# Green Chemistry

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### Synthesis of functionalized tetrahydrofuran derivatives from 2,5dimethylfuran through cascade reactions

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A three-step strategy is proposed for the functionalization of the methyl group of 2,5-dimethylfuran, encompassing the ring opening of 2,5-dimethylfuran to 2,5-hexanedione, its further aldol condensation with aldehydes, and hydrogenation-cyclization of the condensation intermediate to generate alkylated tetrahydrofuran. Active and selective catalysts could be identified for the aldol condensation and hydrogenation-cyclization reactions.

#### Introduction

Due to the depletion of fossil reserves, lignocellulosic biomass, mostly composed of carbohydrates (75%), has gained great interest as a huge reservoir of renewable carbon with an annual production estimated at 180 billion metric tons per year.<sup>1</sup> Hence, current research programs target the conversion of carbohydrates into value added chemicals.<sup>2</sup> For instance, lactic, itaconic and succinic acids, as well as ethanol and 1,3propanediol, are industrially produced by the fermentation of carbohydrates.<sup>3</sup> Other catalytic routes convert carbohydrates into sorbitol,<sup>4</sup> xylitol,<sup>5</sup> furfural,<sup>6</sup> ethylene glycol,<sup>7</sup> and alkylpolyglycosides.<sup>8</sup>

Among the different intermediates that can be produced from carbohydrates, furanic compounds hold a strategic place. In particular, furfural and 5-hydroxymethylfurfural (HMF) can be synthesized by the acid-catalyzed dehydration of hexoses and pentoses,<sup>6,9</sup> respectively. These two bio-based furanic derivatives can be further oxidized, hydrolyzed or reduced to

generate valuable downstream chemicals,<sup>10</sup> such as methyland dimethylfuran or tetrahydrofuran,<sup>11</sup> levulinic acid,  $\gamma$ -valerolactone,<sup>12</sup> and diketones,<sup>13</sup> as well as furoic, furandicarboxylic<sup>14</sup> maleic,<sup>15</sup> and fumaric acids,<sup>16</sup> and even hydrocarbons.<sup>17</sup>

Despite their great potential, the amount of furanic derivatives potentially synthesized from carbohydrates is rather limited. Functionalizing bio-based furanic derivatives in a minimum number of synthetic steps is of huge interest to increase the molecular diversity and complexity. It is well established that the nature of the chemical group on the 2 position of the furanic ring will govern the reactivity of the 5 position of furans. In this view, one interesting reaction is the functionalization of furanic compounds with alcohols and olefins, which has been seldom explored. The Friedel-Crafts reaction can be employed for alkylating aromatic substrates using  $\pi$ -activated alcohols or the corresponding esters in the presence of Lewis acid catalysts. However, in the case of (alkyl) furans, the reaction often leads to polymerization reactions and requires the use of strong acids (e.g., HClO<sub>4</sub>, CF<sub>3</sub>SO<sub>3</sub>H, HBF<sub>4</sub>), noble metal salts (PdCl<sub>2</sub>, triflates) and hazardous solvents (e.g., dichloromethane, dioxane).18 Furans can also undergo alkylation reactions with alkenes following a Heck-type reaction mechanism. Nonetheless, the reaction requires Pd(II) salts or complexes, oxidants (e.g., copper salts, benzoquinone, pyridine) to regenerate Pd(II) from Pd<sup>0.19</sup>

As an alternative to alkylation reactions, herein we report a catalytic route for selectively functionalizing the methyl group of an important furanic derivative, *i.e.* dimethylfuran (DMF). DMF can be produced either by the hydrogenolysis of HMF,<sup>11</sup> or from fructose through directly а tandem dehydration/hydrogenolysis reaction.20 Despite the fact that conversion of DMF to *p*-xylene through the Diels-Alder/dehydration sequence was extensively reported,<sup>21</sup> only few examples are related to other synthetic manipulations.<sup>22</sup> Therefore, the exploration of strategically new reactivity of DMF to functionalize biomass derived furans appears to be of importance. The strategy presented here

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consists of three consecutive steps (Scheme 1): (i) acidcatalyzed ring opening of DMF to 2,5-hexanedione (HxD), (ii) basic-catalyzed aldol condensation of HxD with aldehydes, and (iii) hydrogenation-cyclization of the functionalized HxD to a tetrahydrofuran derivative. To the best of our knowledge this is the first time that the functionalization of the methyl group of DMF is reported.



