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Continuous-Flow *O*-alkylation of Bio-Based Derivatives with Dialkyl Carbonates in the Presence of Mg–Al hydrotalcites as Catalyst Precursors

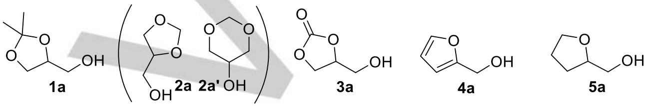
Lisa Cattelan,[a], [b] Alvise Perosa,[a] Piero Riello,[a] Thomas Maschmeyer,[b] and Maurizio Selva*[a]

Abstract: The base-catalysed reaction of OH-bearing bio-based derivatives (BBDs) including glycerol formal, solketal, glycerol carbonate, furfuryl alcohol and tetrahydrofurfuryl alcohol with non-toxic dialkyl carbonates (dimethyl and diethyl carbonate) was explored under continuous-flow (CF) conditions in the presence of three Na-exchanged Y- and X-faujasites (FAUs) and four Mg–Al hydrotalcites (HTs). Compared to previous etherification protocols mediated by dialkyl carbonates, the reported procedure brings about substantial improvements not only in terms of (chemo)-selectivity, but also for the recyclability of catalysts, work-up, ease of product purification, and importantly, process intensification. Characterisation studies proved that both HT30 and KW2000 hydrotalcites acted as catalyst precursors: already during the thermal activation pre-treatments, the typical lamellar structure of hydrotalcites was gradually broken down into a MgO-like phase (periclase) or rather a magnesia–alumina solid solution which was the genuine catalytic phase.

Introduction

In the past 15 years, an enormous effort has been devoted to the identification of the most promising biomass-derived compounds. Among the available analyses, an extensive work carried out by the US Department of Energy in 2004 and its revisitation in 2010 still represent cornerstones in this field. For the first time, they offered rational criteria for the selection of the so-called “top 10” platform chemicals, namely a small group of bio-based derivatives (BBDs) that could be utilized as building blocks for higher-value products and materials.[1] Although this approach has been refined further over the years,[2] current ”top ten” lists of biomass-derived platform compounds still include most of the originally identified compounds, particularly mono- and di-carboxylic functionalised acids, 3-hydroxybutyrolactone, a bunch of bio-hydrocarbons derived from isoprene, glycerol and derivatives, and few other sugars such as sorbitol and xylitol. These considerations have inspired us to try and integrate green protocols mediated by dialkyl carbonates ($ROCO_2R$, DAlCs [3]) with the chemical valorisation of bio-based platform molecules. Necessarily such an activity requires a multidisciplinary approach, combining aspects of organic and physical chemistry as well as chemical engineering and materials science.

Within this context, our attention has been focused on five model OH-bearing BBDs (Scheme 1).



Scheme 1. Model OH-bearing BBDs.

They include solketal (**1a**), glycerol formal (**2a**/**2a’**), and glycerol carbonate (**3a**): these compounds are among the most celebrated derivatives of glycerol and their applications span across multiple sectors: from fine chemicals, cosmetics and pharmaceuticals to bio- fuels and lubricants, bio-based solvents and polymers.[4] The availability of glycerol is mostly fueled by plant-oil-based biodiesel manufacture generating large amounts of glycerol as a co-product.[5] The other two compounds of Scheme 1, specifically furfuryl alcohol (**4a**) and its hydrogenated homologue tetrahydrofurfuryl alcohol (**5a**), are derived from furfural which in turn, is generated prior by the dehydration of sugar components (glucose and xylose) that constitute a large portion of lignocellulosic biomass.[6] Both **4a** and **5a** find uses as modifiers and templates for polymers, as fibers and nanocomposites,[7] as well as sources of polyols.[8]

In addition the presence of a OH-capped tether (hydroxymethylene group) enables an avenue for the derivatisation of all five compounds (**1a**-**5a**): of particular note, esterification and alkylation protocols allow to expand the potential of OH-BBDs through the synthesis of substantially value-added products, including intermediates, solvents and biologically active molecules as glycerol ethers, esters and carbonates,[9] and additives for biodiesel blends based on furanyl ethers derivatives.[6a]

The combined effect of a high reaction temperature (200-220 °C) and a base catalyst (K_2CO_3) allowed an almost exclusive *O*-alkylation of GAs. The reaction showed excellent features from both synthetic and environmental standpoints, since it not only proceeded with etherification selectivities and yields as high as 99% and >80%, respectively, but it also coupled the use of renewable and/or non-toxic reactants as glycerol acetals and DAlCs in a catalytic process with no by-products other than CO_2 (which did not present a disposal problem) and alcohols that were recyclable for the synthesis of dialkyl carbonates. Only trace amounts of by-products from competitive transesterification processes were detected.

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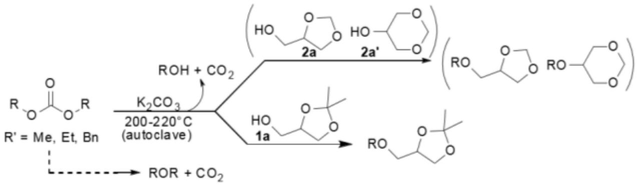
However, under the explored batch conditions, the sequence suffered from two major drawbacks: i) slow alkylation kinetics, i.e. reactions could require up to 80 hours for completion; ii) extensive competitive decarboxylations of dialkyl carbonates with formation of the corresponding dialkyl ethers,[11] (dashed path, Scheme 2).



Scheme 2. The etherification of glycerol acetals with dialkyl carbonates in the presence of K2CO3 catalyst (top). The dashed path shows a concurrent decarboxylation reaction of dialkyl carbonates.

This necessitates the use of a high excess of alkylating agents, and importantly, it involved the co-generation of an autogenous pressure of ≥ 60 bar, both these aspects hindered the scale-up of the process. However, the benefits and disadvantages stimulated us to devise a new broad-based protocol aimed at expanding the alkylating capabilities of dialkyl carbonates to different OH-bearing BBDs, and at the same time, minimising the limitations described above. The implementation of a continuous-flow (CF) procedure was an attractive option with which to reach the conversion target, since it offered the best possible control of the reaction parameters (T, p, and reactants molar ratio) to improve the process kinetics, productivity and safety. Under CF-conditions, however, alkaline carbonates needed anion activators (polyethylene glycols) and/or specifically shaped reactors (e.g. continuous-stirred-tank-reactors, CSTR) in order to perform as catalysts,[12] since not only they (alkaline carbonates) were too weak bases, but they were also partially soluble in both reactant DAlCs and in the co-produced alcohols (Scheme 2).[13] Alternative solid systems had to be considered. Candidates were chosen from the families of faujasite (FAU) and Mg-Al hydrotalcite (HT) solids. Both Y- and X-type FAU have been extensively reported by us as catalysts for DAlCs-promoted *N*, *O*, and *S*-alkylations of a large variety of nucleophiles, including anilines, benzyl alcohols, aminophenols, aminobenzyl alcohols, mercaptophenols, mercaptobenzoic acids, hydroxybenzoic acids, and functionalised phenols of the lignin scaffold.[14] Yet HTs have been investigated almost exclusively as catalysts for transesterifications with dialkyl carbonates,[15] while only few reports described the methylation of some phenols and benzyl alcohol with dimethyl carbonate over Mg-Al hydrotalcites as such or over modified HT systems.[16] In fact, the role of the catalyst is still being debated.

The present work demonstrates that the use of HTs allows for the setup of a particularly robust catalytic CF-method for the etherification of OH-bearing BBDs with DAlCs. For example, at 210 °C and ambient pressure, the model reaction of solketal (**1a**) with dimethyl carbonate shows the formation of the corresponding methyl ether with quantitative conversion and >99% selectivity in the presence of calcined HT Pural® MG30 (cHT30; Mg/Al= 0.5) as a catalyst.

The CF-protocol can be extended to the reaction of substrates of Scheme 1 with both dimethyl and diethyl carbonate: quantitative conversion and O-alkylation selectivity comparable to those of solketal, are achieved over calcined HTs catalysts, except for the case of furfuryl alcohol (**4a**) for which only the transesterification derivative (furan-2-ylmethyl methyl carbonate) can be obtained. Overall, the CF-procedure not only exemplifies an original approach for the upgrading of OH-bearing biobased substrates, but it can also overcome the safety/scale-up limitations of batchwise reactions since it operates at atmospheric pressure and with a productivity [~2 g/(g$_{cat}$·h)] on ether derivatives which is up to 200-fold higher than that of batch methods.

Results and discussion

The apparatus used for continuous-flow (CF) reactions was comprised of an HPLC pump, an oven containing a tubular reactor filled with the catalyst, a Rheodyne sampling valve, and a back-pressure regulator (details are reported in SI).

Dialkyl carbonates including dimethyl- and diethyl-carbonate, and compounds **1a**-**5a** were commercially available ACS grade compounds.

Catalysts. Three alkali metal exchanged X- and Y-type faujasites (FAUs) including two commercially available NaX and NaY solids, and a CsY zeolite were used. The latter was prepared as described in the experimental section.

Four hydrotalcites (HTs) were also used. Three of them were labelled as HT30, HT63 and HT70: these were from Sasol Italy. A fourth sample was labelled as KW2000 and it was sourced from Kyowa Kagaku Kogyo Company Limited. Some features of these HT solids are summarized in Table 1.

Table 1. Hydrotalcites used in this work

Entry	**Label of sample**	**MgO: Al$_2$O$_3$ (%)**	**Surface area (m²/g)** [b]	**Source**	**Post-Synthesi residues (%)**
1	HT30	30:70 [a]	250	Pural® MG30, Sasol	Na: $1.5\ 10^{-3}$ [c] K: $1.7\ 10^{-3}$ [c]
2	HT63	63:37 [a]	230	Pural® MG63, Sasol	
3	HT70	70:30 [a]	180	Pural® MG70, Sasol	
4	KW2000	64:36 [a] (65:35)[d]	190	Kyowa Kagaku Kogyo Co. Ltd	Na: 2.5 10 [d] K: $1.1\ 10^{-2}$ [d]

[a] % Wt ratio specified by the Supplier. [b,c] Data specified by the Supplier. [d]Determined by ICP measures

In the case of KW2000, ICP analysis were used to determine post-synthesis residues of Na and K (see experimental).

