Diversified upgrading of HMF via acetylation, aldol condensation, carboxymethylation, vinylation and reductive amination reactions

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ABSTRACT

Multiple sustainable methodologies were developed for the chemical upgrading of HMF: i) at 30–90 °C, highly selective base-catalyzed acetylation and carboxymethylation reactions of HMF with nontoxic reagents as isopropenyl acetate (iPAc) and dimethyl carbonate (DMC) were achieved to prepare the corresponding ester and carbonate products, (5-formylfuran-2-yl)methyl acetate (5-formylfuran-2-yl) methyl carbonate, respectively; ii) based on the combined use of iPAc/DMC with acetone, a tandem protocol of acetylation/transcarbonation and aldol condensation was designed to synthesize a variety of HMF-derived α,β-unsaturated carbonyl compounds; iii) in water as a solvent, a chemoselective Pd-catalysed reductive amination of HMF with amino-alcohols also including glycerol derivatives, was developed using H_2 at atmospheric pressure; iv) finally, both HMF and its ester and carbonate products successfully underwent Wittig vinylation reactions promoted by a methyl carbonate phosphonium salt ($[Ph_3PCH_3]$ $[CH_3OCO_2]$), to obtain the corresponding olefins. The vinylation reagent (the salt) was a DMC derivative. In all cases i-iv), not only processes occurred under mild conditions, but post-reaction procedures (work-up and purification) were optimized to isolate final products in high yields of 85–98%.

1. Introduction

5-Hydroxymethyl-2-furfural (HMF) is among the most promising platform chemicals derived from the acid-catalyzed hydrolysis of lignocellulose. [1] As illustrated by several comprehensive reviews, [2,3,4] the multiple functionalization of HMF makes it a suitable substrate for a range of reactions, including oxidations, hydrogenations, etherifications, couplings, condensations, and others. [5,6] Carbon-carbon and carbon-heteroatom bond forming processes are an exemplificative large family of transformations where the reactivity of the HMF carbonyl with a variety of nucleophiles has been investigated for the construction of bio-based organic frameworks. [7,8,9,10] A model case is the aldol condensation, particularly with acetone as a donor, which has been explored to produce renewable polymers and pigments. [11,12,13,14] Another relevant route is the reductive amination of HMF for the synthesis of nitrogen functionalized compounds of interest in the pharmaceutical and surfactants sectors. [15,16] Less studied but not less noteworthy is also the conversion of HMF to the corresponding olefins via Wittig-type reactions: an example is the vinylated homologue 5-hydroxymethyl-2-vinylfuran (HMFV) which undergoes free radical polymerization to yield renewable glues. [17] On the other hand, remarkable strategies for the upgrading of HMF have been designed by taking advantage of its benzyl alcohol-like reactivity. Among them, one of most investigated reactions was the (trans)esterification, particularly the acetylation to 5-formylfuran-2-yl)methyl acetate (HMF-acetate or AMF) which thanks to its lower hydrophilicity and improved stability has been proposed as an alternative platform to HMF. [18] Several acetyl donors including acetic anhydride, acetic acid and even simple esters, and catalysts (pyridine, sodium acetate, I_2, etc., [19,20,21]) or biocatalysts (e.g. Lipase Cal-B, [22,23]) proved effective for the synthesis of AMF. Intriguingly, albeit similar to the transesterification reaction, the transcarbonation of HMF with organic carbonates is a largely unexplored field. To the best of our knowledge, notwithstanding HMF-derived carbonates are expected to display attractive properties as intermediates and monomers for polycarbonate materials, only one paper has reported a bio-catalyzed carboxymethylation of HMF with dimethyl carbonate for the synthesis of (5-formylfuran-2-yl) methyl carbonate (HMFC) in 91% yield. [22] Reduction of 5-hydroxymethylfurfural is also a key reaction towards a variety of chemicals and biofuels such as, 2,5-bis(hydroxymethyl)furan, 2,5-dimethylfuran, and linear derivatives such as HHD (1-hydroxyhexane-2,5-dione) and polyols, just to name a few. [24]

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Most if not all of these strategies, however, have issues. These include: i) the limited thermal and chemical stability of HMF which easily undergoes undesired polymerization or degradation to humins and char; [25,26,27] ii) the challenging control of the selectivity between mono- and bis-substituted products in aldol-type reactions; [28] iii) the explosive potential and corrosivity of acetic anhydride, and its legal restrictions for large-scale manufacturing in many countries; [29, 30] iv) the use of tailored solvents, e.g. deep-eutectics (DES), to cope with the separation of equilibrium mixtures obtained in (trans)esterification reactions; [22] v) the poor atom economy, the use of harmful solvents and organohalogens, and the formation of stoichiometric salts to dispose of in Wittig-type reactions; [31] vi) severe catalysts poisoning by heavy byproducts during hydrogenation and hydrogenolysis of HMF. [24] Not to mention that even storage of HMF must be controlled (at T below 4 °C) to avoid aging of the substrate and spontaneous formation of dimers and oligomers. [2] This scenario clearly highlights that the design of innovative protocols for the upgrading of HMF still remains a highly desirable target.

In light of these considerations, as a part of our longstanding interest in the development of greener protocols for the conversion of biomass derived platform chemicals, [32,33,34] we conceived the functionalization of HMF and its derivatives in a logic as much as possible integrated in the green chemistry principles. [35] The five transformations described above, namely acetylation, transcarbonation, aldol condensation, reductive amination, and Wittig vinylation were approached by favoring the use of safe reagents and solvents, and catalytic processes. **Scheme 1** summarizes the selection of experimental conditions used in this work and the major results achieved.

Nontoxic isopropenyl acetate (iPAc) and dimethyl carbonate (DMC) were selected as acetylating and carboxymethylating agents (reactions A and B) to replace harmful and corrosive compounds (Ac_2O, acetyl halides, haloformates), and poorly active reactants (AcOH). Both iPAc and DMC served also as solvents. The use of alkaline heterogenous catalysts such as calcined hydrotalcites and alkali metal carbonates (C-HT-30 and M_2CO_3; $M = K$, Cs) was optimized to facilitate work-up, product separation and catalyst recycle. The same catalysts were used in combination with acetone for the aldol condensation (C). Renewable aminated glycerol derivatives 3-amino- (3-APD) and 2-amino-propanediol (2-APD) were investigated for the reductive amination reaction in the presence of water as a solvent (D). Simpler model substrates as ethanolamine (EA) and propanolamine (PA) were also used.

Finally, the latent ylide reactivity of the Wittig vinylation reagent developed in our laboratories, [36] methyltriphenylphosphonium methylcarbonate ($[MePPh_3]$ $[MeOCO_2]$) was exploited for the vinylation of the carbonyl (E). Contrarily to conventional ylides used for Wittig olefinations, the Wittig vinylation reagent is synthesized simply by heating Ph_3P and dimethyl carbonate without added bases or co-product salts to dispose of. [31]

All the designed strategies proved not only efficient, but also scalable routes that afford gram-scale quantities of 12 HMF derivatives (85–98% yields), 7 of which novel.