#### Experimental

#### Chemicals

Benzaldehyde ( $\geq$ 99.5%), 2,5-dimethylfuran (99%) and 2,5hexanedione ( $\geq$ 98%), all supplied by Sigma-Aldrich, were used as reagents. Benzaldehyde was freshly distilled under vacuum before use and stored under nitrogen at 4 °C, whereas the other reagents were used as received. Hydrogen (>99.99%) was procured from Air Liquide and was used for the hydrogenationcyclization reactions. Silicagel (60 Å, 40-63 µ), provided by Carlo Erba, was used for purifying the reaction products. 1-Butanol (99.8%), chloroform-d (99.8%), dichloro-methane ( $\geq$ 99.8%), dimethyl sulfoxide-d6 (99.9%), ethyl acetate (99.5%) and toluene ( $\geq$ 99.5%), all supplied by Sigma-Aldrich, were used as solvents. Besides, acetone ( $\geq$ 99.8%) and a mixture of heptane isomers (pure) were procured from Carlo Erba, while ethanol absolute ( $\geq$ 99.98%) was provided by VWR Chemicals. All the solvents were used as received without further purification.

Amberlyst<sup>®</sup>A26 (grey beads, Sigma-Aldrich), Amberlyst<sup>®</sup>A15 (pink beads, Sigma-Aldrich) and Aquivion<sup>®</sup>PW98 (white powder, Solvay) were used in the acid-base catalyzed reactions without activation.  $Mg_6Al_2(CO_3)(OH)_{16}\cdot 4H_2O$  (white powder, Sigma-Aldrich) was calcined and activated before use using the protocols described below. Pd/C, Pt/C and Ru/C, all with 5 wt.% metal loading, were supplied by Johnson Matthey. Phosphomolybdic acid was supplied by Sigma Aldrich.

#### Activation of Mg<sub>6</sub>Al<sub>2</sub>(CO<sub>3</sub>)(OH)<sub>16</sub>·4H<sub>2</sub>O

First,  $Mg_6Al_2(CO_3)(OH)_{16}\cdot 4H_2O$  was calcined to regenerate the metal oxides. The sample was heated to 450 °C at a rate of 5 °C/min, held at 450 °C for 3 h, and cooled down to room temperature under dry nitrogen. Subsequently, the calcined sample was subjected to either gas or liquid-phase rehydration

according to reported protocols.<sup>23</sup> On the one handrie gase phase rehydration, the sample was flowed with the wet fitting that at room temperature for 24 h. On the other hand, in liquidphase rehydration, the sample was introduced into ultrapure water and stirred at room temperature for 2 h, followed by filtration, drying under vacuum, and storage under nitrogen atmosphere.

#### **Catalytic tests**

#### Aldol condensation of HxD with benzaldehyde (bzd)

The aldol condensation reaction of HxD with bzd was performed in a 10-mL round bottom glass flask with a screw-sealing cap. In a typical test, a given amount of catalyst was introduced into the reaction flask under magnetic stirring. Then, 10 mmol of bzd (around 1.06 g, 2 equiv with respect to HxD) were added, followed by 5 mmol of HxD (around 0.57 g). In the case of the use of solvent, 6 mL of ethanol, toluene or 1-butanol were added. After sealing, the reactor was placed in an oil bath, the reactor mixture was stirred and the temperature was adjusted to the desired value.