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MgO as such and a 30:70 physical mixture of MgO (Aldrich, particle size: 325 mesh; surface area: 114 m^2/g; average pore diameter: 9.4 nm) and basic γ-Al_2O_3 (Macherey-Nagel, pH 9,5 ± 0,3; particle size: 50-200 µm; surface area: 130 m^2/g) were also used as additional catalysts for two comparative tests.

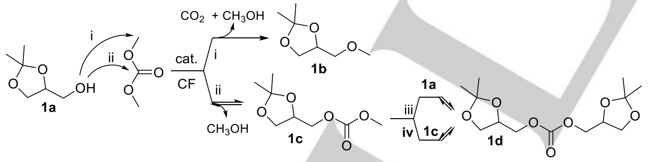
The reaction of solketal (**1a**) *with DMC*. This reaction was chosen as a model to investigate the activity of different catalysts and the effect of three major reaction parameters, *i.e.* temperature, pressure, time, and reactants molar ratio.

CF-tests over different catalysts. The performance of FAUs and HTs catalysts were compared using the above described CF-apparatus. Temperature and pressure for initial tests were selected according to our previous results obtained for both batch alkylation and CF-transesterification reactions of glycerol acetals with dialkyl carbonates:[10,11] in particular, experiments were carried out at T and p in the range of 200-275 °C, and 5-50 bar, respectively.

Each of the investigated catalyst was used to fill the inner volume of the CF-reactor as uniformly and completely as possible.[17] Therefore, the amounts of solid samples were adjusted according to their apparent density: NaY, NaX, CsY, KW2000, HT30, HT63, and HT70 were used as such in slightly different quantities of 0.68, 0.54, 0.86, 0.52, 0.73, 0.51, and 0.85 g, respectively. Each catalyst was dehydrated under vacuum (70 °C, 18 mm, overnight) before use. In all tests, the same 1.83 M solution of solketal in DMC [DMC:solketal molar ratio (W)=5] was fed to the reactor at a total volumetric flow rate (F) of 0.1 mL min^{-1} corresponding to a contact time of about 10 minutes. The excess DMC served both as a reagent and a carrier/solvent.

During the CF-experiments, periodic GC/MS analyses of the mixtures collected at the reactor outlet, allowed to evaluate both the reaction conversion (measured with respect to solketal as the limiting reagent) and the products distribution. Each test was duplicated to check for reproducibility; in each reaction, fresh samples of the same batch of catalysts were used.[18]

Several reactions took place under the conditions explored, i.e. the double electrophilic reactivity of dimethyl carbonate accounted for the formation of *O*-methyl and transesterification derivatives **1b** and **1c**, respectively (Scheme 3: paths i and ii).



Scheme 3. Major products of the CF-catalytic reaction of solketal with DMC.

Subsequently, compound **1c** plausibly underwent a further transesterification with solketal and/or a dismutation reaction that afforded the symmetric carbonate product **1d** (Scheme 3: paths iii and iv). The structures of **1b**, **1c**, and **1d** were assigned by GC/MS and NMR analyses, and by comparison to authentic samples previously synthesized by us. Moreover, some unidentified side-products were also observed. These compounds are referred to as "others" and their GC/MS data are consistent with a ring-opening reaction of the acetal ring followed by methylation and transesterification of the corresponding (linear) derivatives.

At 250-275 °C and 10 bar, FAUs proved unsuitable catalysts for the reaction investigated. At best, the conversion of solketal was moderate (60-70%). The more basic NaX and CsY systems were slightly more active than NaY, but they favoured the transesterification product **1c** with a selectivity of 60-70%.[19] NaY improved the formation of the *O*-methyl derivative **1b** (up to 40%), but it also induced side-reactions leading to a sizeable amount of unidentified by-products. In all cases, conversion and selectivity were steady after 180 min and they did not substantially vary when CF-tests were prolonged up to 18 hours (SI section: Figures S2a-b, and Table S1).

This behaviour neatly contrasted our previously reported results for the reaction of benzyl-type alcohols with DMC during which the corresponding *O*-methyl ethers were achieved in substantially quantitative yields and selectivity in the presence of NaX and NaY catalysts.[20] Unlike aromatic or benzyl substrates,[14,21,22] the cycloaliphatic structure of solketal was plausibly more weakly coordinated by the FAU surface, thereby altering the reaction outcome. According to the HSAB principle, other Authors have also proposed that hard nucleophiles such as aliphatic alcohols prefer the hard electrophilic site of DMC (*i.e* the carboxyl carbon), rather than the softer methyl group.[23]

The scenario completely changed in the presence of HTs. Particularly, KW2000 allowed to improve the conversion and, even more remarkably, the methylation selectivity. Reactions were carried out under the same conditions of Figure 2b (275 °C 10 bar, W=5; F=0.1 mL/min), but they were followed for a longer time (18-20h). Figures 1a-b summarise the performance of HT catalysts with emphasis on KW2000.

All the hydrotalcites investigated were, on average, better catalysts than FAUs, but KW2000 offered a performance far superior than other HTs (HT30, HT63, and HT70) (Figure 1a). The KW2000-catalyzed reaction proceeded with a very good conversion and *O*-methylation selectivity of 99% and 89%, respectively (dashed green line and blue bar); particularly, the ring of the reactant acetal was substantially preserved, avoiding further transformations, and only traces of the transesterification product **1c** were observed. The second best hydrotalcite, *i.e.* HT30, still allowed a substantially quantitative process (conversion 96%), although the methyl derivative **1b** did not exceed 60% of the total of observed products (second group of bars, from left).

The reaction catalysed by KW2000 and HT30 were explored in greater depth by analysing samples of the mixture collected at the CF-reactor every 60 minutes for up to 20 hours (see SI section, Figures S3a-b). In the presence of KW2000, a steady and almost complete conversion was obtained after just one hour, while the *O*-methylation selectivity reached a maximum of 95% in 4 h and it only slight decreased to 87-89% at the end of the test (18-20 h; Figure S3a). The HT-30 catalysed process showed that in the first 4 hours, the conversion was below 80% and the transesterification compound **1c** was the dominant product (Figure S3b); while, after 18-20 h, the residual solketal was in trace amounts (2-5%) and a steady formation of both **1b** and unidentified products was observed (~60% and ~40%, respectively). Albeit with a different products distribution, both the reactions displayed an initial (induction) period during which mixtures of products formed. Thereafter, conversion and selectivity stabilized: the almost exclusive formation of ether **1b** was noticed in the case of KW2000. Based on this catalyst, three additional short experiments (4 hours each) were carried out to examine the effect of the temperature in the range of 200-275 °C. Other conditions were kept unaltered (10 bar, W=5; F=0.1 mL/min). (Figure 1b).

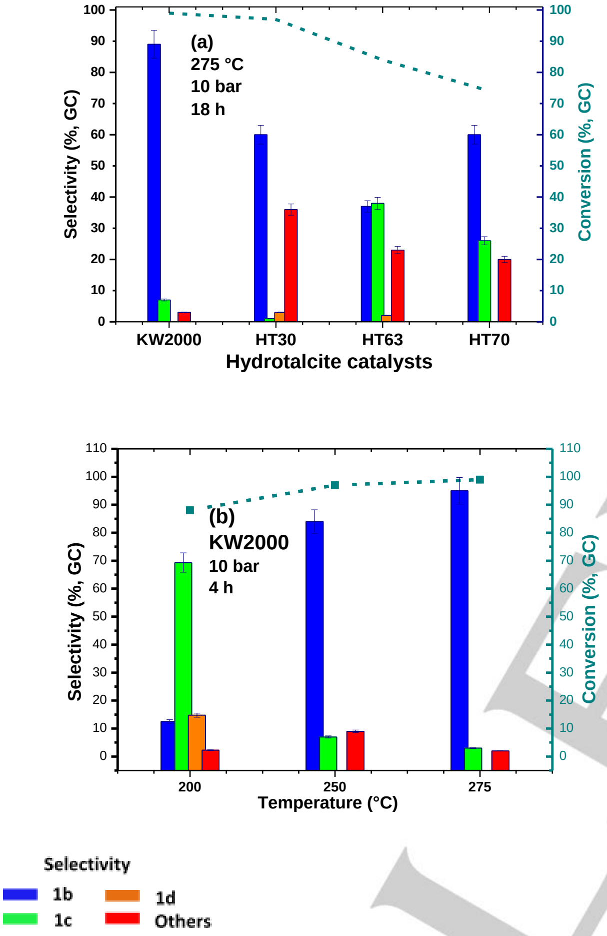


Figure 1. Trends of conversion and products distribution for the CF-reaction of solketal with DMC: a) comparison of different HT catalysts at 275 °C and 10 bar; b) effect of the temperature during tests catalysed by KW2000 at different temperatures. Coloured bars (from left to right) show the selectivity towards the *O*-methyl product (**1b**, ●), the transesterification and/or dismutation derivatives (**1c**, ●, and **1d**, ●, respectively), and unidentified compounds (others, ●). The dashed line (from right to left) shows the trend of solketal conversion. DMC and solketal were used in a 5:1 molar ratio (W), respectively, and the total flow rate was of 0.1 mL/min.

At 200 °C, the transesterification and/or disproportion reactions were the major transformations also on KW2000 (green and ochre bars). However, the *O*-methylation process was triggered by an increase of the temperature, and it was progressively favored over 250 °C.

In the presence of KW2000, further tests were also devised to investigate on the effects of the pressure and the DMC:solketal molar ratio (W) (see SI section, Figures S4a-b). At 275 °C (W=5; F=0.1 mL/min, 4 h), if the pressure was either decreased or increased to 5 and 50 bar, respectively, the conversion slightly diminished (from 99% to ~95%), but the methylation selectivity dropped from 95% to 75-80% because of the onset of transesterification and unidentified side-reactions. Pressure plausibly acted on the partition of reactants between the liquid and the vapour phases and consequently, on the contact of solketal and DMC with the catalyst surface. A similar behaviour was already noticed by us during the investigation of thermal (catalyst-free) transesterification of both glycerol acetals and glycerol with DMC.[24] Yet, at 275 °C and 10 bar (F=0.1 mL/min, 4 h), if W was decreased from 5 to 1.1, both the conversion and the *O*-methylation selectivity fell to 58% and 62%, respectively, with a sizeable formation of products **1c**, **1d** and "others".

