub>	rt	BF <sub>3</sub> ·OEt <sub>2</sub> (1.0)	3	20 (11) <sup>c</sup>
4	AcOH	35-40	BF <sub>3</sub> ·OEt <sub>2</sub> (3.0)	3	53 (0) <sup>c</sup>
5	Cyclohexane	reflux	FeCl <sub>3</sub> (0.1)	7	73 (48) <sup>c</sup>
6 <sup>d</sup>	Cyclohexane	reflux	FeCl <sub>3</sub> (0.1)	24	80 (48) <sup>c</sup>
7	Toluene	reflux	FeCl <sub>3</sub> (0.1)	7	26 (16) <sup>c</sup>

<sup>a</sup>Reaction conditions: 5 mmol cyclohex-2-en-1-one **1**, 5 mmol pentane-1,2-diol **2c** and 150 wt% of 4Å MS in 10 mL solvent. <sup>b</sup>Determined on unconverted 1,2-diol in <sup>1</sup>H-NMR of crude reaction mixture. <sup>c</sup>Isolated yields. <sup>d</sup>Pentane-1,2-diol (2 equiv.).

In general, the conversions were relatively satisfactory for each of these reactions (except for entry 3). On the other hand, isolated yields of acetals were very low, even though no other product formation was observed in the crude reaction mixture during GC/MS analyses. The isomerisation of the double bond, leading to insoluble oligomerisation by-products, may be an explanation for this significant difference between conversion and isolated yield, as well as volatility. In addition, with equal conversions, FeCl<sub>3</sub> allowed to obtain a yield 3 times higher than *p*-TSA, in a significantly shorter reaction time (Table 3, entry 5). In the view of increasing the conversion as well as yield of the reaction, 2 equivalents of the diol were used, with only a slight effect on the conversion and no effect on the isolated yield of the product (Table 3, entry 6). Having in mind the mechanism of the reaction, Dean-Stark trapping of water in toluene was also tested. Unfortunately, the solvent change had a detrimental effect on the conversion as well as on the yield (Table 3, entry 7). In addition, FeCl<sub>3</sub> is a very cheap catalyst based on one of the most abundant metals on Earth's crust. These conditions are mild and make it a catalyst of choice for this acetalisation reaction in a context of sustainable chemistry.

To improve the yields and conversions of this reaction a new solvent screening was carried out, this time in the presence of FeCl<sub>3</sub> as catalyst (Table **Error! Reference source not found.**, for more details see also Table S2 in SI).

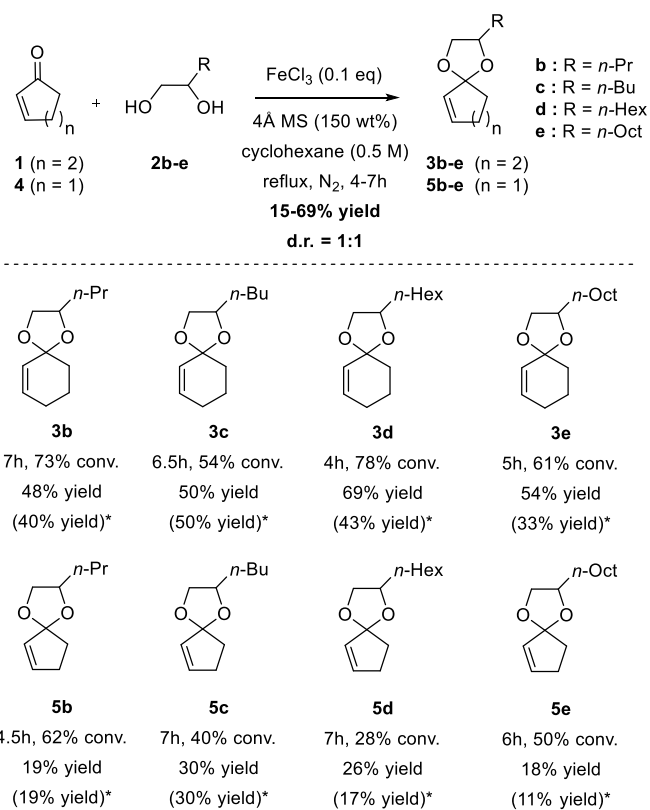
**Table 4.** Screening of solvents in the acetalisation of cyclohex-2-en-1-one **1** with decane-1,2-diol **2e** in the presence of FeCl<sub>3</sub>.<sup>a</sup>