2. Experimental

2.1. General

Reagents and solvents were commercially available compounds and were used as received unless otherwise stated. HMF, isopropenyl acetate, acetone, dimethyl carbonate, ethanolamine, propanolamine, 2-aminopropanediol, 3-aminopropanediol, Na_2CO_3, K_2CO_3, Cs_2CO_3, d_6-acetone, Pd/C (5 wt%), D_2O, $CDCl_3$ were sourced from Sigma Aldrich (now Merck). Hydrotalcites HT-30 and HT-63 were a generous gift of Sasol Italy SpA. Ionic liquids $[MePPh_3]$ $[MeOCO_2]$ and $[MeNPh_3]$ $[MeOCO_2]$ were synthesized according to a procedure previously reported by us. [37] GCMS– (EI, 70 eV) analyses were performed on a HP5-MS capillary column ($L = 30$ m, $\varnothing = 0.32$ mm, film = 0.25 mm). ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. The chemical shifts were reported downfield from tetramethylsilane (TMS), and $CDCl_3$ or D_2O were used as the solvents.

2.2. General procedure for the iPAc-mediated acetylation and tandem acetylation-aldol condensation of Hmf

Experiments were performed under different conditions (details are in **Table 1**). In a typical procedure for the acetylation of HMF, a 5-mL round-bottomed flask equipped with a condenser and a magnetic stir bar, was charged with a mixture of HMF (0.5 mmol), isopropenyl acetate (1.5 equivs.), and the catalyst (15 wt% or 10–70 mol%, depending on the chosen catalyst). The flask was then heated at the desired temperature, at atmospheric pressure. Aliquots of the reaction mixture were withdrawn at intervals and analyzed by GC/MS to determine the conversion of HMF and product selectivity.

The same procedure was used for the tandem acetylation-aldol condensation process except for the addition of acetone (up to 16 molar equivs with respect HMF). Details are in **Fig. 1** and **Scheme 5**.

The same procedure was also used for experiments carried under a N_2 pressure (8 bar, **Table S2** and **Figure S1**) or above 60 °C. In this case, however, a stainless-steel autoclave (inner volume 10 mL) was the reaction vessel.

A typical work-up is reported for the isolation of the acetylated product **2** [(5-formylfuran-2-yl)methyl acetate)] when the acetylation of HMF was scaled up by a factor of 10 (HMF: 5 mmol; HMF:iPAc=1:1.5 mol:mol; $T = 30$ °C; $p = 1$ atm; Cs_2CO_3 in 70 mol% (1140 g); $t = 15$ min). Once the experiment was complete, the solid catalyst and the eventual formed char/humins were filtered off using a short column for chromatography (length = 15 cm; inner diameter = 1 cm) filled with celite and silica (5 g each) and washed with MeOH (20 mL). The excess solvent was rotary evaporated ($p = 10$ mbar) affording compound **2** in a 92% yield and a >98% purity by GC–MS. The product was further characterized by ^1H and ^{13}C NMR and (see SI). Data were in agreement with those reported in the literature. [20]

The tandem product **3a** ((E)-(5-(3-oxobut-1-en-1-yl)furan-2-yl) methyl acetate) was isolated from the reaction of HMF (0.5 mmol), iPAc (1.5 equivs), acetone (16 equivs.), in the presence of Cs_2CO_3 (10 mol%) as a catalyst,. Once the reaction was complete (15 h at $T = 56$ °C), the solid catalyst and the eventual formed char/humins were filtered off using a short column for chromatography (length = 15 cm; inner diameter = 1 cm) filled with celite and silica (5 g each) and washed with MeOH (20 mL). Then, the excess solvent was rotary evaporated ($p = 10$ mbar) affording compound **3a** in a 88% yield and a >99% purity by GC–MS. The product was further characterized by ^1H and ^{13}C NMR and GC–MS analyses (see SD section for details).

2.3. General procedure for the DMC-promoted carboxymethylation of HMF and further aldol condensation

Experiments were performed under different conditions (details are in **Table 2**). In a typical procedure for the carboxymethylation of HMF, a 5-mL round-bottomed flask equipped with a condenser and a magnetic stir bar, was charged with a mixture of HMF (0.5 mmol), DMC (1.3 mL, 30 equivs.), and the catalyst (50–100 wt% or 10 mol%, depending on the chosen catalyst). The mixture was set to react at the desired temperature (30–90 °C) and atmospheric pressure. Aliquots of the reaction mixture were withdrawn at intervals and analyzed by GC/MS to determine the conversion of HMF and product selectivity.

A typical work-up is reported for the isolation of the carboxymethylated product **4** [(5-formylfuran-2-yl)methyl acetate)] when the reaction of HMF was scaled up by a factor of 10 (HMF: 5 mmol; HMF: DMC=1:30 mol:mol; C—HT30=100 wt%;). Once the experiment was complete (36 h at 90 °C; $p = 1$ atm, the solid catalyst and the eventual formed char/humins were filtered off using a short column for chromatography (length = 15 cm; inner diameter = 1 cm) filled with celite

Table 1
The reaction of HMF with iPAc at 30 °C, in the presence of different catalysts.

Entry	Catalyst	Cat. Loading[a]	t (h)	Conv. (%)[b]	Products, (%, GC)[b]		Yield (%)[c]	
					2 (AMF)	3a	2 + 3a	2
1	none		24	–	–	–		
2	Amb-15	15 wt%	24	≥99	93	7	96	
3	C-HT-30		24	–	–	–		
4	C—HT-63		24	4	≥99	–		
5	H_2SO_4	10 mol%	0.5	≥99	≥99			19
6	AcOH		24	3	≥99			
7	$[Ph_3PCH_3]$ $[OCO_2CH_3]$		2	≥99	≥99	–		93
8	$[Ph_3NCH_3]$ $[OCO_2CH_3]$		4	≥99	95	5		
9	Na_2CO_3		48	72	≥99	–		
10	K_2CO_3		2	≥99	91	9	96	
11	Cs_2CO_3		1	≥99	91	9	93	89
12	Cs_2CO_3	70 mol%	0.1	≥99	98	2	95	94

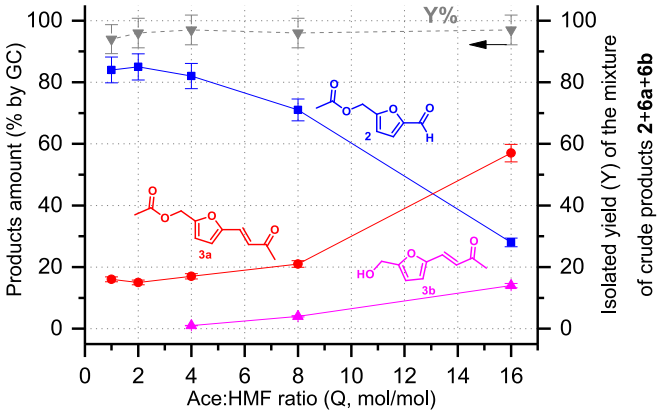


Fig. 1. The effect of HMF:acetone molar ratio in the reaction between HMF and iPAc. Conditions: HMF (0.5 mmol), iPAc (1.5 equivs.), Cs_2CO_3 (10 mol%), and acetone (Ace:HMF=1:1–16:1 molar ratio); T = 30 °C; t = 15 h. Left-to-right: (-■-) Amount (%, GC) of compound **2**; (-●-) amount (%, GC) of compound **3a**; ; (-▲-) amount (%, GC) of compound **3b**. Right-to-left: (- -★- -) Isolated yield of products **2** + **3a**+**3b** (total of three products). .