Two effects might plausibly account for this result at a constant F: i) the higher the DMC amount (W=5), the higher the rate (and conversion) of DMC-mediated reactions. Under these conditions even though (reversible) transesterifications took place, the corresponding products (**1c** and **1d**) were observed in only minor amounts, because these compounds were consumed by the onset of the parallel irreversible *O*-alkylation reaction which proceeded almost to completion (Scheme 3 and Figures 1a and S3-4). However, if W<5, particularly at W=1.1, less energy demanding reaction pathways, *i.e.* transesterification processes, became more evident and so, the quantities of derivatives **1c** and **1d** increased.

ii) a low DMC:solketal molar ratio (W=1.1-2) not only disfavored the solvation of the acetal by DMC and the mutual interactions between reactants, but it also facilitated the occurrence of intramolecular side-processes including, for example, the ring opening of solketal ("others" as by-products) adsorbed over the catalyst surface.

CF-tests with calcined HTs. When heated at ~200 °C, hydrotalcites release water, but in the proximity of 300 °C (near the temperature used in Figure 1) and above, a collapse of the typical layered structure of HTs occurs with formation of Mg/Al mixed oxides.[25] These facts prompted us to explore the catalytic activity of calcined hydrotalcites (c-HTs) in the reaction of solketal with DMC. c-HTs were prepared by heating Pural® (HT30, HT63, HT70) and KW2000 solids at 450 °C in a dried air-flow for 16 hours.[26] c-HTs showed quite similar apparent densities and were used in the same amount (0.5 g each) for catalytic tests. In all cases, a 1.83 M solution of solketal in DMC [DMC:solketal molar ratio (W)=5] was fed to the reactor at a total volumetric flow rate (F) of 0.1 mL min^{-1}. Experiments proved that calcined hydrotalcites, particularly c-HT30, dramatically improved the reaction outcome: not only both the solketal conversion and the *O*-methylation selectivity increased, but also the c-HT30 catalyst was active at temperature and pressure remarkably lower than those previously used. With other conditions unaltered (W=5, F=0.1 mL/min), reactions could be run at temperatures and pressures as low as only 210 °C and 1 bar.

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Figure 2 details the performance of c-HT30 during 20 hours of time-on-stream, while Table 2 compares the activity and the *O*-methylation selectivity of different c-HTs. Each test was duplicated to check for reproducibility (see note 18).

The outcome of the reaction catalyzed by c-HT30 exemplified one of the best ever reported *O*-methylation reaction of alcohol-like functions mediated by DMC: solketal was quantitatively transformed in the methyl ether **1b**, and a steady efficiency was ensured for up to at least 20 hours. The comparison of Figures 2 to Figures 1 and S2a-b also indicated that not only the calcination of HTs, but even the thermal treatment during high-temperature (275 °C) reactions considerably modified the catalytic properties of both HT30 and KW2000.

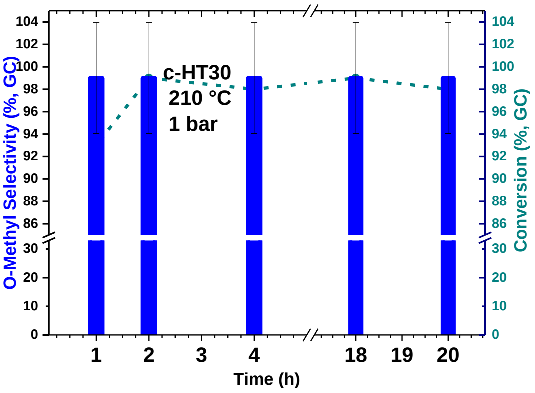


Figure 2. CF-reaction of solketal with DMC in the presence of c-HT30 catalyst at 210 °C and ambient pressure. Trends of *O*-methylation selectivity and conversion of solketal with time (blue bars and dashed green profile). Other conditions: W=5, F=0.1 mL/min.

At the same reaction temperature (210 °C) used for c-HT30, other c-HT catalysts allowed conversion and *O*-methylation selectivity not exceeding 88% and 27%, respectively, even when operating at 10 bar (Table 2: compare c-HT70, c-KW2000, and c-HT63 in entries 2-4, columns 4-7). Minor improvements were achieved at 225 °C (entries 2-4, columns 8-11). Only at 275 °C (10 bar, W=5, F=0.01 mL/min), did the reaction proceed with complete conversion of solketal to the methyl derivative **1b** over all c-HTs catalysts.

The ability of calcined hydrotalcites to promote the investigated reaction was contrasted with other CF-experiments in which c-HTs were replaced by either MgO (0.85 g of a mixture of MgO in 60% wt with ground glass Raschig rings) or a physical mixture of MgO and basic γ-Al_2O_3 in 30:70 molar ratio, respectively (0.85 g) which mimicked the formal composition of HT30. Both these solids were calcined at 450 °C for 6 hours before use. Under the conditions described above (275 °C, 10 bar, W=5, F=0.01 mL/min), the two catalysts gave modest results: the best one was MgO by which the reaction proceeded with conversion and *O*-methyl selectivity of only 80% and 48%, respectively.

Notwithstanding MgO and γ-Al_2O_3 were recently reported to catalyse both *O*- and *N*-alkylations mediated by DMC,[27,28] these solids were obviously inadequate for the reaction investigated.

The study so far demonstrated that KW2000 and HT30 were the most promising catalysts. To continue exploring the potential of such materials, in particular of the calcined system c-HT30, the investigation was focused on the scope and limitations of the CF-etherification of other OH-bearing bio-based derivatives with both dimethyl and diethyl carbonate.

Scope of the reaction: different reactants, mass balance, and productivity. Substrates of Scheme 1 including glycerol formal (**2a**+**2a'**), glycerol carbonate (**3a**), furfuryl- and tetrahydrofurfuryl-alcohols (**4a** and **5a**) were set to react with DMC or DEC under CF-conditions. Accordingly, a homogeneous solution of dialkyl carbonate and the substrate was delivered for 6 hours to the CF-reactor filled with c-HT30 (0.5 g) as a catalyst. The total flow rate was of 0.1 mL/min. All CF-tests were repeated twice to check for reproducibility.

Results are shown in Table 3 which reports reaction conditions, isolated yields (Y) and productivity (P: grams of products obtained in one hour per g of catalyst) for each of the studied processes, and Scheme 4 which summarizes the reactions and the structure of the products. For the sake of completeness, Table 3 also includes the above described results of the reaction of solketal with DMC.

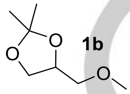
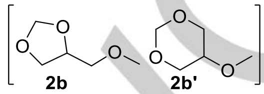
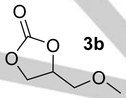
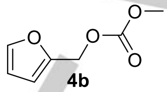
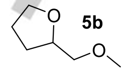
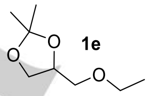
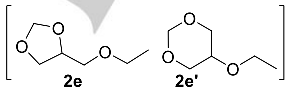
Reactions could be carried out at atmospheric pressure, but the operating temperature and the reactants molar ratio must be optimised case-by-case in the range of 210-275 °C and 5-20, respectively: except for compound **4a**, a quantitative conversion was reached for all the other substrates with *O*-alkylation selectivity of 65-99%.

Table 2. Comparison of c-HTs catalysts for the reaction of solketal with DMC

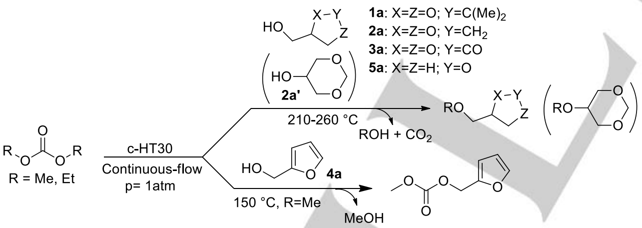
			Reaction Temperature							
			210 °C				225 °C			
Entry	**Catalyst**	**p/t (bar/h)**	**Conv.'n (%)[a]**	**Sel.(%)[b]**			**Conv.'n (%)[a]**	**Sel.(%)[b]**		
				1b	**1c**	**Others**		**1b**	**1c**	**others**
1	c-HT30	10/18	99	99	-	-	99	99	-	-
2	c-HT70		88	27	49	24	95	40	42	18
3	c-KW2000		85	15	61	24	93	20	68	12
4	c-HT63		78	2	68	30	87	8	61	31

[a,b] Conversion of solketal and selectivity towards the *O*-methyl derivative **1b**, the transesterification compound **1c**, and other products (including the disproportionation derivative **1d** and unidentified by-products), respectively. Other conditions: W=5, F=0.1 mL/min.

Table 3. The CF-reactions of substrates **1a**-**5a** with both DMC and DEC in the presence of c-HT30 catalyst.[a]

Entry	Substrate	Dialkyl carbonate	W[b] ratio	T (°C)	Conv.'n (%)[c]	Sel. (%)[d]	Product		
							Structure	Y[e] (%)	P[f] [gprod/(gcat h)]
1	1a	DMC	5	210	99	99	 **1b**	92	2.64
2	2a/2a'	DMC	5	220	99	99	 **2b** **2b'**	81	1.92
3	3a	DMC	20	210	98	65	 **3b**	55	0.42
4	4a	DMC	10	150	88	91	 **4b**	80	1.26
5	5a	DMC	5	260	99	92	 **5b**	82	1.94
6	1a	DEC	5	250	99	99	 **1e**	92	2.04
7	2a/2a'	DEC	5	275	99	99	 **2e** **2e'**	84	1.62

[a] Reactions were carried out for 6 hours (20 hours only for **1a**, entry 1) at ambient pressure and at a total flow rate of 0.1 mL/min. [b] Dialkyl carbonate:substrate molar ratio. [c] Conversion of the substrate (determined by GC). [d] Selectivity towards the shown product (determined by GC). [e] Isolated yield was evaluated by the work-up of a mixture collected at the reactor outlet for 6 hours (15 hours for **1a**, entry 1). [f] Reaction productivity was calculated on isolated yields.



Scheme 4. The etherification of OH-bearing BBDs **1a-3a** and **5a** (top). The transesterification of furfuryl alcohol with DMC (bottom).

All products were isolated and characterised by NMR and GC/MS (details are in the SI section).