#### One-pot hydrolysis of DMF with aldol condensation with bzd

The reaction was performed in a 10-mL round bottom glass flask with a screw-sealing cap. In a typical one-pot reaction between DMF and bzd, two solid acid and basic catalysts, i.e. PW98 and A26, respectively, were added to the reaction flask. Then, 20 wt% of ultrapure water (with regards to DMF) were introduced, followed by 15 mmol of bzd (around 1.59 g, 3 equiv with respect to DMF) and 5 mmol of DMF (around 0.48 g). The reactor was further introduced into a pre-heated oil bath and the reaction mixture was stirred.

#### Hydrogenation-cyclization of HxD

The hydrogenation-cyclization reaction of HxD was performed in a stainless-steel autoclave reactor from Taiatsu (30 mL). In a typical reaction, around 0.4 g of HxD (2 mmol) was loaded into the autoclave. Next, the catalyst pre-reduced under hydrogen at 180 °C for 30 min using a heating ramp of 5 °C/min, and 2 mL of absolute ethanol were added to the autoclave. The autoclave was then sealed, purged with hydrogen for three times, pressurized with hydrogen at room temperature, and heated to the desired temperature. After the reaction, the reactor was cooled down to room temperature.

#### Analytical methods

Gas chromatography analyses of the reactants and products were performed on a Varian Bruker 450 GC equipped with a flame ionization detector (FID) and a DB-WAX UI column (30 m x 0.32 mm x 0.25  $\mu$ m). The calibration was performed using biphenyl as internal standard and acetone as solvent.

Flash chromatography was used to separate the reaction products using a silicagel column. Silicagel was placed in a beaker with an elution of heptane and ethyl acetate (80:20 v/v) and stirred with a glass stick to degas the gel. Then, the gel was transferred to a glass column. The mixture of condensation products was first concentrated by rotation evaporation and re-

diluted with dichloromethane before introduction into the top of the column. An elution mixture of heptane and ethyl acetate (80: 20 v/v) was used to separate the different compounds. In the case of hydrogenation products, the silicagel was prepared with heptane, and the product mixture was re-diluted using silica powder (solid deposition method), because one of the products was relatively apolar. Gradient elution was employed to separate the different products with a heptane/ethyl acetate volume ratio varying from 100 : 0 to 50 : 50. After separation, glass tubes were used to collect the different product fractions, while Thin-Layer Chromatography (TLC) was used to track the entire separation. TLC was performed on 0.20 mm silicagel 60 with fluorescent indicator UV<sub>254</sub> plates. The TLC plates were revealed by reaction with a 20% v/v phosphomolybdic acid solution in ethanol. After collecting the different product fractions, the solvent was removed by rotation evaporation, and solvent traces were further dried under high vacuum.

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of the different products were recorded on a Bruker Advance 300 MHz NMR spectrometer. Chemical shifts were given with respect to TMS.

#### **Catalyst characterization**

Thermogravimetric analysis (TGA) was used to characterize the nature of adsorbed species on the spent catalysts after reaction. The thermal profiles were measured on a SDT-Q600 instrument with a flow gas system. The catalysts (~10 mg in a Pt crucible) were treated from room temperature to 700 °C with a heating rate of 10 °C.min<sup>-1</sup> at 100 mL(STP).min<sup>-1</sup> air flow.

FT-IR spectra were measured on the spent catalysts by dispersing the catalysts in KBr (1 mg catalyst in 150 mg KBr). The spectra were measured from 500-4000 cm<sup>-1</sup> on a Perkin Elmer One FT-IR instrument with 4 cm<sup>-1</sup> resolution. Each spectrum was measured using 30 scans. Before analysis, the samples were washed with warm ethanol (3 times), dried in an oven overnight at 60 °C, and grinded.

The nature and surface composition of the spent Pt/C was analyzed by X-ray photoelectron spectroscopy (XPS) using a Kratos Axis Ultra DLD apparatus equipped with a hemispherical analyzer and a delay line detector. The spectra were recorded using an Al monochromated X-ray source (10 kV, 15 mA) with a pass energy of 20 eV (0.1 eV/step) for high resolution spectra, and a pass energy of 160 eV (1 eV/step) for survey spectrum in hybrid mode and slot lens mode, respectively. The adventitious C1s binding energy (284.4 eV) was used as an internal reference.