Entry	Solvent	Time (h)	Conversion <sup>b</sup> Yield (%)
1	AcOEt	24	6
2	Toluene	25	27

3	THF	23	14
4	Petroleum ether	80	39
5	Hexane	21	23
6	Cyclohexane	5	61 (54) <sup>c</sup>

<sup>a</sup>Reaction conditions: 2.5 mmol cyclohex-2-en-1-one **1**, 2.5 mmol 1,2-diol **2e**, FeCl<sub>3</sub> (0.1 eq), 150 wt% of 4Å MS in 5 mL solvent. <sup>b</sup>Determined on unconverted 1,2-diol in <sup>1</sup>H-NMR of crude reaction mixture. <sup>c</sup>Isolated yields.

In AcOEt, toluene and THF (Table 4, entries 1-3), conversions remained very low for each of the 1,2-diols (for more details see Table S1 in SI). Conversions were higher in the case of nonpolar solvents such as petroleum ether and hexane (Table 4, entries 4 and 5). The reaction resulting in the loss of a water molecule, using distilled THF or drying petroleum ether beforehand for 48 hours on molecular sieves made sense but did not bring any improvement. In addition, the best conversions were again observed by performing the reaction in cyclohexane, which was confirmed as a surprising solvent of choice for this acetalisation reaction. Our optimized reaction conditions were applied on cyclohex-2-en-1-one **1** or cyclopent-2-en-1-one **4** and various diols **2b-e** leading to formation of acetals **3b-e** and **5b-e**, respectively (Figure 4).



Note: \* yield after column chromatography

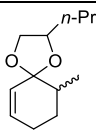
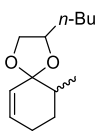
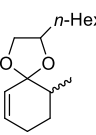
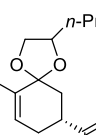
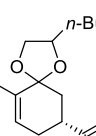
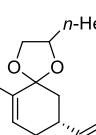
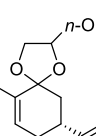
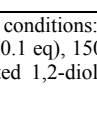

**Figure 4.** Acetalisation of cyclohex-2-en-1-one **1** and cyclopent-2-en-1-one **4** by various diols studied in this work.

It should be noted that FeCl<sub>3</sub> is completely insoluble in cyclohexane until the addition of both substrates with the reacting mixture turning immediately orange. This suggested that diols **2a-e** could act as bidentate ligands for Fe(III) species, allowing for the solubilization, catalytic activity, and chemoselectivity.

After purification on silica gel, acetals **3b-e** were isolated with yields between 48 and 69%, with an excellent chemoselectivity for this catalytic system, the expected acetals being the only

products formed. These acetals were found to have earthy and mushroom olfactory notes. With cyclopent-2-en-1-one **4** as the starting material, the reaction was found to be relatively fast, but conversions reached a maximum after 4-5 hours. This significant difference between conversion and yield was attributed to a degradation of the product. During purification on silica gel, the weak acidity of the silica gel could lead to a partial break down back to the ketone and starting 1,2-diol by hydrolysis. Finally, the volatility of the formed acetal has been also questioned. In this respect, the reaction was tested at a lower temperature (80 °C), but no conversion was observed. Formed acetals **5b-e** exhibited, like compounds **3b-e**, earthy, fresh, and mushroom notes. The acetalisation conditions were further applied to 6-methylcyclohex-2-en-1-one **6** and (*R*)-carvone (*R*)-**7** leading to formation of acetals **8** and **9**, respectively (Table 5).