Solketal and glycerol formal (**1a** and **2a**/**2a'**) could be quantitatively converted into the corresponding methyl and ethyl ethers (**1b** and **2b**/**2b'**) by using DMC and DEC as *O*-alkylating agents. Two facts emerged: i) regardless of the dialkyl carbonate, the etherification of glycerol formal was more energy demanding than that of solketal: methyl and ethyl ethers **2b**/**2b'** and **2e**/**2e'** were obtained at 220 and 275 °C, respectively, while compounds **1b** and **1e** formed at the lower temperatures of 210 and 250 °C (compare entries 1-2 and 6-7). A similar difference was observed also in the transesterification of glycerol acetals with dialkylcarbonates (DAlCs).[24] The higher density of glycerol formal (1.21 g mL^{-1}) with respect to solketal (1.07 g mL^{-1}) might play a role. ii) The synthesis of ethyl ethers required a considerably higher temperature (250-275 °C) than that of methyl ethers (210-220 °C; compare entries 1 and 6, 2 and 7). This result was in line with the trend noticed in a number of processes mediated by DAlCs, including transesterifications, decarboxylations, etherifications, and alkylations.[11] Steric reasons most plausibly account for the lower electrophilic reactivity of DEC compared to DMC.

Products were recovered in good-to-excellent isolated yields (81-92%); though, the more volatile derivatives of glycerol formal gave slightly poorer results because of some technical difficulties in the separation from DMC or DEC (**2b**/**2b'**: 81%; **2e**/**2e'**: 84%; entries 2 and 7).[29] Isomeric ethers **2b**/**2b′** and **2e**/**2e′** were obtained in the same (3:2) relative ratio of the starting acetals **2a** and **2a'**.

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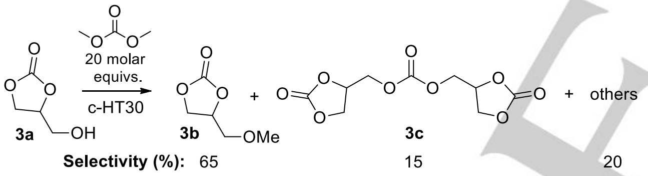
The reaction productivity – calculated on the isolated yield – allowed further remarkable considerations: if compared to our previously reported batch-wise (autoclave) method[10] which allowed P values of 0.01-0.02 $g_{prod}/(g_{cat}\ h)$ for the synthesis of compounds **1b** and **2b**/**2b'**, the CF-procedure boosted the productivity by a factor of 100-200 [up to ~ 2 $g_{prod}/(g_{cat}\ h)$; entries 1 and 2], thereby substantiating the synthetic potential of such a protocol. The overall mass balance for the alkylation of glycerol acetals was also validated by NMR of crude mixtures collected at the reactor outlet and gravimetric analyses of the catalytic bed carried out before and after CF-tests: both such checks indicated that neither heavy products nor noticeable coke formation (on the catalyst) occurred even after prolonged experiments (up to 20 hours, entry 1).

A similar outcome was also observed for the CF-reaction of tetrahydrofurfuryl alcohol (**5a**) with DMC, in which we obtained the corresponding *O*-methyl ether (**5b**) with 92% and 80% selectivity and isolated yield, respectively (entry 5). Though, a higher operating temperature of 250 °C was necessary.

The control of the chemoselectivity was significantly more difficult for the reactions of glycerol carbonate (**3a**) and furfuryl alcohol (**4a**).

Glycerol carbonate was sensitive to the competitive reactions of transesterification[24b] and decarboxylation [30, 31] producing higher carbonate homologues and glycidol, respectively. In this case, a *O*-methylation selectivity of 65% was achieved at 210 °C in the presence of a large excess of the alkylating agent (entry 3 and Scheme 5).



Scheme 5. The CF-reaction of glycerol carbonate with DMC in the presence of c-HT30 (the structure of **3c** was assigned by GC/MS; others were unidentified by-products).

Due to dilution/solvation effects, these conditions contribute to minimise the contact between glycerol carbonate and the catalytic surface, thereby limiting undesired decarboxylation reactions. Of note, the methylation productivity (0.42) of the process was two-fold higher than the best previously reported value (0.21) obtained in a batch reaction of glycerol carbonate with DMC catalysed by Al_2O_3.[32]

Furfuryl alcohol (**4a**) proved too reactive to allow the formation of the corresponding alkyl ether. At T≥180 °C, the reaction of **4a** with DMC gave polymeric by-products, which blocked the catalytic bed rapidly. However, at a lower temperature (150 °C), a highly selective transesterification occurred, providing furan-2-ylmethyl methyl carbonate (**4b**) in 80% isolated yield (entry 4). This equilibrium reaction was also favored by a large DMC excess (10 molar equivs. with respect to **4a**). Of note, previously reported syntheses of **4b** were only ever based on the reaction of furfuryl alcohol with a harmful phosgene derivative such as methyl chloroformate;[33] the process described here was the first successful example of the same preparation using DMC as a nontoxic reagent.

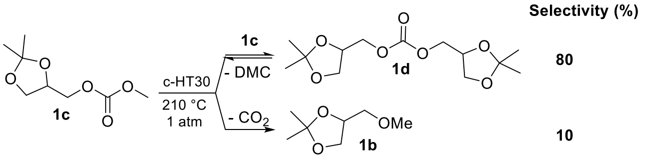
Experiments of Table 4 proved that c-HT30 was not only an efficient catalyst, but it could also be recycled without loss of performance. As an example, once the CF-alkylation of solketal was run for 20 hours (entry 1), a simple cleaning cycle of the catalytic bed with methanol (50 mL at 1 mL/min, 50 °C, atmospheric pressure) allowed to reset the system to its initial conditions, and to restart the same or a new reaction (*e.g.* the alkylation of glycerol formal). No differences of activity were appreciated when a used c-HT30 catalyst was compared to a freshly calcined HT30 sample, thereby confirming the robustness of the CF-procedure. This was further substantiated by the very low metal leaching from the catalyst: after the test of entry 1 (Table 4), ICP measures demonstrated that the Al and Mg concentrations in the stream recovered at the outlet of the reactor were 40 and 85 ppb, respectively (see experimental and SI sections for details). The estimated mass loss of the catalytic bed corresponded to 38 µg per 20 working hours. Very low level of metal leaching was observed also for others reactions catalyzed by HT-derived Mg/Al mixed oxides: two examples are the transesterifications of natural fats and liquid-phase Michael additions.[34]

It was also estimated that, after vacuum distillation of mixtures collected at the reactor outlet, up to 80% of the unreacted DMC (and its azeotrope with MeOH,[35]) and DEC could be recovered and recycled with minimal generation of wastes.

Overall, the CF-procedure proved versatile and suitable to different reactants, both carbonates and alcohols. In particular, c-HT30 provided a rational long term stability and selectivity (with no appreciable leaching or poisoning phenomena) and a productivity which could be orders of magnitude higher than that achieved by batch alkylation methods. To the best of our knowledge, a result comparable to that of c-HT30 was reported only in the continuous-flow *O*-methylation of primary alcohols with DMC that was catalyzed by γ-Al_2O_3.[28] However, this protocol could hardly be extended: sec-alcohols gave substantial side reactions of eliminations to alkenes promoted by the acidity of the catalyst;[36] moreover, even at 150 °C, DMC underwent an extensive decarboxylation reaction to dimethyl ether.[37] γ-Al_2O_3 would have posed a chemoselectivity concern also for functionalised alcohols used in this study: glycerol acetals (solketal and glycerol formal) and furfuryl alcohol are extremely sensitive to ring aperture and polymerisation reactions catalysed by acids, while, glycerol carbonate would undergo a rapid release of CO_2.

It should be noted that the decarboxylation of dialkyl carbonates may be catalyzed by FAUs,[11] or by hydrotalcites as such.[38] However, under the CF-conditions here explored, we observed that calcined HTs were far less efficient for the same process. This was corroborated by an additional test in which solketal methyl carbonate (**1c**) was set to react at 210 °C and ambient pressure over a catalytic bed of c-HT30. At a conversion of 75%, compound **1c** underwent a predominant disproportion reaction towards bis((2,2-dimethyl-1,3-dioxolan-4-yl)methyl) carbonate

(**1d**, 80%), rather than the decarboxylation to derivative **1b** (10%) (Scheme 6).



Scheme 6. CF-reaction of **1c** over c-HT30 at 210 °C and ambient pressure. Cyclohexane was used as a solvent (5 molar equivs. with respect to **1c**). Total flow rate: 0.1 mL/min.

Product **1d** was isolated in a 58% yield and it was fully characterised by GC/MS and NMR analyses (see SI section). Albeit indirectly, this test confirmed that c-HT30 could also improve the efficiency of the alkylation reactions desired here.

Characterization and role of the catalyst. The performance of the investigated catalysts was consistent with structural modifications induced by calcination and, potentially during the reactions itself. The two most active systems, KW2000 and HT30, were therefore subjected to a more in-depth analysis and characterization.

A total of four samples were examined for XRD analyses: two of them (f-KW2000 and f-HT30) were fresh solids never used for catalytic tests; the other two specimens (c-KW2000 and c-HT30) were calcined catalysts used for reactions carried out under the conditions of Table 2 (For details, see Table S2 in the SI). The XRD patterns are shown in Figures 3 for fresh materials, and Figures 4 and 5 for calcined solids, respectively.

Fresh solids were constituted by at least two phases in which the hydrotalcite structure (ICSD 81963) was present along with large fractions of: i) Periclase (MgO: ICSD 9863; 60±1 wt%) in f-KW2000; ii) Boehmite (aluminum oxide-hydroxide: ICSD 36340; 53±1 wt%) in f-HT30. The quantitative relationships between the constituent phases were obtained by the Rietveld analysis shown in Figures 3c-d. For comparison, XRD patterns were acquired also for fresh solid samples of HT63 and HT70: these materials were single phase hydrotalcites (for further details, see Figures S31, SI section).

The XRD pattern of c-KW2000 showed the presence of cubic MgO (periclase) along with an extremely dispersed or amorphous phase responsible for a broad peak detected at 2θ=35° (Figure 4). The pattern was consistent with typical XRD of c-HT systems characterized by an Al/(Al+Mg) molar fraction up to about 50% (≈55wt% of Al_2O_3).[39] [40] A Rietveld analysis was then carried out by considering that: i) in addition to MgO, both Al_2O_3 and the spinel Al_2MgO_4 could be the other most probable components of the c-KW2000 system;[41] ii) if the thermal degradation of a hydrotalcite occurred at 300-500°C, metastable phases of MgO and finely dispersed Al_2O_3 or solid solutions of Al_2MgO_4/Al_2O_3 and/or MgO/Al_2O_3 could form. [42] Among aluminas, k-Al_2O_3 (ICSD 94485) gave the best fit of the XRD pattern (Figure 4). It was also noticed that the refined cell of MgO was smaller (4.190±0.001 Å) than that of pure MgO (4.2112 Å), thereby indicating the formation of a solid solution (s.s.) of alumina in magnesia where Al occupied 15% of cationic sites.[42] By assuming that the s.s. dissolved the Al_2O_3 phase, the Rietveld quantitative analysis of Figure 4 allowed to estimate proportions of Al_2O_3 (39 wt%) and MgO (61 wt%) very close to the nominal composition of the sample. This indirectly supported the presence of almost pure Al_2O_3 as the amorphous phase. Finally, the s.s. was totally absent in the fresh sample of KW2000 (Figure 3b) in which periclase showed a unit cell parameter of 4.213±0.002 Å.