#### Thermodynamic calculations

The heat and entropy of reaction ( $\Delta H_r^o$  and  $\Delta S_r^o$ , respectively) were computed by DFT using *Spartan* software. The heat of formation ( $\Delta H_{f,i}^o$ ) of the different compounds was computed using a T1 method, while the entropy of formation ( $\Delta S_{f,i}^o$ ) was computed using the B3LYP hybrid functional method and a 6-311+G\*\* basis set. All the calculations were conducted in the gas phase without taking into account solvation effects. The heat and entropy of reaction were calculated from the heat and entropy of formation of the reactants (R) and products (P)

$$\Delta S_{r}^{o} = \sum_{i=0}^{P} \Delta S_{f,i}^{o} - \sum_{i=0}^{R} \Delta S_{f,i}^{o}$$
<sup>(2)</sup>

Given the heat and entropy of reaction, the free energy of reaction  $(\Delta G_r^o)$  was calculated as follows

$$\Delta G_r^o = \Delta H_r^o - T \Delta S_r^o \tag{3}$$

The equilibrium constant,  $K_{eq}$ , for each reaction was computed using the expression

$$\Delta G_{r,T}^{o} = -RT \ln(K_{eq}) \tag{4}$$

where R is the constant of perfect gases ( $8.314 Pa.m^3.mol^{-1}.K^{-1}$ ). Besides, the equilibrium constant for the aldol condensation reaction of HxD with bzd can be expressed as follows

$$K_{eq} = \frac{[X][H_2O]}{[HxD][bzd]} = \frac{x^2}{(1-x)^*(n-x)}$$
(5)

where [HxD], [bzd] and [ $\underline{X}$ ] are the equilibrium concentrations of HxD, bzd and product  $\underline{X}$ , respectively, and *n* is the number of bzd equivalents with respect to HxD.

$$X yield = \frac{K_{eq}(n+1) - \sqrt{K_{eq}^2(n+1)^2 - 4nK_{eq}(K_{eq}-1)}}{2(K_{eq}-1)}$$
(6)

#### **Results and discussion**

In a first set of experiments, 5 mmol of DMF (around 0.46 g) was reacted in 2 mL of water and heated at 100 °C in the presence of Aquivion<sup>®</sup>PW98 perfluorinated sulfonic acid resin (MW = 980 g/mole). Our choice was motivated by the hydrophobic properties of PW98 combined with its water tolerance for having a stable catalyst. DMF hydrolysis took place selectively over PW98 and HxD could be generated in quantitative yield after only 2 h. The catalyst was further filtered and HxD was separated from water by distillation.

Next, the aldolization of HxD was investigated using bzd as a representative aldehyde to obtain the target mono condensation product (E)-7-phenylhept-6-ene-2,5-dione (X). This reaction is not easy due to the symmetry of HxD, leading to the double condensation product, (1E,7E)-1,8-diphenylocta-1,7-diene-3,6-dione ( $\underline{\mathbf{Y}}$ ), and to possible polymerization driven by consecutive condensation reactions. The conversion of the reactants and the yield of products were determined by gas chromatography and confirmed by <sup>1</sup>H NMR. In this section, Amberlyst-26 (A26) and hydrotalcite were selected as solid base catalysts and the results are presented in Table 1. A26 is a macroreticular ion exchange resin constituted of styrene and divinylbenzene, and functionalized with quaternary R-NH<sub>3</sub>+HO<sup>-</sup> groups (0.8 mmol/g). We chose A26 because of its strong basicity, high ion exchange capacity and great resistance in the reaction media. On the other hand, hydrotalcites are a wellknown family of anionic clay materials consisting of a layered structure with positively charged brucite like layers and interlayers containing the charge balancing anions and water molecules. Hydrotalcites have been widely reported as active

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Table 1. Catalytic aldolization of HxD with bzd in the presence of A26 and HTC basic catalysts