**Table 5.** Acetalisation of **6** and (*R*)-**7** with diols **2b-e** catalysed by FeCl<sub>3</sub>.<sup>a</sup>

Entry	Product	FeCl <sub>3</sub> (equiv.)	Time (h)	Conversion <sup>b</sup> Yield (%)	d.r.
1	 <b>8b</b>	0.1	6	46 (27) <sup>c</sup>	29/11/50/10
2	 <b>8c</b>	0.1	5	54 (17) <sup>c</sup>	29/17/22/32
3	 <b>8d</b>	0.1	6	47 (21) <sup>c</sup>	26/12/37/25
4	 <b>9b</b>	0.1	26	62 (12) <sup>c</sup>	18/31/24/27
5	 <b>9c</b>	0.3	21	38 (27) <sup>c</sup>	16/31/26/27
6	 <b>9d</b>	0.1	26	56 (32) <sup>c</sup>	18/31/23/28
7	 <b>9e</b>	0.3	21	60 (21) <sup>c</sup>	20/29/20/31
8	 <b>9b</b>	0.2	31	37 (30) <sup>c</sup>	15/32/26/27
9	 <b>9c</b>	0.2	31	37 (21) <sup>c</sup>	26/12/37/25

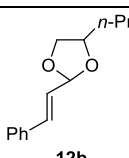
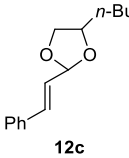
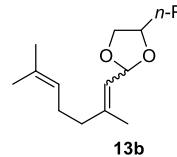
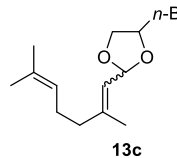
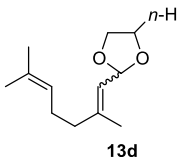
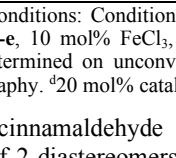
<sup>a</sup>Reaction conditions: 5 mmol substrate **6** or (*R*)-**7**, 5 mmol 1,2-diol **2b-d**, FeCl<sub>3</sub> (0.1 eq), 150 wt% of 4Å MS in 10 mL solvent. <sup>b</sup>Determined on unconverted 1,2-diol in <sup>1</sup>H-NMR of crude reaction mixture. <sup>c</sup>Isolated yields.

The presence of a stereogenic center on each of the two starting materials **6** and (*R*)-**7** and the creation of new stereogenic spiro quaternary carbon atom resulted in acetal formation as a mixture of 4 diastereomers. Diastereomeric ratios were determined by the integration of GC/MS peaks and showed that the reaction had little to no diastereoselectivity. As before, the difference between conversion and yield could be explained by the partial hydrolysis of acetal during chromatographic purification on silica gel. Mass loss could also be due to evaporation occurring during work-up.

The odor of isolated acetals **9b-d** was found to be close to that of the starting carbonyl compound (*R*)-**7** with notes remaining in the sweet mint area.

The acetalisation of linear  $\alpha,\beta$ -unsaturated aldehydes were carried out in order to continue exploring the scope and limitations of the reaction. In this context, two  $\alpha,\beta$ -unsaturated aldehydes were tested, *trans*-cinnamaldehyde **10** and citral **11**, an equimolar mixture of *E* and *Z* stereoisomers (Table 6). **Error! Reference source not found.**

**Table 6.** Acetalisation of **10** and **11** with diols **2b-e** catalyzed by FeCl<sub>3</sub>.<sup>a</sup>

Entry	Product	Time (h)	Conversion <sup>b</sup> Yield (%)	d.r.
1	 <b>12b</b>	5	24 (32) <sup>c</sup>	55/45
2	 <b>12c</b>	5	39 (35) <sup>c</sup>	56/44
3	 <b>13b</b>	24	76 (45) <sup>c</sup>	21/17/35/26
4	 <b>13c</b>	24	85 (32) <sup>c</sup>	22/19/34/25
5	 <b>13d</b>	5	71 (49) <sup>c</sup>	21/17/35/27
6 <sup>d</sup>	 <b>13d</b>	6	N.D.	N.D.

<sup>a</sup>Reaction conditions: Conditions: 5 mmol of substrate **10** or **11**, 5 mmol of 1,2-diol **2b-e**, 10 mol% FeCl<sub>3</sub>, 150 wt% of MS in 10 mL cyclohexane at reflux. <sup>b</sup>Determined on unconverted 1,2-diol. <sup>c</sup>Isolated yields after column chromatography. <sup>d</sup>20 mol% catalyst was used. N.D. = not determined.