The XRD patterns of c-HT63 and c-HT70 solids were very similar to that of c-KW2000 (see Figure S32, SI section).

By contrast, the diffraction pattern of c-HT30 - containing a higher fraction of Al – was totally different (Figure 5). The Rietveld analyses carried out as mentioned above, allowed to identify the presence of a s.s. MgO/Al_2O_3, the spinel Al_2MgO_4, and k-Al_2O_3, and to estimate that the corresponding amounts of these three phases were 15, 63, and 22 wt%, respectively. Although the obtained fit was not as good as the previous one (cfr R_{wp} indexes of Figures 4 and 5), the calculated proportions of Al_2O_3 (69 wt%) and MgO (31 wt%) were very close to those of the nominal composition of the sample.

BET results were in substantial agreement with the trend of surface area that was usually observed for fresh and calcined HTs:[25a, 45] notwithstanding fresh samples of KW2000 and HT30 were not pure hydrotalcite phases, an increase of S_{BET} was noticed once both solids were calcined at 450 °C (Table S2: 108 and 199 m^2/g for f- and c-KW2000, and 136 and 247 m^2/g for f- and c-HT30, respectively).

Overall, the comparative bulk characterisation indicated that fresh solids, both f-KW2000 and f-HT30, acted as precursors of active catalysts for the *O*-alkylation reactions investigated here. Such active phases were composed by a solid solution of Mg/Al oxides along with amorphous alumina, and they formed during thermal treatments of the hydrotalcites investigated.[27,39,40] This matched the behaviour described in the literature which is summarized in Scheme 7.[25]

$$Mg_{1-x}Al_x(OH)_2(CO_3)_{x/2}\cdot mH_2O \xrightarrow{25\text{-}200\ °C} Mg_{1-x}Al_x(OH)_2(CO_3)_{x/2}$$

$$x/2\ MgAl_2O_4 + (1\text{-}3x/2)\ MgO \xleftarrow{250\text{-}500\ °C}$$

Scheme 7. The decomposition of Mg–Al hydrotalcite.

Above 250 °C, HTs decompose because of the release of water and extensive dehydroxylation and decarbonation reactions of the OH^- and CO_3^{2-} intralayer anions. However, the produced phases ($MgAl_2O_4$, Al_2O_3 or Al-doped MgO) are often as small nuclei hardly distinguishable from each other,[43,44] thereby making not only the outcome of thermal process, but also the precise nature of mixed oxides still not completely resolved.

These considerations allowed us to formulate a hypothesis to explain why in the investigated *O*-alkylation reactions, KW2000 could be used as such (Figure 1: f-KW2000), while HT30 was active only upon calcination (Figure 2 and Table 3). Since the two solids showed quite different chemical compositions in which the layered HT structure coexisted with large proportions of Periclase in f-KW2000 or Boehmite in f-HT30 (Figures 3a and 3b, respectively), it was plausible that the breakdown of Scheme 7 took place under different conditions: in the case of f-KW2000, the process could be completed during the CF-alkylation reactions with heating at 275 °C, while the collapse of f-HT30 required a more energy demanding transformation which was achieved only during a high temperature calcination at 450 °C.

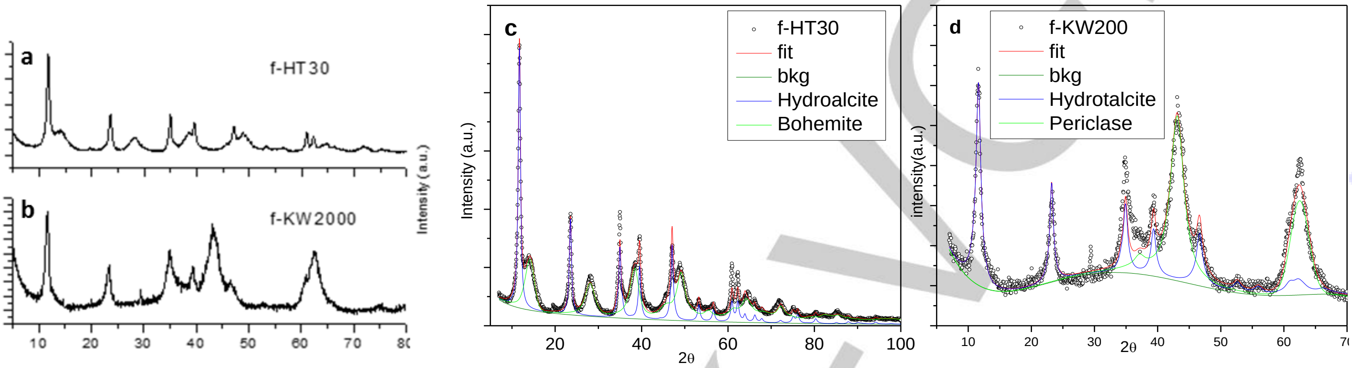


Figure 3. f-HT30 and f-KW2000 samples. Left: XRD patterns. Right: Rietveld fit.

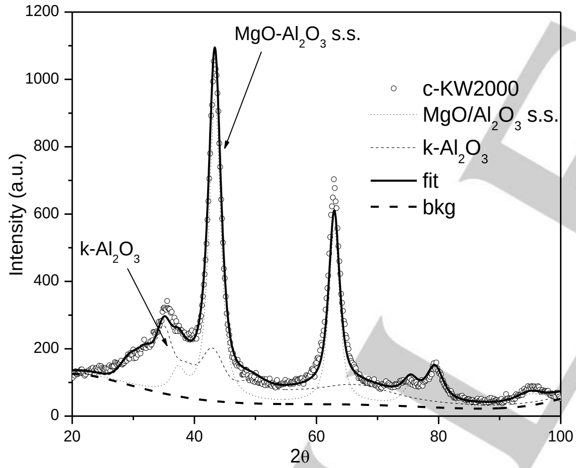


Figure 4. XRD pattern and Rietveld fit of c-KW2000 (R_{wp}=9.5%).

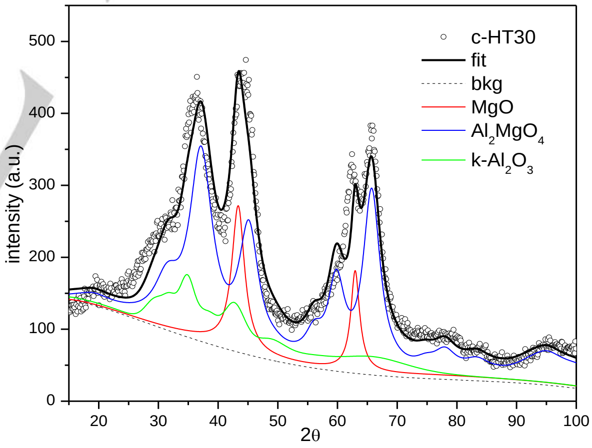


Figure 5. XRD pattern and Rietveld fit of c-HT30 (R_{wp}=11.6%).

Another question was the different performance of the investigated c-HT systems. Mg/Al mixed oxides obtained by calcination of HTs, are often defined as amphoteric solids.[27,40,46] This dual (acid/base) activity has been invoked to account for both the nucleophilic and electrophilic activation of organic substrates promoted by c-HTs in several model reactions including transfer hydrogenations and aldol condensations of ketones,[27,47] transesterification and carbonylation processes,[48] as well as eliminations and condensations of alcohols.[43,49]

The basicity of c-HT systems has been the subject of many fundamental investigations that generally agreed to define basic sites of different strength including OH groups (weak), Mg–O or Al–O pairs (medium), and low-coordinated O^{2-} anions (strong).[25,39,50] In this respect, the density of total basic sites determined by CO_2-TPD profiles of HT30 and HT70 solids after calcination at 450 °C, was of 1.35 and 3.00 μmol/m^2, respectively.[51] This finding was consistent with the Mg/Al ratio of the samples: the higher the Al content (the more electronegative metal cation),

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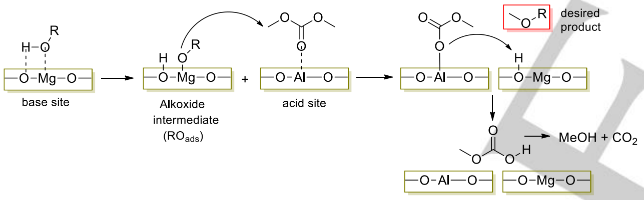
the higher the nucleation of Al-rich phases, and the lower the average basicity of the solid.[27,40,47] In particular, the segregation of a large amount of a spinel phase observed by XRD analysis of c-HT30 (Al_2MgO_4: 63 wt %; Figure 5) probably determined a partial coverage of the sites at the surface of MgO, thereby decreasing the basicity with respect to c-HT70 solid (the latter was mostly composed of a solid solution of alumina in magnesia: Figure S32). An extensive analysis of these aspects was carried out by Cavani *et al.*[25,50,52] that concluded how the Al/Mg ratio of c-HTs induced a variability of surface properties, but in the range 2.0 < Mg/Al < 3.5, all materials possessed basic sites mostly of medium strength, while interestingly, Lewis acid sites were manifest at low Mg/Al ratios in the form of coordinatively unsaturated Al^{3+} species. Moreover, c-HTs were less basic than MgO. The same Authors then proposed that in the presence of c-HTs of Mg/Al=2 as catalysts, a cooperative mechanism via a synergetic effect of basic and Lewis acidic sites could explain the selective O-methylation of phenol with methanol in the gas phase.[52]

A similar formulation appeared consistent with the behavior of c-HTs described by Figure 2 and Tables 2-3. Results were obviously not due to a purely basic mechanism since the most performant catalyst c-HT30 was less basic than c-HT70 and by far, than pure MgO. On the other hand, among the tested c-HTs, c-HT30 had not only a different bulk structure (Figure 5), but also the lower Mg/Al ratio which plausibly favored the occurrence of Lewis acidic sites. c-HT30 apparently displayed the best compromise of acid/base properties to hypothesize the mechanism of Scheme 8.