and silica (5 g each) and washed with MeOH (20 mL). The excess DMC and solvent (MeOH) were rotary evaporated (p = 10 mbar) affording compound **4** in a 89% yield. The product was further characterized by ^{1}H and ^{13}C NMR and GC–MS analyses (see SD section for details). Data were in agreement with those reported in the literature. [22]

2.3.1. Aldol condensation of compound 4 and acetone

A mixture of compound **4**, acetone (16 equivs.), and Cs_2CO_3 (10 mol %) was charged in a 10-mL round bottom flask, equipped with a condenser and a magnetic stir bar. The flask was heated at the reflux temperature (56 °C) for 6 h. Once the reactions were complete, the solid catalyst and the eventual formed char/humins were filtered off using a short column for chromatography (length = 15 cm; inner diameter = 1 cm) filled with celite and silica (5 g each) and washed with MeOH (20 mL). The excess acetone was removed by rotary evaporation (p = 10 mbar). Then, compound **3c** was purified by FFC on silica gel (eluant: petroleum ether:ethyl acetate = 1 : 1 v/v) and isolated in a 85% yield. The product was then characterized by ^{1}H and ^{13}C NMR and GC–MS (see SD section for details).

2.3.2. Aldol condensation of HMF and acetone

The same procedure described for the aldol condensation of **4** was repeated by using HMF as the substrate. The corresponding product **3b** was isolated in a 97% in 3 h. The product was then characterized by ^{1}H and ^{13}C NMR and GC–MS (see SD section for details, **Figures S2–4**).

2.4. General procedure for the reductive amination of HMF

In a typical experiment, HMF (0.5 mmol), the amino alcohol of choice (1.1 equivs.; RNH_2: R=$(CH_2)_nOH$, n = 2–3, $CH(CH_2OH)_2$, $CH_2CH(OH)CH_2OH$]), water (1 mL), 5% Pd/C as a catalyst (3 mol% of Pd with respect to HMF) were mixed in a 5-mL glass tubular reactor, equipped with a pierced glass stopper and a magnetic stir bar. The reactor was placed inside a 10 mL stainless steel autoclave which was purged by three N_2-vacuum cycles. The mixture was then pressurized with H_2 (1–10 bar) and set to react at T = 50–75 °C for t = 30–60 min. Conversion of HMF and product selectivity were determined by ^{1}H NMR analysis.

The products **5a-5d** (Table 3 **and** Scheme 8) were isolated after reactions run under the best conditions found for the reductive amination (p (H_2) = 1 bar, T = 75 °C, t = 45 min). Once reactions were complete, the solid catalyst was filtered, and the crude residue was purified by FFC on silica gel (eluant: MeOH). Then, the excess solvent was rotary evaporated (p = 10 mbar). Compounds **5a, 5b, 5c, 5d** were isolated in 96%, 97%, 93%, 95% yields, respectively. The products were characterized by ^{1}H and ^{13}C NMR (see SI for details).

2.5. General procedure for the WITTIG vinylation of HMF and its derivatives 2 and 4

In a typical procedure, a 10-mL round bottom flask equipped with a condenser and a magnetic stir bar, was charged with a mixture of HMF or its derivatives **2** or **3** (0.5 mmol), $[Ph_3PCH_3]$ $[CH_3OCO_2]$ (1.2 equivs.), and 2Me-THF (5 mL) as a solvent. The mixture was set to react at the reflux temperature (80 °C) for 2 h. Once the reaction was complete, the excess of solvent was removed by rotary evaporation (p = 10 mbar), and the liquid residue purified by FCC on silica gel (eluant: Et_2O). Vinylated compounds **6a, 6b**, and **6c** (Scheme 9) were isolated in 98%, 96% and 95% yields, respectively.

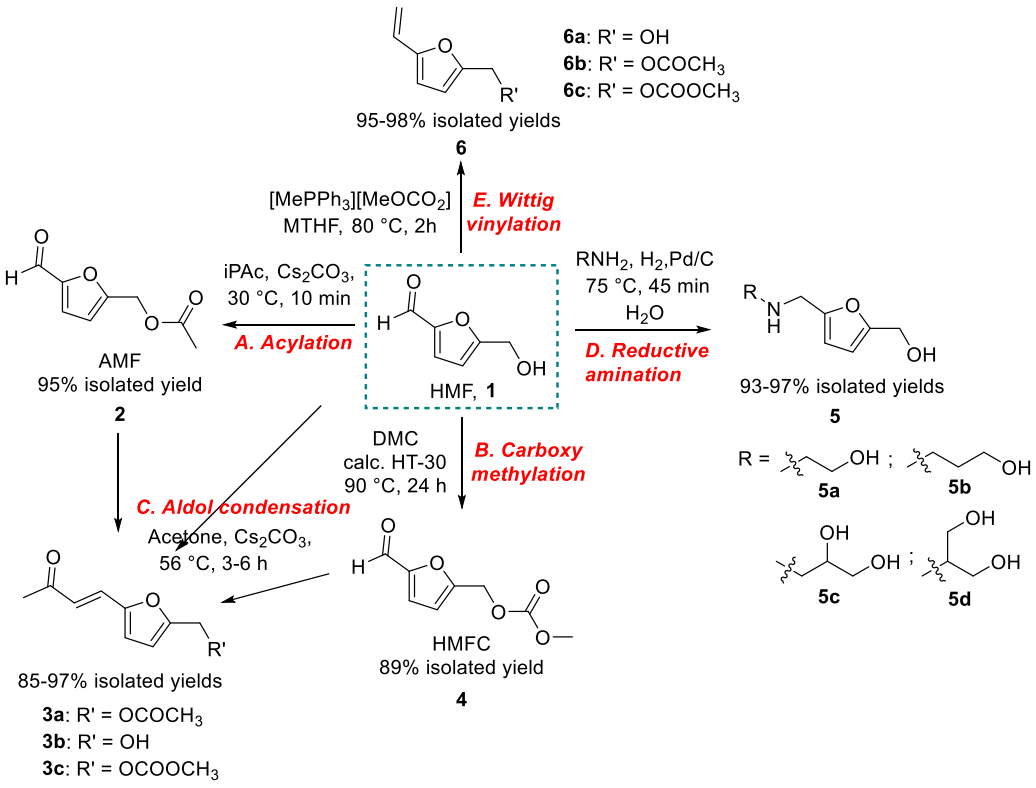
3. Results and discussion

3.1. General

All reactions were run in duplicate to ensure reproducibility: unless otherwise specified, the conversions, GC and NMR yields and isolated yields differed by less than 5% from one another. Catalysts used in this work were selected from the current literature among most active systems for esterifications, transcarbonations, aldol condensations, and reductive amination reactions.