*Trans*-cinnamaldehyde **10**, stereoisomerically pure, led to a mixture of 2 diastereomers, whose ratio was about 55/45 (Table 6, entries 1,2). The yields and conversions were low, in contrast with what was further observed for **13b-e** (derived from citral **11**). In these cases, good conversions and yields were obtained (Table 6, entries 3-5, 7) with 10 mol% FeCl<sub>3</sub>. Tentative reaction with 20 mol% catalyst led to many by-products (Table 6, entry

6). Indeed, side reactions of **11** in acidic medium led to the formation of various terpenes and terpenoids such as *p*-cymene (confirmed by GC/MS analysis). The creation of new stereogenic centers combined with the *E/Z* stereochemistry of the double bond led to the formation of 4 stereoisomers, distinctly visible on the GC/MS chromatogram.

In line with our previous work on metal-catalyzed reactions and our interest to transpose batch reactor protocols to continuous flow reactors,<sup>20-27</sup> we evaluated various solid catalysts such as supported metal nanoparticles or salts for this reaction on cyclohex-2-en-1-one **1**. These catalysts being heterogeneous and polar (with TiO<sub>2</sub> or SiO<sub>2</sub> as the support), initial catalyst testing was performed in anhydrous acetonitrile, methanol, and toluene, but without success. Among a large set of supported mono- or bimetallic NPs (with Re, Ru, Mo, W, Fe, Pd, Ni), only Fe and Re NPs gave some results, and most remarkably Re NPs (Table 7, entries 1-4, only the most interesting results are presented). For the sake of comparison, we also tested FeCl<sub>3</sub> supported on Montmorillonite which proved a useful catalyst for hydroalkoxylation reactions in previous studies performed in our laboratory.<sup>20,22</sup> The best results obtain with Fe-MMT gave a conversion of ca. 40% in 5 mL of cyclohexane, and yields higher than with Re/SiO<sub>2</sub>, but they remained lower than what was observed in homogenous conditions (Table 7, entries 5-8). It could be interesting to continue to investigate silica supported Re and Fe NPs, with a higher metal content.

**Table 7.** Acetalisation of cyclohex-2-en-1-one **1** with diol **2e** catalyzed by Fe-MMT and Re NPs supported on SiO<sub>2</sub>.<sup>a</sup>

Entry	Catalyst	Catalyst loading (mol%)	Time (h)	Conversion <sup>b</sup> Yield (%)
1	1%Re/SiO <sub>2</sub>	0.13	4.5	39 (2) <sup>c</sup>
2 <sup>d</sup>	1%Re/SiO <sub>2</sub>	0.13	4.5	23 (4) <sup>c</sup>
3	2%Re/SiO <sub>2</sub>	0.26	20	40 (14) <sup>c</sup>
4	2%Re/SiO <sub>2</sub>	0.26	4.5	52 (1) <sup>c</sup>
5	2.79%Fe/MMT	0.9	20	43 (21) <sup>c</sup>
6	2.79%Fe/MMT	1.25	20	37 (15) <sup>c</sup>
7	2.79%Fe/MMT	1.25	20	43 (15) <sup>c</sup>
8 <sup>d</sup>	2.79%Fe/MMT	1.25	20	14 (13) <sup>c</sup>

<sup>a</sup>Reaction conditions: 5 mmol of substrate, 5 mmol of 1,2-diol in 5 mL cyclohexane at reflux. <sup>b</sup>Determined on unconverted 1,2-diol. <sup>c</sup>Isolated yields. <sup>d</sup>20 mol% catalyst was used. <sup>e</sup>10 mL solvent was used.

### 3. Conclusions

The objective of this work was to synthesize spiranic acetals by setting up a simple and resource-sober acetalisation reaction specifically efficient with  $\alpha,\beta$ -unsaturated carbonyl compounds. After optimizing the reaction parameters (catalysts, solvents, time), a relatively efficient reaction protocol was established, based on the use of cheap and abundant FeCl<sub>3</sub> as the catalyst, with mild conditions and in accordance with the principles of sustainable chemistry. The scope of this methodology was evaluated using several types of substrates: various 1,2-diols and cyclic-unsaturated ketones and then extended to linear-unsaturated aldehydes. A total of 24 compounds were prepared with moderate to good yields but excellent selectivities since only acetal formation was observed. Control experiments with more conventional catalysts confirmed the consistency of the model and showed its superior efficiency, particularly on  $\alpha,\beta$ -unsaturated compounds.