Scheme 8. Proposed mechanism for the reaction of OH-bearing BBDs (ROH) and DMC at the HT surface.

Both nucleophilic and electrophilic partners were activated by the catalyst. After the adsorption of an OH-bearing BBD (ROH: Scheme 1) on Brønsted basic sites (*e.g*. Mg–O pairs), a deprotonation reaction followed with the formation of the alkoxide intermediate RO_{ads}. Whereas the dialkyl carbonate (DMC in Scheme 8) was activated by Lewis acid sites (Al^{3+} cations) in the HT framework. An electrophilic activation of DAlCs by metal cations was already noticed by us in FAU catalysts.[22] Then, RO_{ads} underwent a $B_{Al}2$-type reaction on adsorbed DMC to produce the desired methyl ether (ROMe) and methyl hydrogen carbonate ($MeOCO_2H$). The latter was an unstable derivative, which spontaneously decomposed into MeOH and CO_2. RO_{ads} could also attack the carboxyl carbon of DMC to form the corresponding transesterification product ($ROCO_2Me$; $B_{Ac}2$ mechanism, see Scheme 3). However, the transesterification as an equilibrium process was forced to backtrack by the irreversible O-methylation reaction. The product distribution was also steered by the temperature. In-line with previously reported results,[3,10-11,15,33] alkylation and transesterification processes involving DAlCs are discriminated between based on their different energy demands: methylations occur only at relatively high temperatures usually, above 150 °C. A different situation was manifest for the four fresh HT solids investigated here, of which f-KW2000 was the best catalytic system (Figure 1). As mentioned above, the composition of f-KW2000 containing a large excess of periclase (Figure 3b) could facilitate the decomposition of the solid towards a catalytically active phase (s.s. MgO/Al_2O_3) even at the temperature of 275 °C used for CF-tests. KW2000 however, showed remarkable similarities to HT63 and HT70 samples for the comparable Mg/Al ratios (Table 1), and the bulk structure obtained by calcination (cfr Figure 4 and S32). This was further substantiated by the same catalytic performance of the three calcined solids (c-KW2000, c-HT63 and c-HT70) in the *O*-methylation of solketal of Table 2. Therefore, although f-KW2000 could be converted into a catalyst at 275 °C (and 10 bar), the corresponding active phase of Mg/Al oxides had to be more basic and consequently, less efficient than c-HT30.

The effect of post-synthetic alkaline impurities on the catalytic activity of c-HTs was finally considered. Although the doping with alkali metal carbonates and hydroxides was known to increase the basicity and the activity of HT-systems, the necessary quantity of alkaline dopants must corresponded to an amount of alkali metals (Na, K) of 0.5-10 wt%.[53] These values were at least 250- and 20-fold higher than those of HT30 and KW2000, respectively (Table 1). Reasonably, alkalinity based on Na- or K-residual salts in the investigated catalysts had a negligible, if any, role in the catalysis of *O*-alkylation reactions by DAlCs.

Conclusions

The investigation integrates an archetypical green reaction involving nontoxic and renewable reactants with an efficient continuous flow procedure for the synthesis of alkyl ethers of a class of biobased derivatives. Calcined hydrotalcites, particularly c-HT30, have proved effective to highly chemoselective transformations: functionalised bio-based alcohols and dialkyl carbonates are activated towards *O*-alkylations with respect to the competitive transesterifications and other side-reactions including the ring opening of acetal functions, decarboxylations of dialkyl carbonates, and oligo-/poly-merisations. An *O*-alkylation selectivity as high as 99% at complete conversion is achieved. To the best of our knowledge, this result have no precedents in the class of biomass derived compounds investigated.

The analysis of the bulk structure of fresh and calcined hydrotalcites here investigated is consistent with the formation of catalytically active phases constituted by Al/Mg mixed oxides. These are originated either upon calcination or simply heating to reaction temperature and their composition varies between different HTs. The activity of the more performant catalyst (c-HT30) is compatible with both a lower density of basic sites and, at the same time, a more pronounced acid character than other solids of the family.

Overall, the CF-protocol provides multiple advantages of which the most relevant ones include the high process safety, the recycle of solvents/unconverted reagents and reuse of catalysts, and the simplification of downstream operations for the isolation and purification of products with a benefit on productivity (greater by orders of magnitude) with respect to batch methods.

Experimental Section

General

Solketal (**1a**), Glycerol formal (GlyF, **2a+2a'**), tetrahydrofurfuryl alcohol (**4a**), furfuryl alcohol (**5a**), dimethyl carbonate (DMC), diethyl carbonate (DEC) and MgO were ACS grade from Aldrich. If not otherwise specified, they were employed without further purification. Glycerol carbonate (**3a**) was from JEFFSOL® and used as received. Solketal methylcarbonate (**1c**) was prepared via the transesterification reaction of Solketal with DMC, by adjusting a method developed by us.[10]

GC-MS (EI, 70 eV) analyses were run using a HP5-MS capillary column (L=30 m, Ø=0.32 mm, film=0.25 µm) and CG/FID analyses were run using an Elite-624 capillary column (L=30 m, Ø=0.32 mm, film=1.8 µm). ^{1}H NMR were recorded at 400 or 300 MHz, ^{13}C NMR spectra at 100 MHz, and chemical shifts were reported in δ values downfield from TMS; $CDCl_3$ was used as the solvent.

Catalysts

Faujasites of formula $M_z[(AlO_2)_z(SiO_2)_w]\cdot mH_2O$ (M=Na, Cs; X- and Y-type: z=86 and 56, w=104 and 136, m=264 and 250, respectively) included NaX and NaY faujasites from Aldrich and a CsY zeolite synthesised by a conventional ionic exchange reaction of NaY with aq. CsCl.[18] The percentage of ionic exchange ($Na^+ \rightarrow Cs^+$) was 58%: it was evaluated through atomic emission according to a procedure already reported by us.[54]

Before their use, they were dehydrated under vacuum (70 °C, 18 mm, overnight).

Hydrotalcites (HTs) were aluminium magnesium hydroxyl carbonate hydrates of formula $Mg_{2x}Al_2(OH)_{4x+4}(CO_3)\cdot nH_2O$ (x = 0.5-2.3). Four commercial HTs were considered (their Mg/Al molar ratio is given between parentheses): KW2000 (1.8); PURAL® MG 30 (0.5), MG 63 (1.9) and MG 70 (2.3). KW2000 was from Kyowa Chemical Industry Co., Ltd., while PURAL® MG solids were from CONDEA/Sasol Germany GmbH, Inorganic Specialty Chemicals. According to the manufacturer specifications, these materials are aluminium magnesium hydroxycarbonate hydrates $Mg_{2x}Al_2(OH)_{4x}+4(CO_3)\cdot nH_2O$ with x varying between 0.5 and 2.3. Carbonate content is about 10 wt.% and the maximum loss on ignition (3 h, 1000 °C) is in the 40–45% range. All HTs were used both as-received and after calcination. If used as received, solids were dehydrated under vacuum (70 °C, 18 mm, overnight) before being loaded in the CF-reactor. Otherwise, the calcination treatment was carried out according to a procedure already reported for HTs:[21] solid samples (5 g) were heated in a quartz reactor (in the upright position) under a flow of dry air at 450 °C for 16 h. The heating rate was 30 °C/min.

Catalyst characterisation

Adsorption–desorption isotherms of nitrogen were obtained at the liquid nitrogen temperature using a Micromeritics ASAP 2010 system. Each sample has been degassed at 130 °C overnight before measuring the N_2 physisorption isotherm. From the data, the Brunauer–Emmett–Teller (BET) equation was used to calculate the specific surface area

X-ray powder diffraction (XRPD) analyses were recorded with a Philips X'Pert powder diffractometer (Bragg–Brentano parafocusing geometry). A nickel-filtered Cu Ka1 radiation (l ¼ 0.15406 nm) and a voltage of 40 kV were employed. XRD patterns were carried out for all fresh (as-received) hydrotalcites and the corresponding calcined solids.

Inductively coupled plasma (ICP) analysis were performed on a Perkin Elmer Nexion 300XX Inductively Coupled Plasma Mass Spectrometer (ICP-MS).

CF-Apparatus

The apparatus used for the investigation was assembled in house according to the chart reported in Figure S1. An HPLC pump was used to deliver liquid reactants to a stainless steel tubular reactor (L=12 cm, Ø=1/4", 1.16 cm^3 inner volume) containing the catalyst whose amount was chosen based on the apparent density of both hydrotalcites and faujasites. Typical catalyst loadings were in the range of 0.5-0.85 g (see Figures 1-2 and Tables 2 and 3). The reactor was placed in the upright position in a thermostated oven, and heated at the desired temperature. A Swagelok back pressure regulator placed at the outlet of the reactor, was used to keep the pressure constant over the whole system throughout the reaction. When experiments were carried at ambient pressure, the BPR was bypassed. A Rheodyne Model 7725i injector, equipped with a 10 µL sample loop, was placed before the BPR and used for sampling.

SAFETY WARNING. Operators of high pressure equipment should take proper precautions to minimise the risk of personal injury.[55] The individual components that we describe work well, but they are not necessarily the only equipment of this type available.

General procedure for the CF-reactions of 1a, 2a+2a', 3a, 4a, 5a with DMC

A typical reaction was carried by using the CF-apparatus described above through the following procedure. The oven was set at a temperature of 150 °C and N_2 was flushed for one hour throughout the system. Then, the reacting mixture (Dialkyl carbonate and the bio-based alcohol) was allowed to flow for 10 minutes at 1 mL/min, while the BPR and the oven were set to the operating pressure and temperature (5-60 bar, and 150-300 °C, respectively). Once T and p were stabilised, the reactants flow was adjusted at the desired rate (0.07-0.2 mL/min). The reaction mixture was collected through a Rheodyne® valve (7725i fitted with a 10 µL sample loop) at time intervals of about 30 minutes, diluted with 1.5 mL of diethyl ether and analysed by GC/FID or GC/MS.

Change of reaction conditions. The oven and the BPR were set to the new desired values of T and p, respectively. Under these conditions, the reactants mixture was flushed for 10 minutes at 1 mL/min. Then, the flow was adjusted at the chosen rate and a new experiment started.

