

# High-Yield Synthesis of 1-Hydroxyhexane-2,5-dione via Hydrogenation/Hydrolysis of 5-Hydroxymethyl-furfural in Ionic Liquid-Assisted Multi-Phase Systems

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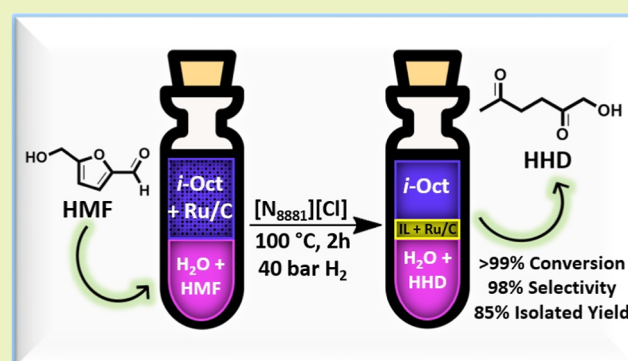
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Supporting Information

**ABSTRACT:** Different multiphase (MP) systems comprising immiscible liquid water, a hydrocarbon, and an ionic liquid (IL) were investigated for the combined hydrogenation/hydrolysis of 5-hydroxymethylfurfural (HMF) to 1-hydroxyhexane-2,5-dione (HHD) in the presence of 5% Ru/C as a catalyst. Excellent control of selectivity was achieved using a water, isooctane, and methyltrioctylammonium chloride ( $[N_{8881}][Cl]$ ) liquid triphase: at 100 °C and 40 bar of  $H_2$ , HHD was obtained as an exclusive product (98%), and it was isolated in an 85% yield at complete conversion of HMF. Both the reagents and the products were partitioned in the aqueous phase, while, by tuning the relative proportions of the MP components, the catalyst (Ru/C) could be perfectly segregated in the IL layer, where it could be recycled and reused up to six times without any loss of activity and selectivity, in a robust semi-continuous mode. Under such conditions, a reaction productivity of up to 9.7 mmol HHD ( $g_{cat} \cdot h$ )<sup>-1</sup> was reached with negligible metal leaching (<0.67 ppb).

**KEYWORDS:** 5-hydroxymethylfurfural, 1-hydroxyhexane-2,5-dione, multiphase catalysis, ionic liquids, bio-based platform chemicals, hydrogenation, hydrogenolysis



## INTRODUCTION

The design of sustainable chemical processes through the upgrading of biomass derivatives is a primary goal of modern chemistry, grounded on multiple global needs such as the preservation of natural resources, water conservation, reduction of CO<sub>2</sub> emissions, and, more generally, the prevention of pollution and climate change mitigation.<sup>1–5</sup> Lignocellulosic biomass plays a preeminent role in this scenario, not only for its abundance but also for its chemical richness that makes it a source of highly differentiated platform molecules, ranging from primary fractions of sugars and aromatics obtained by the breakdown of cellulose and lignin to a variety of secondary derivatives such as furans.<sup>6–10</sup> To the latter class belongs 5-hydroxymethylfurfural (HMF), the hydrolysis-dehydration product of lignocellulose-based hexoses (glucose and mannose).<sup>11–14</sup> HMF is considered one of the most promising bio-based products because of its multiple functionalization and versatility toward a range of reactions, including oxidations, etherifications, couplings, condensations, hydrogenations, and hydrolysis.<sup>15,16</sup> Hydrogenations, in particular, have been extensively investigated to achieve both carbonyl- and ring-reduction products as 2,5-bis(hydroxymethyl) furan (BHMF) and 2,5-bis(hydroxymethyl) tetrahydrofuran (BHMTFH), respectively (Scheme 1, bottom: center and left).