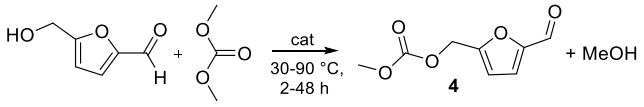
3.2. The acetylation of HMF

Isopropenyl acetate (iPAc) is a privileged reagent for the catalytic transesterification with alcohols not only because it is nontoxic and



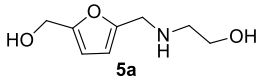
Scheme 1. Pathways for the upgrading of HMF developed in this work.

Table 2
The reaction of HMF with DMC at 90 °C, in the presence of different catalysts.



Entry	Catalyst	Cat. Loading[a]	T (°C)	t (h)	Conv. (%)[b]	Product 4, Yield (%)[c]
1	none	–	30	24	–	–
2	$[Ph_3PCH_3]$	10 mol%	30	24	59	53
3	$[OCO_2CH_3]$		90	2	≥99	56
4	Cs_2CO_3	10 mol%	30	24	73	69
5		70 mol%			75	68
6		10 mol%	90	2	≥99	45
7	C-HT-30	15wt%	30	24	–	–
8		50 wt%	90	48	74	70
9		100 wt%		24	95	93

Table 3
The Pd/C catalyzed reductive amination of HMF with ethanolamine in water.



5a

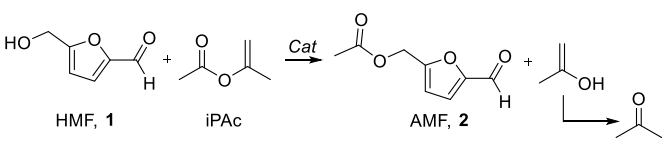
Entry	T (°C)	*p* (bar)	t (min)	5a, Yield (%)[a]
1	50	10	60	19
2	75			≥99
3	75	5		≥99
4		3		≥99
5		1		≥99
6		1	45	≥99
7			30	46

[a] Yield of **5a** determined by ^{1}H NMR.

inexpensive, but also due to the fact that the overall transformation is irreversible thanks to the formation of the enol of acetone as co-product. Based on our previous works and interest on this subject, [34] the acetylation of HMF with isopropenyl acetate (iPAc) was investigated (Scheme 2).

The acetylation protocol required a full design of experimental conditions since the reaction had no precedents in the literature. Both acid and base catalysts were selected for this study: they were either commercially available products or systems *ad-hoc* prepared through procedures described elsewhere by us and by others (**Table S1**). Among heterogeneous catalysts, an organic acid resin as Amberlyst-15, basic alkali metal carbonates (Na_2CO_3, K_2CO_3, and Cs_2CO_3), and two amphoteric solids (C—HT30 and C—HT63) comprised of mixed Mg/Al oxides, were employed. The latter (C—HT30 and C—HT63) were obtained by high-temperature calcination of commercial and cheap hydrotalcites Pural® MG30 and Pural® MG63 (HT30 and HT63) supplied by CONDEA/Sasol GmbH. The full characterization of these solids was reported previously: [36] amphoteric properties were ascribed to the coexistence of basic sites including OH groups, Mg-O or Al-O pairs and low-coordinated O^{2-} anions, and Lewis-acid sites in the form of coordinatively unsaturated Al^{3+} species. [37] Homogenous (organo) catalysts were basic ionic liquids, particularly methyl triphenyl onium methylcarbonates ($[MeQPh_3]$ $[MeOCO_2]$; $Q = P$, N) prepared by the methylation of both triphenylphosphine and triphenylamine with dimethyl carbonate (DMC), [37] and conventional liquid acids as H_2SO_4 and AcOH (entries 7–8).

The reactants (HMF and iPAc) were mutually miscible in all ratios.



Scheme 2. The acetylation of HMF with iPAc.

Experiments were therefore carried out using a solution of HMF (0.5 mmol) and iPAc (1.5 molar equivs.), the latter used also as solvent. The catalyst loading could not be strictly the same for all catalysts because of the different composition/stoichiometry of the solid and liquid systems (**Table S1**): with respect to HMF, Amberlyst-15 and calcined hydrotalcites were used in a 15 wt%, while (for most tests) alkali metal carbonates and ionic liquids were employed in 10 mol%. Preliminary tests indicated that the reaction must be run as close as possible to ambient temperature, to minimize HMF degradation and preserve the carbon balance. Experiments were carried out at 30 °C and monitored over a wide time range of 0.1 48 h. The most representative results are summarized in Table 1 which also includes a blank test without any catalyst.

All reactions were carried out using a mixture of HMF (0.5 mmol) and iPAc (1.5 molar equivs.). [a] Catalyst loading was calculated with respect to the weight (entries 2–4) or the molar amount (entries 5–9) of HMF. [b] Conversion of HMF and amounts of products (%) were determined by GC. No other products, but **2** and **3a** were detected. [c] Isolated yields of the mixture of crude products **2** + **3a** and of product **2** were determined after rotary-evaporation and filtration on celite/silica of the final reaction mixture.

No reaction took place without catalyst (entry 1), while the catalytic experiments proved the feasibility of the desired acetylation of HMF with iPAc. Except for C—HT solids and AcOH which were substantially ineffective (entries 3–4 and 6), both Amberlyst 15 (entry 2), H_2SO_4 (entry 5), the ionic liquids (entries 7–8) and alkali metal carbonates (entries 9–11) allowed a very high HMF conversion, in most cases quantitative. However, different reaction rates, product distribution, and yields were observed. The acetylated derivative of HMF [**2**, AMF: (5-formylfuran-2-yl)methyl acetate] was always the major product (>90%, by GC), but non-negligible amounts of compound **3a** [Scheme 5: (5-(3-oxobut-1-en-1-yl)furan-2-yl)methyl acetate; up to 9%] were detected, thereby indicating that acetone released by the acetylation reaction (Scheme 2) underwent aldol condensation with the HMF carbonyl.

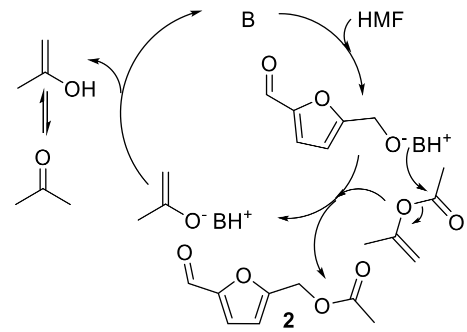
No products other than **2** and **3a** were detected in all tests. Both **2** and **3a** were isolated by rotary-evaporation and filtration on celite/silica, and their structures were assigned by GC–MS, ^{1}H NMR and ^{13}C NMR analyses (details are in the SD section).