System cleaning and restart. At the end of each experiment, the oven and the BPR were set to 50 °C and atmospheric pressure, respectively, while a cleaning solution of methanol (50 mL at 1 mL/min) was allowed to flow through the system. The pump was then stopped and the oven was allowed to cool at rt. The CF-reactor was then disassembled and the catalytic bed could be replaced by a fresh one.

Reaction of Solketal (1a) and DMC with alkali metal exchanged faujasites (FAUs) as catalysts

The above described procedure was used to tests Faujasites as catalysts. Before use, each zeolite was dehydrated under vacuum (70 °C, 18 mm, overnight): 0.68, 0.54, and 0.86 g of NaY, NaX, and CsY, respectively, were charged in the CF-reactor. In all tests, a 1.83 M solution of solketal in DMC [DMC:solketal molar ratio (W)=5] was fed to the reactor at a total volumetric flow rate (F) of 0.1 mL min^{-1}. CF-reactions were performed under a constant pressure of 10 bar, while T was set at 250 and 275 °C, respectively. Experiments were followed for 3 hours. Two additional runs with both NaY and NaX catalysts were carried out for up to 18 hours.

Reaction of Solketal (1a) and DMC with hydrotalcites

As-received hydrotalcites. HTs were dehydrated under vacuum (70 °C, 18 mm, overnight): 0.52, 0.73, 0.51, and 0.85 g of KW2000, HT30, HT63, and HT70, respectively, were used for CF-tests. A 1.83 M solution of solketal in DMC [DMC:solketal molar ratio (W)=5] was fed to the reactor at a total volumetric flow rate (F) of 0.1 mL min^{-1}. At 275 °C, reactions were performed under a constant pressure of 10 bar, and they were followed for 18 hours (Figure 3a). In the case of KW2000, additional experiments were carried out under the following conditions: i) T= 200 and 250 °C, p= 10 bar, W=5, F=0.1 mL/min; ii) T=275 °C, p= 5 and 50 bar, W=5, F=0.1 mL/min; ii) T=275 °C, p= 10 bar, W= 1.1, 2, 3.5, F=0.1 mL/min.

Calcined hydrotalcites. After calcination at 450 °C (see above for details), 0.5 g of each solid (c-KW2000, c-HT30, c-HT63, and c-HT70, respectively) was used for CF-tests. In all cases, a 1.83 M solution of solketal in DMC [DMC:solketal molar ratio (W)=5] was fed to the reactor at a total volumetric flow rate (F) of 0.1 mL min^{-1}. At 10 bar, reactions catalysed by c-KW2000, c-HT30, c-HT63, and c-HT70 were run at 210, 225, and 275 °C, respectively, for 18 hours. In the case of c-HT30, experiments were also performed at 210 °C and atmospheric pressure.

Two additional reactions were also conducted by replacing c-HT catalysts by either MgO (0.85 g) or a physical mixture of MgO and basic γ-Al_2O_3 (particle size:50-200 μm, surface area: 130 m^2/g, pH:9.5±0.3) in a 30:70 molar ratio, respectively (0.85 g). Both MgO and the mixture MgO/γ-Al_2O_3 were calcined at 450 °C for 6 hours before use. Then, CF-tests were run at 275 °C, 10 bar, W=5, and F=0.01 mL/min.

The use of different substrates and carbonates

Reaction of Solketal and diethyl carbonate (DEC). According to the above-described general procedure, the reaction of glycerol acetals (**1a** and **2a+2a'**) was performed using DEC and c-HT30 (0.5 g) as an alkylating agent and a catalyst, respectively. CF-reactions were carried out at 250 and 275 °C, and ambient pressure. A mixture of DEC and the chosen glycerol acetal in a 5:1 molar ratio was delivered at 0.1 mL/min to the CF-reactor.

Different substrates. According to the above-described general procedure, the reactions of DMC with glycerol formal (**2a**+**2a'**), glycerol carbonate (**3a**), furfuryl alcohol (**4a**), and tetrahydrofurfuryl alcohol (**5a**) were investigated in the presence of c-HT30 (0.5 g) as a catalyst. Reactions were optimised case-by-case under the following conditions: i) 220 °C, 1 bar, glycerol formal:DMC in a 1:5 molar ratio; ii) 210 °C, 1 bar, glycerol carbonate:DMC in 1:20 molar ratio; iii) 150 °C, 1 bar, furfuryl alcohol:DMC in 1:10 molar ratio; iv) 260 °C, 1bar, tetrahydrofurfuryl alcohol:DMC in 1:5 molar ratio. The flow rate was set at 0.1 mL/min in all cases.

Isolation and characterisation by NMR and GC/MS of all products (**1b**, **2b+2b'**, **3b**, **4b**, **5b**, **1e**, and **2e+2e'**) is reported in the SI section.

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Keywords: *O*-alkylation • bio-based derivatives • dialkyl carbonates • continuous flow • hydrotalcites

[1] (a) T. Werpy, G. Petersen, A. Aden, J. Bozell, J. Holladay, J. White, A. Manheim, D. Eliot, L. Lasure and Jones, S. In Top value added chemicals from biomass. Volume 1-Results of screening for potential candidates from sugars and synthesis gas, US DOE (No. DOE/GO-102004-1992), **2004**, Washington, DC.; (b) J. Bozell and G. R. Petersen, *Green Chem*., **2010**, *12*, 539-554.

[2] T. J. Farmer and M. Mascal, In Introduction to Chemicals from Biomass, 2nd Ed., J. Clark and F. Deswarte, Eds., John Wiley & Sons, Ltd, Chichester, **2015**, UK.

[3] P. Tundo and M. Selva, *Acc. Chem. Res.,* **2002**, *35*, 706-716.

[4] (a) L. Moity, A. Benazzouz, V. Molinier, V. Nardello-Rataj, M. K. Elmkaddem, P. de Caro, S. Thiébaud-Roux, V. Gerbaud, P. Marion and J.-M. Aubry, *Green Chem.,* **2015**, *17*, 1779–1792; (b) W. K. Teng, G. C. Ngoh, R. Yusoff and M. K. Aroua, *Energy Conv. Manag.,* **2014**, *88*, 484–497; (c) M. O. Sonnati, S. Amigoni, E. P. Taffin de Givenchy, T. Darmanin, O. Choulet and F. Guittard, *Green Chem*., **2013**, *15*, 283–306; (d) *Advances in Biorefineries: Biomass and Waste Supply Chain Exploitation*, K. W. Waldron, Ed.; Woodhead Pub. Ltd, **2014**.

[5] M. Pagliaro and M. Rossi, *The Future of Glycerol*, 2nd Ed.; **2010**, RSC Publishing, Cambridge, UK.

[6] (a) M. Balakrishnan, E. R. Sacia and A. T. Bell, *Green Chem*., **2012**, *14*, 1626–1634; (b) Y. Gu and F. Jerome, *Chem. Soc. Rev.,* **2013**, *42*, 9550-9570; (c) R. Mariscal, P. Maireles-Torres, M. Ojeda, I. Sadaba and M. Lopez Granados, *Energy Environ. Sci*., **2016**, *9*, 1144—1189.

[7] (a) W. G. Trindade, W. Hoareau, J. D Megiatto, I. A. T. Razera, A. Castellan and E. Frollini, *Biomacromolecules,* **2005**, *6*, *2485-2496*; (b) W. Chaikittisilp, K. Ariga and Y. Yamauchi, *J. Mater. Chem. A,* **2013**, *1*, 14–19; (c) L. Pranger and R. Tannenbaum, *Macromolecules,* **2008**, *41*, 8682-8687.

[8] M. Chatterjee, H. Kawanami, T. Ishizaka, M. Sato, T. Suzuki and A. Suzuki, *Catal. Sci. Technol.,* **2011**, *1*, 1466–1471.

[9] (a) M. Sutter, E. D. Silva, N. Duguet, Y. Raoul, E. Metay and M. Lemaire, *Chem. Rev.*, **2015**, *115*, 8609-8651; (b) A. E. Dıaz-Alvarez, J. Francos, B. Lastra-Barreira, P. Crochet and V. Cadierno, *Chem. Commun*., **2011**, *47*, 6208–6227; (c) B. J. Nikolau, M. A. Perera, L. Brachova and B. Shanks, *Plant J.*, **2008**, *54*, 536-545.

[10] M. Selva, V. Benedet and M. Fabris, *Green Chem.*, **2012**, *14*, 188-200.

[11] M. Selva, M. Fabris and A. Perosa, *Green Chem.*, **2011**, *13*, 863–872.

[12] A. Bomben, M. Selva, P. Tundo and L. Valli, *Ind. Eng. Chem. Res.* **1999**, *38,* 2075-2079.

[13] (a) A. Y. Platonov, A. N. Evdokimov, A. V. Kurzin and H. D. Maiyorova, *J. Chem. Eng. Data*, **2002**, *47*, 1175-1176; (b) M. Selva, C. A. Marques and P. Tundo, *J. Chem. Soc., Perkin Trans. I* **1994**, 1323-1328.

[14] (a) M. Selva, P. Tundo and A. Perosa, *J. Org. Chem.*, **2001**, *66*, 677-680; (b) M. Selva, P. Tundo and A. Perosa, *J. Org. Chem.*, **2003**, *68*, 7374-7378; (c) M. Selva and P. Tundo, *J. Org. Chem.*, **2006**, *71*, 1464-1470; (d) M. Selva, A. Perosa and M. Fabris, *Green Chem.*, **2008**, *10*,

1068; (e) J. N. G. Stanley, M. Selva, A. F. Masters, T. Maschmeyer and A. Perosa, *Green Chem.*, **2013**, *15*, 3195.

[15] (a) A. Takagaki, K. Iwatani, S. Nishimura and K. Ebitani, *Green Chem.*, **2010**, *12*, 578-581; (b) M. G. Álvarez, M. Plísková, A. M. Segarra, F. Medina and F. Figueras, *Appl. Catal. B: Environmental* **2012**, *113–114*, 212–220; (c) P. Liu. M. Derchi and E. J.M. Hensen, *Appl. Catal. A: General,* **2013**, *467*, 124–131; (d) L. Zheng, S. Xia, Z. Hou, M. Zhang and Z. Hou, *Chin. J. Catal.,* **2014**, *35*, 310–31.