Entry	Catalyst	Solvent	bzd/HxD (molar ratio)	Time (h)	Т (°С)	HxD conversion (%)	<u>X</u> yield (%)	<u>Y</u> yield (%)	<u>X</u> + <u>Y</u> sel (%)	Sel. to other products (%)
1	A26	Ethanol	1	1	60	33	10	1	33	67
2		Toluene	1	1	60	37	14	1	41	59
3		Toluene	1	1	110 <sup>b</sup>	58	15	3	31	69
4		-	1	0.25	100	83	30	6	43	57
5		-	2	0.25	100	87	45	15	69	31
6		-	3	0.25	100	80	47	15	78	22
<b>7</b> ª		-	2	0.25	100	17	4	0	24	76
8	HTC-liq	-	2	7	120	36	10	1	31	69
9		-	2	7	140	50	34	7	82	18
10		-	2	5	160	73	48	10	79	21
10 <sup>a</sup>		-	2	5	160	77	34			
11	HTC-gas	-	2	7	140	53	35	5	75	25
12		-	2	5	160	70	37	11	69	31

<sup>a</sup> After recycling; <sup>b</sup> Under reflux

and stable solid base catalyst for biomass transformations.<sup>24</sup> The difference between A26 and HTC catalysts in term of basicity is the strength of the basic sites as HTC is known to have basic sites with different strength<sup>25</sup> whereas only strong basic sites are present on A26. In the case of A26, the use of solvents (toluene, ethanol) exerted a negative effect on both the activity and selectivity (Table 1, entries 1-4) which can be due to dilution that affects the conversion of HxD and the yield to X. Under solvent-fre conditions, a HxD conversion of 83% was achieved at 100 °C for a bzd/HxD molar ratio of 1 with 30% and 6% yield of products  $\underline{X}$  and  $\underline{Y}$ , respectively, but with only 43% total selectivity (X+Y). A bzd/HxD molar ratio of 2 enhanced the yield of products X and Y to 45% and 15% after 15 min with 69% total selectivity and 87% HxD conversion (Table 1, entry 5). A higher bzd/HxD molar ratio of 3 did not affect appreciably the catalytic performance (Table 1, entry 6). In all cases, the reaction was far from chemical equilibrium, with  $\underline{X} + \underline{Y}$  equilibrium yields of 70% and 78% at 100 °C for bzd/HxD ratios of 2 and 3, respectively, according thermodynamic calculations (Fig. S1). The A26 activity dropped significantly after the 1st run with a decrease of the HxD conversion and X yield from 83% to 17%, and from 45% to 4%, respectively (Table 1, entry 7). As mentioned above, multiple condensation reactions could occur simultaneously. Indeed, heavy condensation products were observed on A26 after reaction as inferred from FT-IR (Fig. S2) and TG analysis (Fig. S3), leading to poisoning. Heavy molecules with high retention time were also detected by GC analysis in the solution after the reaction.

Hydrotalcite (HTC), an abundant mineral in nature with basic properties, was also used for conducting the aldol condensation reaction of HxD and bzd. Before use, the HTC was calcined and activated by rehydration in liquid- and gas-phase conditions (denoted as HTC-liq and HTC-gas, respectively) as described in the ESI in order to tune the basicity. The catalytic tests were carried out at solvent-free conditions for a bzd/HxD molar ratio of 2. In the case of HTC-liq, the HxD conversion increased from 36% to 73% from 120 °C to 160 °C (Table 1, entries 8-10). The highest yield of X (48%) was achieved at 160 °C after 5 h. A similar behavior was observed for HTC-gas (Table 1, entries 11, 12). HTC-liq led to a higher yield of product X compared to HTC-gas (48% vs. 37%). The different selectivity at 160 °C between both catalysts could be ascribed to the different density of basic OH groups.<sup>26</sup> For HTC-liq, the yield of X dropped from 48% to 34% after the 2nd catalytic run, while the HxD conversion kept almost unchanged. In contrast, the yield of X and Y declined dramatically after the 3<sup>rd</sup> run after only 30 min (11% and 1%, respectively), together with the HxD conversion (25%). TGA analysis of the spent HTC reveals an additional weight loss appearing at 533°C for the spent HTC-gas and 525 °C for the spent HTC-liq, which was not present in the fresh