Under acid conditions, the reaction rates apparently followed the order of acid strengths of the catalysts, i.e. H_2SO_4 > Amberlyst 15 > AcOH (entries 5, 2 and 6). Very fast conversion (99% in 0.5 h) was achieved with H_2SO_4, but massive HMF degradation took place: the reacting solution turned from pale yellow to black immediately after the catalyst addition and the yield of **2** did not exceed 19%. In the presence of Amberlyst 15, a much slower reaction was observed with a satisfactory isolated yield (**2** + **3a**=96%; **2**:**3a** = 93:7, after 24 h). Acid catalysis conditions enhanced the electrophilic character of the carboxyl carbon of iPAc (as reported for acid-catalyzed transesterification reactions of conventional esters): however, from Table 1, this (acid) activation step was significantly dependent on the nature of the catalyst and in general, except for Amberlyst 15, it brought about a poor acetylation selectivity.

Nucleophilic activation of HMF by both homogeneous and heterogenous basic catalysts proved, however, more efficient for the transesterification reaction which was complete in only a few hours (1–4 h: entries 7–11). Scheme 3 depicts the base-catalyzed reaction pathway.

With respect to acid conditions, a change of the acetylation mechanism occurred in the presence of a base catalyst (B). The latter activated the OH group of HMF by converting it into a more powerful nucleophile as the corresponding alkoxide anion. Then, an acyl nucleophilic substitution followed providing product **2** and an enolate as a leaving group. An acid-base reaction generated an enol that tautomerized to acetone and restored the B species.

The reactivity trend for alkali metal carbonates, particularly the slower conversion with Na_2CO_3- (72% after 48 h: entry 9) compared to the faster reactions observed with K_2CO_3 and even more with Cs_2CO_3 (1–2 h: entries 10–11) was consistent with the effect of ionic radii of alkali metal cations (Cs^+>K^+>Na^+) on solvation and (partial)



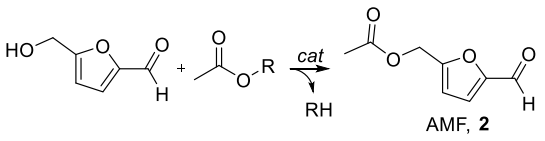
Scheme 3. Base (B) catalysed acetylation of HMF with iPAc.

solubilisation of carbonate salts in the organic mixture. [38,39] For example, in DMC, it was reported that Cs_2CO_3 and K_2CO_3 were almost equally soluble (~0.6 g/L) and about 3 times more soluble than Na_2CO_3. [40] In general, methyl carbonate ionic liquids gave slightly higher yields of the acetylated derivative **2** (up to 93%, 2 h: entry 7) compared to K_2CO_3 or Cs_2CO_3 (89%, 1 h: entry 11). The latter was preferred because it is readily available commercially and can be more easily separated (by filtration) from the product. Interestingly, an additional test with a larger amount of Cs_2CO_3 (from 10 to 70 mol%) allowed to reduce the reaction time to 0.1 h only, and to further favor AMF (**2**: 98%) over the tandem product (**3a**: 2%). Compound **2** was isolated in 94% yield (entry 12). The synthesis was scaled up by a factor of 10 (HMF: 5 mmol, 630 mg) and AMF was achieved in 92% yield within 15 min. To the best of our knowledge, neither such simple conditions nor the use of iPAc and Cs_2CO_3 as a reagent and a catalyst, respectively, were previously reported for the acetylation of HMF. Scheme 4 details for comparison, the results of three effective protocols for the synthesis of AMF using ethyl acetate and acetic anhydride as acetyl donors. [20,23] These processes gave yields of **2** at best comparable to those of the present work (Table 1), but required prolonged reactions or two-steps (protection/deprotection) sequences, harmful solvents, and time-consuming (bio)catalyst/product/ unconverted HMF separations.

3.3. *The tandem acetylation-aldol condensation of HMF*

The formation of compound **3a** during the acetylation of HMF with iPAc (Scheme 2) prompted us to investigate whether the tandem acetylation-aldol condensation process could be exploited for synthetic purposes. Similar strategies based on consecutive acetylation and acetalization tandem cascades were successfully reported by us in the reaction of glycerol and diols with iPAC. [34,41] Starting from the conditions of Table 1 [entry 11: mixture of HMF (0.5 mmol), iPAc (1.5 molar equivs.), and Cs_2CO_3 (10 mol%)] where the tandem derivative **3a** was achieved in up to a 9% amount, a detailed investigation of the effects of temperature (T, from 30 to 120 °C), time (t, from 1 to 15 h), pressure (p, from 1 to 8 bar of N_2), and solvents (polar aprotic such as cyclopentyl methyl ether or diethylene glycol dimethyl ether) were carried out. Results are reported in **Table S2** and **Figure S1**. Prolonging the reaction to 15 h at 30 °C, slightly improved the amount of **3a** to ca 15%, while the change of p and the introduction of solvents were ineffective or detrimental to the aldol condensation. The increase of the temperature apparently favored the tandem product (**3a** up to 74% by GC), but even under an inert atmosphere, the thermal degradation of HMF took place to a considerable extent. At temperatures > 30 °C, the final reaction mixtures were dark and viscous and their purification gave isolated yields of **2** + **3a** (total of the two products) that significantly decreased from 94% at 30 °C, to 52% at 90 °C, respectively.

Although none of the experiments was conclusive, these findings led us to conclude that the aldol reaction was limited by the (insufficient) amount of acetone released by the acetylation process. GC and GC/MS analyses of the reaction mixtures showed that regardless of the



R	Cat	T/t (°C/h)	2 (Yield, %)
Et	CAL-B	40/24	90
Ac	BF_3-OEt_2; BLAP (two steps)	0/0.08 20/0.5	80
Ac	piry	25/18	95

BLAP: bovine liver acetone powder

Scheme 4. Biocatalytic methods recently reported for the synthesis of AMF.

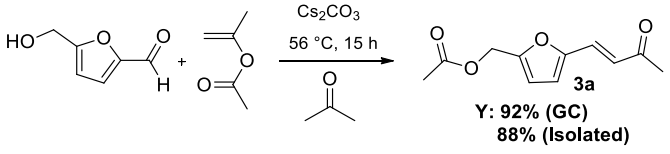
conditions, the conversion of iPAc did not exceed 75%, which meant that at the best, acetone was available in an equimolar quantity with respect to the acetyl derivative **2**. A further set of reactions was then designed by adding acetone to favor the aldol process. A mixture of HMF (0.5 mmol), iPAc (1.5 molar equivs.), and Cs_2CO_3 (10 mol%) was set to react at 30 °C for 15 h, and increasing the amount of acetone from 1 to 16 molar equivalents respect to HMF. Results are reported in Fig. 1 which describes the distribution of products and their isolated yields after purification of the final reaction mixtures by filtration on celite/silica gel.

The formation of the tandem product took advantage of the excess acetone, particularly when the Ace:HMF ratio (Q) was increased from 4 to 16, the amount of **3a** increased as well from 18 to 57% (red profile). Interestingly, albeit no HMF degradation side-processes were noticed, the onset of a straightforward aldol condensation of HMF with acetone, yielding product **3b**, was observed [fuchsia profile; the structure of (E)−4-(5-(hydroxymethyl)furan-2-yl)but-3-en-2-one was confirmed by MS and NMR analyses, (SD section, Figures S2-S4)]. The combined isolated yields of three observed products (total of **2** + **3a**+**3b**) were substantially steady at ca 95% in all experiments (gray profile). These results finally allowed us to succeed in the desired tandem sequence: under the conditions of Fig. 1 ($Q = 16$), but at the reflux temperature (56 °C), compound **3a** was achieved in a 92% yield by GC and 88% isolated yield. (Scheme 5). The sole co-product was the acetyl derivative **2** (8% by GC).