A first basic olfactory evaluation of synthesized compounds showed that most bicyclic acetals have fresh and mushroom notes with low intensities. As for the acetals obtained from citral, the characteristic smell of citrus is still present although additional notes of ginger and mushrooms were also perceived.

## 4. Experimental

### 3.1. Materials and methods

<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Bruker Avance 400 spectrometer. Chemical shifts, reported in ppm, were referenced relative to TMS based on the residual signals of the solvents (<sup>1</sup>H and <sup>13</sup>C). Integration, multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broadened), and coupling constants (Hz) are given. <sup>13</sup>C NMR spectra reported in ppm ( $\delta$ ) relative to CDCl<sub>3</sub> at 77.16 ppm.

GC/MS analyses were carried out with an Agilent 7820A chromatograph coupled to an Agilent 5977B MS detector (Agilent, California). Samples were analysed on a capillary column SAPIENS-5MS (10 m  $\times$  0.10 mm  $\times$  0.10  $\mu$ m, 5% diphenyl-95% dimethylpolysiloxane, Teknokroma, Spain). Operating conditions: carrier gas: He, constant flow, 20 mL/min; injection temp., 250°C, injection volume, 0.2  $\mu$ L, split ratio, 1:50; temp. program: 50 °C held 1 min, 50 °C to 280 °C at 10 °C/min, then held isothermal (10 min), ion source temp., 230 °C; transfer line temp., 300°C; ionization energy, 70 eV; electron ionization mass spectra were acquired over the mass range of 35–550 amu, only the most abundant ions are given

Column chromatography was carried out employing silica gel (spherical, neutral, 63-200  $\mu$ m, Geduran Si 60, Merck KGaA).

High resolution mass spectrometry (HRMS) was performed by the CESAMO on a Agilent 7890A GC gas chromatograph coupled to a JEOL Accutof mass detector. Capillary GC analysis was performed on a TG-5MS (30m $\times$ 0.32mm i.d., 0.25mm) capillary column (5% phenyl methylpolysiloxane, 95% dimethylpolysiloxane) with helium as carrier gas. In the full-scan mode, field ionization (FI) mass spectra were recorded. The field ionization emitter was at 10 kV voltage, with 40 mA emitter current on a 10 $\mu$ m emitter.

Spectral data of one example of the main products are given below. Detailed optimizations, data and spectra for all the compounds presented in this paper are provided in supporting information.

### 3.2. Experimental procedures

A solution of the  $\alpha,\beta$ -unsaturated carbonyl substrate **1**, **4**, **6**, (*R*)-**7**, **10**, **11** (5 mmol, 1 eq.), catalyst FeCl<sub>3</sub> (83.61 mg, 0.5 mmol, 0.1 eq.) and 4Å molecular sieves (150 wt%) in cyclohexane (0.5 M, 10 mL) was prepared. To this solution the suitable 1,2-diol **2a-e** (5 mmol, 1 eq.) was added. Then, the reaction mixture was refluxed under N<sub>2</sub> atmosphere for the time specified for each compound. Once the reaction was completed, it was filtrated, neutralised with saturated aqueous solution of NaHCO<sub>3</sub> (10 mL) and extracted with diethyl ether (3 $\times$ 20 mL). Collected organic layers were washed with brine (50 mL), dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated under reduced pressure. The crude products were then purified by chromatography on silica gel (conditions are specified for each compound) to afford target acetals **3b-e**, **5b-e**, **8b-d**, **9b-e**, **12b-c**, **13b-d**. Representative examples for each combination are given below (the whole set of products is presented in Supplementary data).