catalysts (Fig. S4 and S5). These weight losses can be ascribed to organic molecules adsorbed on catalyst. This hypothesis was confirmed by analyzing the liquid mixture after the reaction by TGA using the same temperature program used for the catalysts. One clear weight loss region was visible at around 540 °C, indicating that one fraction of the reaction residue decomposed at this temperature (Fig. S6). One can mention that an agglomeration of HTC was observed at the end of the reaction. If a comparison is made between the catalysts, the strength of the basicity could be an explanation for the highest activity and selectivity of A26 compared to HTC.

Next, it was interesting to extend the reaction scope. To this aim, a series of *p*-substituted benzaldehyde derivatives (4methoxybenzaldehyde, 4-(methylthio)benzaldehyde and 4phenoxybenzaldehyde) were used in the aldol condensation reaction of 2,5-hexanedionein the presence of A26 as catalyst. The reactions were performed under the same optimal reaction conditions as for the reaction of 2,5-hexanedione with benzaldehyde (Table2, entries 1-3). Overall, the 2,5hexanedione conversion was higher than 80% with a yield of the mono condensation product <u>M</u> in the range 30-40%, which is lower than the yield obtained on benzaldehyde (45%). The yield of the double condensation products <u>D</u> was much lower for the *p*-substituted benzaldehyde derivatives. In all cases, oligomers/polymers were present in solution after reaction.

Table 2. 2,5-Hexanedione aldolization with benzaldehyde derivatives. Reaction conditions: A26 40 wt%, X /benzaldehydes derivatives =  $\frac{1}{2}$  under solvent free conditions, 100 °C.



Formed in situ Scheme 2. One-pot conversion of DMF towards product X

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With these results in hand, we conducted the Area pot hydrolysis of DMF to HxD, followed by the add condensation reaction with bzd, by combining Aquivion PW98 and A26 (Scheme 2). These reactions were conducted at 100 °C using a bzd/HxD molar ratio of 3. To initiate HxD hydrolysis, a catalytic amount of water was added to the reaction system in order to favor the ring opening of DMF. DMF was fully converted after 2 h reaction with 40% and 10% yield of products <u>X</u> and <u>Y</u>, respectively, and 25% yield of HxD (Figure 1). The yield of the different products kept unchanged after 2 h, suggesting a possible deactivation of one or both catalysts, most likely due to side reactions leading to oligomerization products poisoning the catalysts.



Figure 1. One-pot reaction catalyzed by PW98 and A26. Reaction conditions: 100 °C, bzd/DMF = 3, 20 wt% water, 20 wt% PW98, 40 wt % A26.

The final step was the ring closure of the functionalized HxD to the corresponding THF-derivatives by hydrogenationcyclization. Depending on the degree of hydrogenation, four products of interest can be obtained as depicted in Scheme 3. A series of commercial carbon-supported metal catalysts based on Ru, Pd and Pt (5 wt% metal) were tested in the hydrogenation-cyclization of product X (Figure 2).



Scheme 3. Potential products that can be obtained from the hydrogenation of the aldol intermediate.

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With no catalyst, the X conversion was only 10% with 3% yield of A product (hydrogenation of C=C bond). Among the catalysts tested, Ru/C and Pd/C were more selective for C=C bond hydrogenation with A being the major product (38% and 86%, respectively), at 49% and 100% conversion, respectively. In the presence of Pt/C, full X conversion was achieved at short reaction times with B and C as major products. The kinetic profiles of the reaction catalyzed by Pt/C revealed that B was not an intermediate generating C and D (Figure 3). Hence, after 7 h of reaction, 22% yield of product B (hydrogenation of C=C bond and carbonyl group), 58% and 6% yield of ring closure products C and D, respectively, were obtained, together with trace amounts of unidentified products.