The excess acetone prevented both the thermal degradation of HMF and the bis-aldol condensation with (two equivs. of) HMF. This latter reaction was instead, noticed when Ace and HMF reactants were combined in the presence of NaOH as a catalyst. [28] Overall, the protocol of scheme 6 was not only highly effective for the one-pot synthesis of the tandem derivative **3a**, but it exemplified an intrinsically green approach in terms of selection of reagents and (mild) conditions.

Results proved that the aldol condensation was favored by acetone simultaneously supplied as a reagent and released through the iPAc-promoted acetylation. With the aim to shed light on this aspect and discriminate the contribution of the two sources of acetone, an additional experiment was carried out under the conditions of Scheme 6, by replacing acetone with its perdeuterated analogue, CD_3COCD_3. The GC–MS analysis of the reaction mixture allowed us to identify both product **3a** and its d_4-labelled isomer **3a*** (Scheme 6, **left**).

The analytical data recorded in the SIM mode for the most abundant fragment ions of compounds **3a** and **3a*** (m/z = 135 and 139, respectively; Scheme 6, **right**) indicated that the relative amounts of such products were 8% and 92% (see also **Figure S5**). As a first approximation, excluding kinetic and equilibrium isotope effects, [42] this meant that the contribution of the iPAc-derived acetone to the aldol



Scheme 5. The one-pot synthesis of the tandem product **3a**.

condensation, albeit not negligible, was about 10-fold lower than that of CD_3COCD_3.

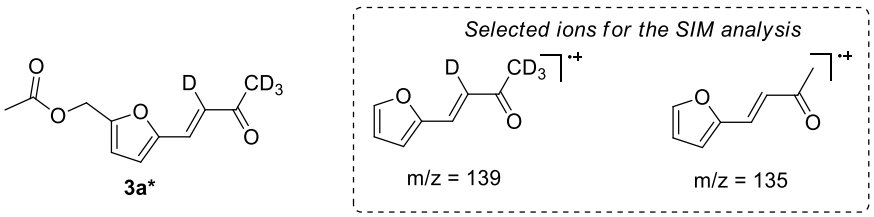
3.4. DMC-promoted transcarbonation (carboxymethylation) of HMF combined to aldol condensation

The basic and amphoteric catalysts described in **Table S1** for the acetylation of HMF, particularly methyl triphenyl phosphonium methylcarbonate ([$MePPh_3$] [$MeOCO_2$]), Cs_2CO_3, and C—HT30 as a mixed Al/Mg oxides solid, were used to investigate also the transcarbonation of HMF with dimethyl carbonate. Based on our previous results on the carboxymethylation of O-nucleophiles, [32] experiments were designed at T in the range of 30–90 °C and with a large excess DMC, which served as both a reagent and a solvent. In a typical experiment a mixture of HMF (0.5 mmol), DMC (30 equivs. with respect to HMF) and the catalyst of choice was heated at the desired temperature. The loading of the catalysts was adjusted case-by-case: with respect to HMF, Cs_2CO_3 and the ionic liquid were employed in 10–70 mol% equivalents, while the calcined hydrotalcite was used in a 15–100 wt% amount (meaning a catalyst mass amount varying from 15% to 100% of the mass amount of HMF). For tests run at reflux conditions (90 °C), the reaction flask was equipped with a condenser thermostated at 70 °C, by which the azeotropic mixture MeOH/DMC (70:30 w/w, bp = 64–67 °C) formed during the process was continuously removed. The main results of this study are summarized in Table 2.

All reactions were carried out using a mixture of HMF (0.5 mmol) and DMC (30 molar equivs.). [a] Catalyst loading was calculated with respect to the molar amount (entries 2–3) or the weight (entries 4–6) of HMF. [b] Conversion of HMF. [c] Yield of product **4** isolated after rotary-evaporation and filtration on celite/silica of the final reaction mixture.

The methyl carbonate derivative of HMF [**4**: 5-formylfuran-2-yl) methyl carbonate] was the only detected product by GC and GC/MS. After each test, compound **4** was isolated by rotary-evaporation the final reaction mixture and filtration/elution of the residue on celite/silica gel (5 g; eluant: Et_2O, 30 mL). The structure of the product was confirmed by GC–MS, ^1H and ^{13}C NMR (see also the experimental section).

Compared to the acetylation with iPAc (Table 1), the reversibility of the reaction of HMF with DMC complicates the process as it requires prolonged experiments and/or higher temperature. At 30 °C, in the presence of basic catalysts ([$MePPh_3$] [$MeOCO_2$]) and Cs_2CO_3], the HMF conversion was 59–73% after 24 h (entries 2 and 4) and was not improved even by increasing the catalyst loading from 10 to 70 mol% (Cs_2CO_3: entry 5). The yield of **4** (53–69%) was consistent with the observed conversion. This result was confirmed also by the amount of unconverted HMF (32–40% compared to the starting quantity of 0.5 mmol) that was recovered after purification/filtration on celite/silica gel. Increasing the temperature to 90 °C prompted a quantitative process in only 2 h, but about half of HMF underwent decomposition as anticipated by the black color of the reactant solution: the yield of product **4** did not exceed 56% (entries 3 and 6). Under such conditions, the recycle/reuse of catalysts was not even attempted because at the end of the process, both homogeneous and heterogeneous systems [([$MePPh_3$] [$MeOCO_2$]) and Cs_2CO_3] were contaminated by the presence of high-molecular weight by-products deriving from HMF degradation.



Scheme 6. Left: d_4-labelled product **3a*** observed in the reaction of HMF with d_6-acetone; right: ions selected for SIM GC–MS analysis of products **3a** and **3a***, respectively.

The calcined hydrotalcite (C—HT30) was considerably less active than basic catalysts and not effective at 50 wt% and 30 °C (entry 7). However, at higher loading (100 wt%: 1:1 mass ratio with HMF) with respect to HMF, C—HT30 could be used successfully at 90 °C to reach an almost complete conversion (95%) and an isolated yield of **4** of 93% (24 h: entry 9). The milder catalytic performance of this (amphoteric) system apparently prevented the degradation of HMF and the catalyst was perfectly suited for recycle. After filtration, a pale yellow solution was separated from solid C—HT30. The latter was dried under vacuum (70 °C, 5 mbar, overnight) and reused for another reaction carried out under the conditions of entry 9 in Table 2. The overall sequence was repeated for 4 subsequent experiments. Results are reported in Fig. 2.

The catalyst could be recycled without any significant change of its performance: both the conversion (blue bars) and the yield of product **4** (red bars) were steady at 94–95% and 91–93%, respectively.

The synthesis was also scaled up by a factor of 10 (HMF: 50 mmol), affording product **4** in an 89% isolated yield after 36 h. Overall, the protocol was robust and reproducible. The excellent HMF/catalyst tolerability along with the simple downstream operations substantially offset the potential issue of the high loading of C—HT30.