**2-propyl-1,4-dioxaspiro[4.5]dec-6-ene (3b):** Following general procedure (stirring 7 h), product **3b** was isolated after column chromatography (eluent: Pentane/Et<sub>2</sub>O = 99:1, R<sub>f</sub> = 0.54) as a colourless liquid (273 mg, 40%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) mixture of 2 diastereoisomers, δ 5.98 – 5.89 (2×dt, *J* = 10.1 Hz, 2H, H<sub>2</sub>, H<sub>2</sub>'), 5.65 – 5.54 (2×dt, *J* = 10.1 Hz, 2.0 Hz, 2H, H<sub>3</sub>, H<sub>3</sub>'), 4.17 – 4.02 (m, 4H, 2×H<sub>7</sub>, 2×H<sub>7</sub>'), 3.55 – 3.47 (2×t, *J* = 7.5 Hz, 2H, H<sub>8</sub>, H<sub>8</sub>'), 2.04 – 1.99 (m, 4H, 4×H<sub>X,X'</sub>), 1.84 – 1.74 (m, 8H, 8×H<sub>X,X'</sub>), 1.69 – 1.61 (m, 3H, 3×H<sub>X,X'</sub>), 1.54 – 1.41 (m, 3H, 3×H<sub>X,X'</sub>), 1.38 – 1.29 (m, 2H, 2×H<sub>X,X'</sub>), 0.94 (t, *J* = 7.1 Hz, 6H, H<sub>11</sub>, H<sub>11</sub>'). (H<sub>X,X'</sub>: H<sub>4</sub>/H<sub>5</sub>/H<sub>6</sub>/H<sub>9</sub>/H<sub>10</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) mixture of 2 diastereoisomers, δ 133.1, 132.1, 128.8, 127.9, 105.8 (2×C), 76.1, 75.9, 69.5, 69.4, 35.7, 35.6, 34.9, 33.8, 25.0, 24.9, 20.9, 20.8, 19.17, 19.14, 14.2 (2×C). **HRMS (FI)** calcd. for [M<sup>+</sup>] C<sub>11</sub>H<sub>18</sub>O<sub>2</sub><sup>+</sup> m/z 182.13068, found 182.13098, Δ = 1.67 ppm.

**2-propyl-1,4-dioxaspiro[4.4]non-6-ene (5b):** Following general procedure (stirring 4.5 h), product **5b** was isolated after column chromatography (eluent: Pentane/Et<sub>2</sub>O = 98:2, R<sub>f</sub> = 0.35) as a pale-yellow liquid (158 mg, 19%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) mixture of 2 diastereoisomers, δ 6.11 – 6.04 (2×dt, *J* = 5.6 Hz, 2.4 Hz, 2H, H<sub>2</sub>, H<sub>2</sub>'), 5.76 – 5.67 (2×dt, *J* = 5.7 Hz, 2.2 Hz, 2H, H<sub>3</sub>, H<sub>3</sub>'), 4.12 – 4.02 (m, 4H, 2×H<sub>6</sub>, 2×H<sub>6</sub>'), 3.52 – 3.45 (m, 2H, H<sub>7</sub>, H<sub>7</sub>'), 2.43 – 2.38 (m, 4H, 4×H<sub>X,X'</sub>), 2.12 – 2.03 (m, 4H, 4×H<sub>X,X'</sub>), 1.70 – 1.60 (m, 2H, 2×H<sub>X,X'</sub>), 1.54 – 1.32 (m, 6H, 6×H<sub>X,X'</sub>), 0.95 (2×t, *J* = 7.2 Hz, 6H, H<sub>10</sub>, H<sub>10</sub>'). (H<sub>X,X'</sub>: H<sub>4</sub>/H<sub>5</sub>/H<sub>8</sub>/H<sub>9</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) mixture of 2 diastereoisomers, δ 137.6, 136.7, 131.4, 130.8, 120.6, 120.5, 76.4, 76.1, 69.9, 69.8, 35.7, 35.6, 35.1, 34.9, 29.8, 29.6, 19.1 (2×C), 14.24, 14.24. **HRMS (FI)** calcd. for [M<sup>+</sup>] C<sub>10</sub>H<sub>16</sub>O<sub>2</sub><sup>+</sup> m/z 168.11503, found 168.11519, Δ = 0.95 ppm.