Figure 2. Product distribution during catalyst screening. Reaction conditions: 90 °C, 3 h, 5 wt% cat, 20 wt% X in ethanol, 3 MPa  $H_2$ .



Figure 3. Kinetic profiles of the hydrogenation-cyclization reaction of  $\underline{X}$  over Pt/C. Reaction conditions: Pt/C 5 wt%,  $\underline{X}$  20 wt% in ethanol, 90 °C, 30 bar H2.

This was in accordance to the study of Zhou *et al.*<sup>27</sup> who reported that in the presence of Pt/C the main product was hexanediol from HxD. Thus they reported that a physical

mixture of commercial Pt/C and the acid resin Amberlite®IR-120 allows the formation 2,5-dimethyltetrahydrofuran from HxD. 27 Based on this study, to boost ring closure of product **B**, an acid catalyst was added to the reaction mixture. In the presence of a solid acid catalyst such as A15, product **B** could be fully converted into products C and D with 49% and 33% yield, respectively. To increase the selectivity towards product **C**, the effect of the H<sub>2</sub> pressure was optimized in the presence of Pt/C and A15. The reaction was conducted at 90 °C in the H<sub>2</sub> pressure range 10-30 bar (Table 3). Independently of the H<sub>2</sub> pressure, full conversion of X was achieved after 3 h. Traces of diol B were observed at the end of the reaction. A yield of product **C** up to 70% could be achieved at 20 bar H<sub>2</sub> together with 14% yield of product **D**. At 10 bar H<sub>2</sub>, 51% yield of the target product **C** and 5% yield of product **D** were obtained along with 24% yield of product <u>A</u>. The lower yield of product <u>C</u> at 10 bar  $H_2$  can be explained by the lower H<sub>2</sub> solubility in the reaction media. In contrast, when the reaction was performed at 30 bar H<sub>2</sub>, 49% and 33% yield of products **C** and **D**, respectively, were obtained, which can be explained by a higher rate of C towards D and a higher  $H_2$  solubility. To promote the formation of product  $\underline{C}$ , 20 bar H<sub>2</sub> pressure was selected in the following experiments.

Table 3. Effect of the H<sub>2</sub> pressure in the hydrogenation-cyclization of reactant X. Reaction conditions: Pt/C 5 wt%, A15 5 wt%, X 20 wt% in ethanol, 90 °C, 3 h.

	Р	X conv.	A yield	B yield	C yield	D yield
	(bar)	(%)	(%)	(%)	(%)	(%)
ĺ	10	100	24	2	51	5
ĺ	20	100	4	3	70	14
	30	100	1	2	49	33

The effect of the temperature on the hydrogenationcyclization reaction of reactant X over Pt/C and A15 was further investigated at 20 bar H<sub>2</sub> pressure. Full kinetic profiles were measured at 60 °C, 90 °C and 120 °C (Figure 4). In all cases, full  $\underline{X}$  conversion was achieved at very short times. Product  $\underline{A}$  was fast consumed during the first 3 h to form products **C** and **D**, whereas product **B** exhibited very low selectivity (<5%) even at short reaction times. Product **C** exhibited an almost constant selectivity of ca. 70% from 3 h to 17 h, whereas it was totally converted into product **D** after 48 h at 60 °C. Interestingly, this time was reduced to 24 h at 90 °C. Opposing this behavior, product C was preeminent over D at 120 °C even after 64 h reaction (71% selectivity). This observation suggests a partial inhibition of the hydrogenation of product **C** into **D** at 120 °C, which can be explained by a selective deactivation during the reaction.

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Figure 4. Kinetic profiles for hydrogenation-cyclization reaction of of  $\underline{X}$  over Pt/C at 60 °C (top), 90 °C (middle) and 120 °C (bottom). Reaction conditions: Pt/C 5 wt%, A15 5 wt%,  $\underline{X}$  20 wt% in ethanol, 20 bar H<sub>2</sub>.