Compound **4**, once isolated, could be further functionalized by aldol condensation with acetone. Under the best conditions of **Scheme 6**, additional experiments demonstrated that in the presence of excess acetone, the methyl carbonate of HMF was converted into the corresponding α,β-unsaturated carbonyl product **3c** in a 85% isolated yield after 15 h (**Scheme 7**).

Compound **3c** is a new compound (characterization details including NMR and MS spectra are in the SD section). The co-presence of a carbonate group and conjugated $C=C$ and $C=O$ bonds make it a promising building block for new HMF-based oligomers and polymers.

Interestingly, also the Cs_2CO_3-catalysed aldol condensation of HMF with acetone was very satisfactory: compound **3b** was isolated in a 97% yield in 3 h (conditions of **Scheme 7**).

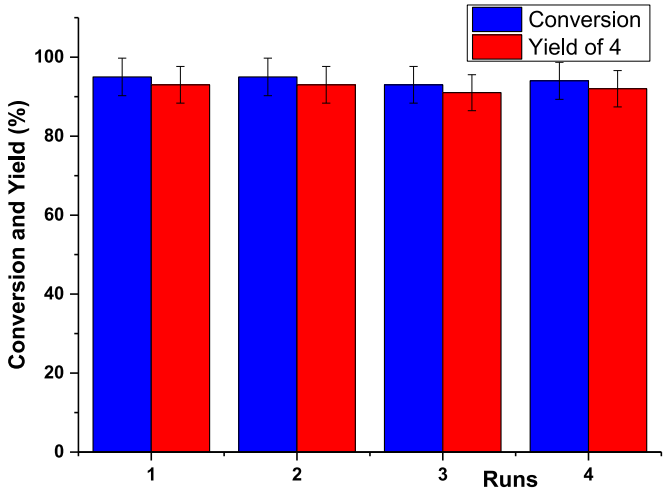


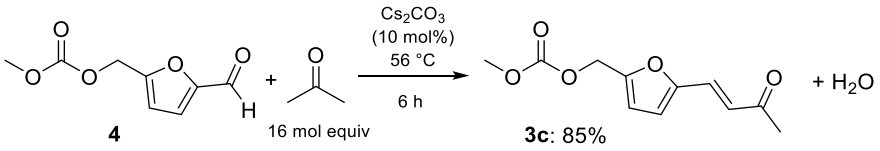
Fig. 2. Recycle tests of C—HT30 (100 wt%). Reaction conditions were those of Table 2, entry 9: HMF (0.5 mmol), DMC (30 molar equivs.), 90 °C, 24 h. Conversion and yield of **4** isolated were determined as in Table 2.

3.5. *Pd/C catalyzed reductive amination of HMF and its derivatives in water*

Notwithstanding the extensive literature on the reductive amination of carbonyl compounds, there are only few examples of the condensation of HMF with primary amines. [43,44] Reductive amination of HMF has been reported by a two-step method involving formation of an HMF-imine intermediate followed by hydride reduction, [45] or by one-pot metal catalyzed reactions with H_2. [44] Catalytic procedures have been preferred over hydride donors (*e.g.* $NaBH_4$) that generate over-stoichiometric amounts of toxic waste to be disposed of. Although, a key challenge of these transformations remains the development of robust protocols able to operate in aqueous solutions which are more suitable for the upgrading of furanics in biorefineries. [46] With the aim to design an easily accessible method having high synthetic value, we opted to investigate the reductive amination of HMF in the presence of commercial Pd/C as a catalyst, OH-functionalized renewable amines such as 2-aminopropanediol (2-APD) and 3-aminopropanediol (3-APD), [47] and water as the solvent. Ethanolamine (EA) and propanolamine (PA) were used as model substrates in the initial experiments. Accordingly, the effects of temperature, pressure and time were explored using a mixture of HMF (0.5 mmol), EA (1.1 equivs.), water (1 mL), 5% Pd/C (3 mol% of active metal with respect to HMF) that was set to react at $T =$ 50–75 °C, under H_2 pressure (p = 1–10 bar) in an autoclave, for 30–60 min. **Table 3** reports the results. Conversion and product selectivity were determined by ^{1}H NMR upon calibration. Any attempt to characterize the reaction products by GC/MS proved unsuccessful.

Experiments proved that none other than the expected derivative of reductive amination of HMF [**5a**: 2-((5-(hydroxymethyl)furan-2-yl) amino)ethan-1-ol] was observed. At 10 bar, increasing the temperature from 50 to 75 °C, a 4-fold increase of the product yield from 19 to ≥99%, was observed after only 1 h (entries 1–2). While the progressive decreasing of p from 10 to 1 bar did not affect the outcome at all: at 75 °C, the reaction was always quantitative with complete selectivity to product **5a** (entries 3–5). It was finally noticed that even the reaction time could be further reduced from 1 to 0.75 min without any appreciable alteration of the **5a** yield (entry 6). Such mild conditions were not previously reported for the reductive amination of HMF with a bidentate nucleophile such as ethanol amine. To the best of our knowledge, this reaction was described only in one recent article where product **5a** was obtained in 86% yield after 6 h at 100 °C (3 bar H_2) in the presence of Ni_6AlO_x as a catalyst and a water/EtOH (1:2 v/v) mixture as a solvent. [47] The process of **Table 3** was also fully chemoselective towards amine **5a**; HMF acetalization products deriving from the attack of the OH group to the carbonyl were never detected.

The reductive amination of HMF was then explored using propanolamine and the two aminodiol regioisomers derived from glycerol, 3-amino-1,2-propanediol and 2-amino-1,3-propanediol (serinol). Experiments carried out under the conditions of entry 6 of **Table 3** [$T = 75$ °C, p (H_2) = 1 bar, t = 45 min] demonstrated the synthetic scope of the protocol. The three tested reactions proved highly efficient yielding the corresponding products **5b, 5c**, and **5d** in 95%, 98% and 97% isolated



Scheme 7. The acetone promoted aldol condensation of compound **4**.

yields, respectively (Scheme 8).

The operative simplicity and effectiveness of the present procedure proved more efficient for the reductive amination of HMF compared to the above quoted methods, [44 47] especially in aqueous solution. Additionally, compounds **5b, 5c**, and **5d** were fully novel HMF-derivatives (further details on isolation and characterization are in the SD section): the presence of multiple (2–3) OH groups and an amine function made these products appealing for further upgrading, for example, in the synthesis of renewable furanic-based polymeric materials.

To confirm the mechanism of formation of **5a d**, additional experiments were carried out by investigating the reaction of HMF with hydroxyamines of Table 3 and Scheme 8 at lower temperatures, both with and without Pd/C. Tests confirmed the generally accepted two-step mechanism for reductive amination. i) Initially, quantitative formation of an imine derivative was observed. Notwithstanding this was formally a dehydration of the HMF carbonyl, no adverse effects of water as a solvent were noticed. The reaction proceeded quickly in all cases at 30 °C and in the absence of any catalyst. ii) In the second step, Pd/C-catalyzed hydrogenation of the $C = N$ bond of the imine at $T \geq 50$ °C yielded the desired amine. The results of this study along with the characterization of all imine intermediates are reported in the SD section (**Figures S6–9** for the investigation and **Figures S23–30** for the characterization).