**2-propyl-10-methyl-1,4-dioxaspiro[4.5]dec-6-ene (8b):** Following general procedure (stirring 6 h), product **8b** was isolated after column chromatography (eluent: Pentane/Et<sub>2</sub>O = 95:5, R<sub>f</sub> = 0.59) as a pale-yellow liquid (261 mg, 27%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) mixture of 4 diastereoisomers, δ 5.88 – 5.80 (m, 1H, H<sub>3</sub>), 5.68 – 5.49 (4×dt, *J* = 10.0 Hz, 2.1 Hz, 1H, H<sub>2</sub>), 4.20 – 3.95 (m, 2H, H<sub>8</sub>), 3.61 – 3.29 (m, 1H, H<sub>9</sub>), 2.04 – 2.00 (m, 2H, H<sub>X</sub>), 1.94 – 1.86 (m, 1H, H<sub>6</sub>), 1.73 – 1.30 (m, 6H, H<sub>X</sub>), 0.86 – 0.91 (m, 6H, H<sub>7</sub>, H<sub>12</sub>). (H<sub>X</sub>: H<sub>4</sub>/H<sub>5</sub>/H<sub>10</sub>/H<sub>11</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) mixture of 4 diastereoisomers, δ 131.6, 131.1, 131.0, 130.7, 129.2, 128.8, 128.1, 127.9, 107.9, 107.8, 107.78, 107.75, 77.2, 77.01, 75.9, 75.5, 70.6, 70.4, 69.9, 69.8, 37.48 (2×C), 37.43, 37.1, 36.4, 35.7, 35.5, 34.6, 28.4, 28.3, 28.2, 28.0, 24.9, 24.4, 24.2, 23.8, 19.2, 19.16, 19.15, 19.12, 14.26, 14.22, 14.21, 14.17, 14.14, 14.10, 14.07, 14.02. **HRMS (ESI)** calcd. for [M+H<sup>+</sup>] C<sub>12</sub>H<sub>21</sub>O<sub>2</sub><sup>+</sup> m/z 197.15361, found 197.15323, Δ = -1.92 ppm.

**(9R)-6-methyl-9-(prop-1-en-2-yl)-2-propyl-1,4 dioxaspiro [4.5]dec-6-ene (9b):** Following general procedure (stirring 21 h), product **9b** was isolated after column chromatography (eluent: Pentane/Et<sub>2</sub>O = 95:5, R<sub>f</sub> = 0.59) as a pale-yellow liquid (319 mg, 27%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) mixture of 4 diastereoisomers, δ 5.73 – 5.65 (m, 1H, H<sub>3</sub>), 4.72 – 4.72 (m, 2H, H<sub>9</sub>), 4.27 – 4.05 (m, 2H, H<sub>11</sub>), 3.69 – 3.44 (m, 1H, H<sub>12</sub>), 2.51 – 2.37 (m, 1H, H<sub>5</sub>), 2.16 – 1.81 (m, 3H, H<sub>X</sub>), 1.75 – 1.67 (m, 6H, H<sub>8</sub> et H<sub>10</sub>), 1.63 – 1.30 (m, 5H, H<sub>X</sub>), 0.97 – 0.92 (m, 3H, H<sub>15</sub>). (H<sub>X</sub>: H<sub>4</sub>/H<sub>6</sub>/H<sub>13</sub>/H<sub>14</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) mixture of 4 diastereoisomers, δ 148.97, 148.94, 148.91, 148.8, 134.8, 134.7, 134.3, 133.9, 128.7, 128.5, 128.2, 128.0, 109.2, 109.18, 109.14, 109.0, 108.53, 108.50, 108.4, 108.3, 77.9, 77.8, 76.0, 75.4, 70.9, 70.8, 70.4, 69.7, 41.1, 40.2, 40.08, 40.05, 39.7, 39.6, 39.0, 38.9, 36.7, 35.67, 35.61, 34.5, 31.14, 31.10, 31.0 (2×C), 20.78, 20.73, 20.72, 20.6, 19.24, 19.22, 19.1, 16.6, 16.5, 16.2, 16.0, 14.3,

14.27, 14.25. **HRMS (FI)** calcd. for [M<sup>+</sup>] C<sub>15</sub>H<sub>24</sub>O<sub>2</sub><sup>+</sup> m/z 236.17763, found 236.17815, Δ = 2.22 ppm.