[16] (a) M. B. Talawar, T. M. Jyothi, P. D. Sawant, T. Raja and B. S. Rao, *Green Chem.*, **2000**, *2*, 266–268; (b) P. Tundo, S. Memoli, D. Hérault and K. Hill, *Green Chem.*, **2004**, *6*, 609; (c) G. Wu, X. Wang, B. Chen, J. Li, N. Zhao, W. Wei and Y. Sun, *Appl. Catal. A: General,* **2007**, *329*, 106-111; (d) G. D. Yadav and J. Y. Salunke, *Catal. Today,* **2013**, *207*, 180-190.

[17] In this way, void spaces and preferential pathways of the reactants mixture through the catalytic bed were minimized if not ruled out. (see P. Harriot In Chemical Reactor Design, Dekker, Inc.; 2003)

[18] In the repeated tests carried out under the same conditions, values of conversion and amount of products (determined by GC/MS) differed by less than 5% from one reaction to another.

[19] D. Barthomeuf, *J. Phys. Chem*. **1984**, *88*, 42.

[20] M. Selva, E. Militello and M. Fabris, *Green Chem.*, **2008**, *10*, 73–79.

[21] Y. Ono, *Cat. Tech*. **1997**, *1*, 31.

[22] (a) F. Bonino, A. Damin, S. Bordiga, M. Selva, P. Tundo and A. Zecchina Angew. Chem. Int. Ed. **2005**, *44*, 4774 –4777; (a) T. Beutel, M. J. Peltre and B. L. Su, *Colloids Surf., A* **2001**, *187-188*, 319-325; c) T. Beutel, *J. Chem. Soc. Faraday Trans.,* **1998**, *94*, 985-993.

[23] P. Tundo, L. Rossi and A. Loris, *J. Org. Chem.,* **2005**, *70*, 2219-2224.

[24] (a) M. Selva, S. Guidi and M. Noè, *Green Chem.*, **2015**, *17*, 1008–1023; (b) S. Guidi, A. Perosa, M. Noè, R. Calmanti and M. Selva, *ACS Sust. Chem. Eng.* **2016**, *4(11)*, 6144–6151.

[25] (a) F. Cavani, F. Trifirò, and A. Vaccari, *Catal. Today*, **1991**, *11*, 173-301; (b) P. Bera, M. Rajamathi, M. S. Hedge, P. Vishnu Kamath, *Bull. Mater. Sci*., **2000**, *23*, 141–145; (c) P. Kustrowski, D. Sulkowska, L. Chmielarz, A. Rafalska-Lasocha, B. Dudek, R. Dziembaj, *Microporous Mesoporous Mater*. **2005**, *78*, *11*–22; (d) K. J. D. MacKenzie, R. H. Meinhold, B. L. Sherriff, Z. Xu *J. Mater. Chem.*, **1993**, *3*, 1263-1269.

[26] M. Hájek, P. Kutálek, L. Smoláková, I. Troppová, L. Capek, D. Kubicka, J. Kocík and D. N. Thanh, *Chem. Eng. J.,* **2015**, *263*, 160–167.

[27] (a) Y. Ono and H. Hattori in Solid Base Catalysts, Springer Series in Chemical Physics 101, Springer **2011**; (b) S. T. Gadge, A. Mishra, A. L. Gajengi, N. V. Shahi and B. M. Bhanage, *RSC Adv*., **2014**, *4*, 50271-50276.

[28] A. J. Parrott, R. A. Bourne, P. N. Gooden, H. S. Bevinakatti, M. Poliakoff and D. J. Irvine, *Org. Proc. Res. Develop.*, **2010**, *14*, 1420–1426.

[29] During the purification of final reaction mixtures, the more volatile ethers **2b**/**2b′** and **2e**/**2e′** were partly carried away in the first distilled fraction of DMC or DEC.

[30] J. S. Choi, F. S. H. Simanjuntaka, J. Y. Oh, K. I. Lee, S. D. Lee, M. Cheong, H. S. Kim and H. Lee, *J. Catal.,* **2013**, *297*, 248–255.

[31] D. J. Darensbourg and A. D. Yeung, *Green Chem.*, **2014**, *16*, 247–252.

[32] F. Leising, Z. Moulongui, Chryso and Tolouse Inst. Nat Polytech. and Agronomique Inst. Nat. Rech., US2015329468 (A1), Nov. 19, **2015**.

[33] (a) Y. Nakao, S. Ebata, J. Chen, H. Imanaka and T. Hiyama, *Chem. Lett*., **2007**, *36*, 606-607; (b) I. Franzoni, L. Guénée and C. Mazet, *Org. Biomol. Chem*., **2015**, *13*, 6338–6343.

[34] (a) Y. Liu, E. Lotero, J. G. Goodwin Jr., X. Mo *Appl. Catal. A: General* 2007, 33,1 138–148; (b) H. A. Prescott, Z.-J. Li, E. Kemnitz, A. Trunsche,, J. Deutsch, H. Lieske, A. Auroux *J. Catal*. **2005**, 234, 119–130.

[35] A. Rodrıguez, J. Canosa, A. Domınguez and J. Tojo, *Fluid Phase Equilibria*, **2002**, *201*, 187–201.

[36] J. Shen, R. D. Cortright, Y. Chen and J. A. Dumesic, *J. Phys. Chem.*, **1994***, 98,* 8067-8073.

[37] Y. Fu, H. Zhu and J. Shen, *Thermochimica Acta*, **2005**, *434*, 88–92.

[38] P. Tundo, F. Aricò, A. E. Rosamilia, S. Memoli *Green Chem*. **2008**, 10, 1182–1189.

[39] J. I. Di Cosimo,V. K. Dıez, M. Xu, E. Iglesia and C. R. Apesteguıa, *J. Catal.*, **1998**, *178*, 499–510.

[40] B.Hallstedt, *J. Am. Ceram. Soc*., **1992**, *75*, 1497-1507.

[41] The Rietveld analysis of these samples was carried out using the method proposed by Lutterotti *et al*. for the analysis of amorphous materials. (L. Lutterotti, R. Ceccato, R. Dal Maschio, E. Pagani *Mater. Sci. Forum* **1998**, *278–281*, 87–92). Particularly, the pattern of an amorphous or nanocrystalline phase was fitted by using the structure of a crystalline phase with the same chemical composition. The XRD spectrum of Al_2O_3 with very broad peaks was used to obtain the pattern of the amorphous phase.

[42] S. Vyas, R. W. Grimes, D. J. Binks and F. Rey, *Phys. Chem Solids,* **1997**, *58*, 1619-1624.

[43] V. Vágvölgyi, S. J. Palmer, J. Kristóf, R. L. Frost and E. Horváth, *J. Coll. Interface Sci.* **2008**, *318*, 302–308.

[44] J. C. A. A. Roelofs, J. A. van Bokhoven, A. J. van Dillen, J. W. Geus and K. P.de Jong, *Chem. Eur. J.,* **2002**, *8*, 5571-5579.

[45] M. G. Alvarez, A. M. Segarra, S. Contrera, J. E. Sueiras, F. Medina, F. Figueras *Chem. Eng. J.* **2010**, *161*, 340–345

[46] (a) M. León, E. Díaz and S. Ordónez, *Catal. Today,* **2011**, *164*, 436–442.

[47] T.M. Jyothi, T. Raja, K. Sreekumar, M.B. Talawar and B.S. Rao, *J. Mol. Catal. A: Chemical*, **2000**, *157*, 193–198.

[48] (a) M. J. Climent, A. Corma, P. De Frutos, S. Iborra, M. Noy, A. Velty and P. Concepción, *J. Catal*., **2010**, *269*, 140–149; (b) A. Navajas, G. Arzamendi, F. Romero-Sarria, M.A. Centeno, J.A. Odriozola and L.M. Gandía, *Catal. Commun.*, **2012**, *17*, 189–193.

[49] V. K. Díez, C. R. Apesteguía and J. I. Di Cosimo *J. Catal*. **2003**, *215*, 220–233.

[50] M. Bolognini, F. Cavani, D. Scagliarini, C. Flego, C. Perego, M. Saba *Catal. Today* **2002**, 75, 103–111

[51] Basicity data were made available by the supplier of commercial PURAL solids (SASOL). Data referred to c-HT30 and c-HT70 samples calcined at 450 °C.

[52] (a) V. Crocellà, G. Cerrato, G. Magnacca, C. Morterra, F. Cavani, L. Maselli, S. Passeri *Dalton Trans*., **2010**, *39*, 8527–8537; (b) V. Crocellà G. Cerrato, G. Magnacca, C. Morterra, F. Cavani, S. Cocchi, S. Passeri D. Scagliarini, C. Flego, C. Perego *J. Catal*. **2010**, *27*0, 125‑135.

[53] (a) S. Abello, F. Medina, D. Tichit, J. Perez-Ramırez, X. Rodriguez, J. E. Sueiras, P. Salagre, Y. Cesteros *Appl. Catal. A: General* **2005**, 281, 191–198; (b) J. M. Fraile, N. Garcıa, J. A. Mayoral, E. Pires, L. Roldan *Appl. Catalysis A: General* **2009**, 364, 87–94; (c) N. N. A. H. Meis, J. H. Bitter, K. P. de Jong *Ind. Eng. Chem. Res*. **2010**, 49(17), 8086–8093; (d) S. Walspurger, P. D. Cobden, O. V. Safonova, Y. Wu, E. J. Anthony Chem. Eur. J. **2010**, 16, 12694 – 12700.

[54] M. Selva, P. Tundo, D. Brunelli and A. Perosa, *Green Chem.*, **2007**, *9*, 463.

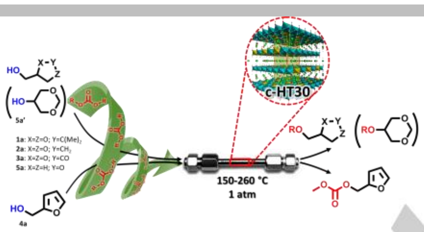
[55] P. G. Jessop, T. Ikariya and R. Noyori, *J. Am. Chem. Soc*., **1996,** *118*, 344.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

A sustainable route for the upgrading of bio-based derivatives is developed through a selective, continuous-flow, and catalytic *O*-alkylation reaction. Dialkyl carbonates are used as *green* alkylating reagents in the presence of hydrotalcites acting as precursors of a catalytic phase comprised of a magnesia-alumina solid solution.



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Continuous-Flow O-alkylation of Bio-Based Derivatives with Dialkyl Carbonates in the Presence of Mg–Al hydrotalcites as Catalyst Precursors