The recycling and reuse of the Pt/C + A15 system was further explored in five consecutive runs at 120 °C for 16 h at 20 bar H<sub>2</sub> (Figure 5). After each run, the catalyst mixture was separated from the reaction mixture by centrifugation, washed with ethanol (x3), and dried in an oven at 80 °C for 10 h under vacuum. The spent catalyst was then re-used without any further purification. Reactant  $\underline{\textbf{X}}$  reached full conversion after each run. Trace amount of product **B** were observed, indicating that the acid catalyst A15 remained active in all the catalytic runs. However, after the 4th and 5th runs, the selectivity of product <u>C</u> dropped dramatically in favor of product <u>A</u>. The amount of catalyst (mostly Pt/C) decreased after each run until 50% Pt after the 5<sup>th</sup> run. A catalytic test with 50% of the initial Pt/C loading and A15 was further conducted, affording 71% selectivity of product **C**. This result points out that the observed change of selectivity after the 3<sup>rd</sup> run cannot be attributed to a decrease of the Pt/C loading after each run, but to an intrinsic change of the hydrogenation performance of Pt/C during reaction.



Figure 5. Evolution of the catalytic performance in consecutive catalytic runs for the hydrogenation-cyclization reaction of X over Pt/C + A15. Reaction conditions: Pt/C 5 wt%, A15 5 wt%,  $\underline{X}$  20 wt% in ethanol, 120 °C, 16 h, 20 bar H<sub>2</sub>.

To gain more insight into the catalyst evolution during the reaction, the spent Pt/C catalyst was analyzed by XPS after the 5<sup>th</sup> run (Table S1 and Fig. S7 and S8). Most of the Pt (90.3 atom %) kept in metal form, suggesting that the apparent decrease of selectivity is not attributed to Pt oxidation. One can note that, about 1.5 wt% sulfur was present on the spent Pt/C after the 5<sup>th</sup> run, which can be ascribed to interactions between A15 and

Pt/C catalysts. Besides, we cannot exclude partial poisoning due to carbon deposits on Pt, which were difficult to ascertain due to the presence of the carbon support.

#### Conclusion

The aldol condensation reaction of 2,5-hexanedione with benzaldehyde was conducted over two basic catalysts, i.e. Amberlyst<sup>®</sup>A26 and a Mg-Al hydrotalcite, affording the monocondensation product with *ca*. 50% yield. Oligomerization products were responsible for catalyst deactivation. One can mention that the selectivity towards X from Y could be steered by converting X as soon as it is formed to the THF products. This strategy required the control of the kinetic of the reactions and the design of an appropriate reactor. Nevertheless, it was possible to directly convert DMF into functionalized 2,5-hexanedione in a one-pot reaction by physically mixing Aquivion<sup>®</sup>PW98 and Amberlyst<sup>®</sup>A26.

Finally, the hydrogenation-cyclization reaction of the monocondensation product towards the THF-derivative was successfully achieved over Pt/C combined with Amberlyst®15. The best selectivity towards the target product was achieved at 120 °C for 16 h at 20 bar H<sub>2</sub> pressure. The catalytic system remained selective to the target product during the first three runs, but favored the synthesis of less hydrogenated products in the 4<sup>th</sup> and 5<sup>th</sup> runs due to partial deactivation of Pt.

In this study, we proposed an original strategy to synthesize THF-derivatives by combining classic aldol condensation and hydrogenation-cyclization reactions. This integrated process can be an attractive route to synthesize alkylated furans in the absence of organic solvents. Noteworthy, this strategy offers

high potential of intensification by designing one-pot reactions combining different steps.

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#### Notes and reference

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All the experimental part is reported on the ESI.

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#### **Graphical Abstract**

# Synthesis of functionalized tetrahydrofuran derivatives from 2,5-dimethylfuran through cascade reactions



# Convenient catalytic route for selectively functionalizing the methyl group of an important bio-based furanic derivatives (DMF).