**4-propyl-2-styryl-1,3-dioxolane (12b):** Following general procedure (stirring 5 h), product **12b** was isolated after column chromatography (eluent: Pentane/Et<sub>2</sub>O = 90:10, R<sub>f</sub> = 0.45) as a transparent liquid (355 mg, 32%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) mixture of 2 diastereoisomers, δ 7.37 – 7.34 (m, 2H, H<sub>5</sub>, H<sub>5</sub>'), 7.28 – 7.18 (m, 3H, H<sub>6</sub>, H<sub>6</sub>', H<sub>7</sub>'), 6.74 – 6.68 (m, 1H, H<sub>3</sub>), 6.16 – 6.09 (m, 1H, H<sub>2</sub>), 5.49 – 5.36 (m, 1H, H<sub>1</sub>), 4.14 – 3.94 (m, 2H, H<sub>9</sub>), 3.57 – 3.44 (m, 1H, H<sub>10</sub>), 1.70 – 1.30 (m, 4H, H<sub>11</sub>, H<sub>12</sub>), 0.91 (t, *J* = 7.0 Hz, 3H, H<sub>13</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) mixture of 2 diastereoisomers, δ 135.98, 135.94, 135.1, 134.4, 128.62 (2×C), 128.61 (2×C), 128.38, 128.33, 127.04 (2×C), 127.00 (2×C), 125.7, 125.6, 104.10, 103.3, 77.1, 76.1, 70.5, 69.9, 35.5, 35.3, 19.17, 19.14, 14.14 (2×C).

**2-(2,6-dimethylhepta-1,5-dien-1-yl)-4-propyl-1,3-dioxolane (13b):** Following general procedure (stirring 24 h), product **13b** was isolated after column chromatography (eluent: Pentane/Et<sub>2</sub>O = 90:10, R<sub>f</sub> = 0.41) as a pale-yellow liquid (536 mg, 45%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) mixture of 4 diastereoisomers, δ 5.59 – 5.47 (m, 1H, H<sub>1</sub>), 5.25 – 5.21 (m, 1H, H<sub>6</sub>), 5.12 – 5.05 (m, 1H, H<sub>2</sub>), 4.15 – 3.89 (m, 2H, H<sub>11</sub>), 3.51 – 3.41 (m, 1H, H<sub>12</sub>), 2.14 – 1.99 (m, 4H, H<sub>4</sub>, H<sub>5</sub>), 1.74 (s, 3H, H<sub>X</sub>), 1.65 (m, 3H, H<sub>X</sub>), 1.57 (s, 3H, H<sub>X</sub>), 1.53 – 1.22 (m, 4H, H<sub>13</sub>, H<sub>14</sub>), 0.95 – 0.90 (m, 3H, H<sub>15</sub>). (H<sub>X</sub>: H<sub>8</sub>/H<sub>9</sub>/H<sub>10</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) mixture of 4 diastereoisomers, δ 144.7, 144.5, 144.3, 144.1, 132.06, 132.04, 131.7, 123.7, 123.6, 122.4, 122.3, 121.2, 121.1, 100.3, 99.9, 99.5, 99.1, 76.6, 75.8, 75.7, 70.55, 70.52, 69.6, 69.5, 39.51, 39.51, 35.58, 35.55, 35.50, 32.6, 32.5, 26.9, 26.1, 26.0, 25.63, 25.61, 23.5, 19.05, 19.03, 19.01, 17.6, 16.9, 16.8, 14.05, 14.04. **HRMS (FI)** calcd. for [M<sup>+</sup>] C<sub>15</sub>H<sub>26</sub>O<sub>2</sub><sup>+</sup> m/z 238.19328, found 238.19400, Δ = 3.01 ppm.

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## Author Contributions

Conceptualization, S.A.; methodology, S.A.; experimental work, E.T., A.R., K.P., D.L., M.K. and L.G. writing—original draft preparation, L.G. and S.A.; writing—review and editing, all authors.; supervision, L.G., J.P. and S.A.; project administration, L.G. and S.A.; funding acquisition, S.A. All authors have read and agreed to the published version of the manuscript.

## 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.

## Appendix A. Supplementary data

Detailed procedures, description of products, NMR spectra and HRMS data.

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