It should be finally noted that any attempt to perform the reductive amination by replacing HMF with derivatives **2** and **4** (the acylated HMF and the methyl carbonate of HMF, respectively) was unsuccessful. A complex mixture of products was obtained in both cases whose characterization/purification failed (Figure S10 exemplifies the case of the reaction of **2** with ethanol amine).

3.6. Wittig vinylation of HMF and its derivatives with triphenyl phosphonium methylcarbonate

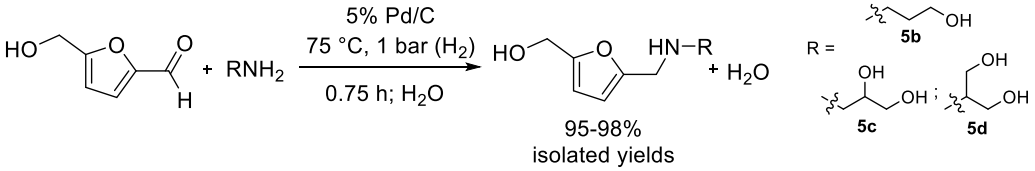
As was mentioned in the introduction, some years ago our group discovered that the ylide-like reactivity of a specific ionic liquid as methyl triphenylphosphonium methylcarbonate ($[MePPh_3][MeOCO_2]$), allowed not only the selective Wittig vinylation of a variety of aldehydes and ketones, but also a considerable improvement of the green metrics of the process (atom economy, E-factor, and mass index) with respect to conventional Wittig reactions. [31] We thought that these advantages could be exploited on HMF. Moreover, a further benefit could be the use of a renewable solvent as methyl tetrahydrofuran (Me-THF) that was itself derived from HMF. Experiments were then designed based on the protocol originally reported by us: a mixture of HMF (0.5 mmol), $[MePPh_3][MeOCO_2]$ (1.2 equivs.), and 2Me-THF (1 mL) was set to react at the reflux temperature (80 °C) under a N_2 atmosphere, for 2 h. Conditions proved successful in providing both the total conversion of HMF and the full selectivity towards the vinyl derivative **6a** [(5-vinylfuran-2-yl)methanol]. This compound was isolated in an excellent 98% yield. In light of this finding, the reaction scope was extended to HMF derivatives **2** and **4**, with equally good results on the formation of the corresponding terminal olefins **6b** [(5-vinylfuran-2-yl)methyl acetate] and **6c** [methyl ((5-vinylfuran-2-yl) methyl) carbonate], respectively. These were isolated in 96% and 95% yields. (Scheme 9).

Products **6a 6c** were purified by FCC on silica gel and fully characterized by NMR and GC/MS analyses (details are in the experimental and SD sections). Only one previous paper described the formation of compound **6a** through a classical Wittig reaction and with a yield of only 69%, [17] while **6b** and **6c** were two new derivatives of HMF. This investigation proved the suitability of the $[MePPh_3][MeOCO_2]$-mediated vinylation for multiple-functionalized substrates as HMF and its homologues **2** and **4**, and corroborated the green advantages of the procedure including the total absence of halides throughout the whole process (and the lack of formation of inorganic halide salts to be disposed of) and the isolation of products by filtration over silica to remove the co-product triphenylphosphine oxide (TPPO).

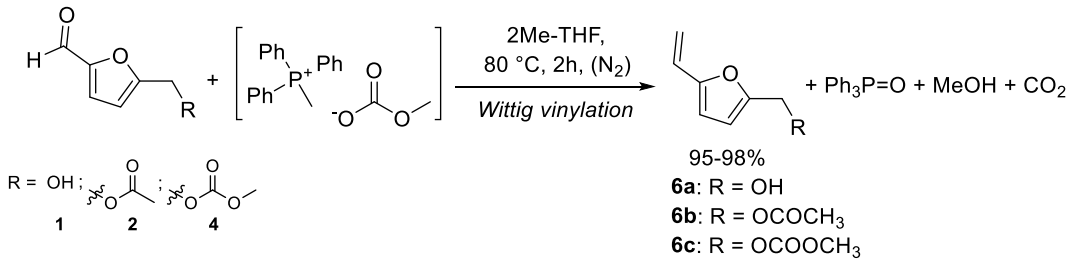
4. Conclusions

The present work described diversified, robust, and greener protocols for the chemical upgrading of HMF. A variety of reactions have been described based on new or improved procedures by which a total of 12 different HMF derivatives were synthesized, isolated, and fully characterized, 7 of which new. The design of the transformations has been inspired by the green chemistry principles regarding the choice of catalytic protocols, the safety and/or renewability of reagents and solvents. Reagents include isopropenyl acetate, dimethyl carbonate, acetone, and a halide-free phosphonium vinylation reagent, that were used to carry out reactions of acetylation, carboxymethylation, aldol condensation, and vinylation, respectively, on HMF and on its homologues: acetylated HMF and the methyl carbonate of HMF. In one case, a combination of acetylation and aldol condensation has been successfully accomplished to achieve a double functionalization of HMF through a one-step tandem sequence. Moreover, the reductive amination of HMF has also been performed in the presence of water as a solvent and glycerol-derived aminodiols.

In order to make the proposed procedures as accessible as possible and avoid any thermal degradation of HMF, the use of commercial catalysts (e.g. Cs_2CO_3 and Pd/C) has been privileged and experiments have been tuned to operate at 30–90 °C and atmospheric pressure. Notwithstanding the mild conditions adopted, high isolated yields of 85–95% were obtained for all products, often in a few hours or less. These results pave the way for both the study of new applications for such products and the design of new upgrading strategies. Just to name a few promising perspectives, polyhydroxylated or vinylated derivatives of HMF could be used in the materials (polymers) chemistry, while



Scheme 8. The reductive amination of HMF with multifunctionalized hydroxyamines.



Scheme 9. The Wittig vinylation of HMF and its derivatives **2** and **4** by [$MePPh_3$] [$MeOCO_2$].

oxygenated tandem products of acetylation-aldol condensation could be suitable as fuel additives.

The work-up and post-reaction treatments of the reported procedures have not been always optimized for what concerns, for instance, the recycle of excess reagents (e.g. DMC and acetone which have been concurrently employed as solvents) and/or the recovery/recycle of the catalysts. However, it should be noted here that not only the reaction steps but also the downstream operations become difficult/delicate in the presence of sensitive substrates such as HMF and its derivatives. Further improvements of such aspects are currently under study in our laboratories and will be the object of future papers.

CRediT authorship contribution statement

Davide Rigo: Conceptualization, Investigation, Methodology, Writing – review & editing. **Daniele Polidoro:** Investigation, Methodology, Writing – original draft. **Alvise Perosa:** Writing – review & editing, Funding acquisition. **Maurizio Selva:** Conceptualization, Supervision, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

The authors report no declarations of interest.

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