The hydrolysis instead and, more specifically, combined reactions of hydrogenation and ring-opening hydrolysis of HMF have been far less studied notwithstanding their potential for the preparation of renewable polyols.<sup>17–20</sup> Among the products of these transformations, an emerging derivative is 1-hydroxyhexane-2,5-dione (HHD: Scheme 1, bottom right), the synthesis of which has been the subject of this work.

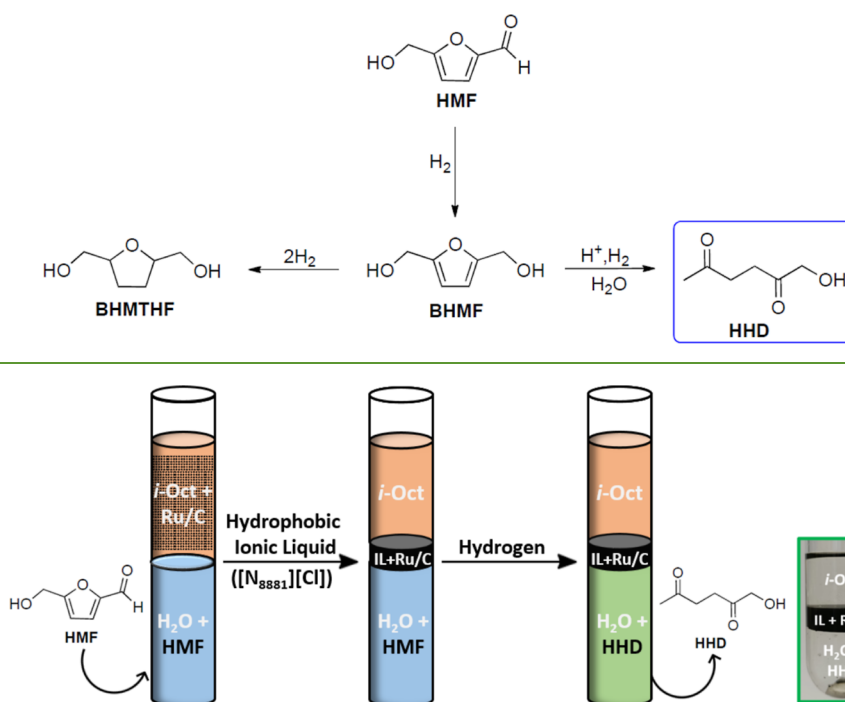
The conversion of 5-HMF to HHD requires specialized catalysts and reaction environments able to display both reduction ability and acidity necessary for C=C bond saturation and furan ring opening,<sup>21</sup> as highlighted also in a recent review article by de Vries and co-workers.<sup>22</sup> However, few such systems have been reported so far.

Heterogeneous catalysts for this synthesis (HMF → HHD) have been designed based on precious late transition metals such as Pt/C in combination with oxalic acid,<sup>23</sup> a bimetallic Rh–Re system on acidic SiO<sub>2</sub>,<sup>24</sup> and a bifunctional Pd/MIL-62

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**Scheme 1. Center and left: major Hydrogenation Products of HMF; right: HHD from Combined Hydrogenation and Hydrolysis of HMF**



**Figure 1.** Pictorial representation of the IL-based MP system designed for the catalytic hydrogenation/hydrolysis of 5-HMF to HHD. The photo in the green-edged inset (bottom right) shows the genuine appearance of the MP reactor at the end of the experiment.

101(Cr).<sup>25</sup> Reactions typically took place at 120–140 °C and 30–80 bar H<sub>2</sub> and proceeded with full conversion and satisfactory selectivity (up to 82%). Interestingly, besides HMF, fructose and inulin were also described as starting substrates for the direct preparation of HHD in the presence of Pd/C with Amberlyst-15 or carbonic acid (under CO<sub>2</sub> pressure in an aqueous solution).<sup>26,27</sup> In all cases, however, HHD was isolated in moderate yields (55–60%). Non-noble metal and homogeneous catalysts were also implemented. For example, a Ni-WO<sub>x</sub>/Al<sub>2</sub>O<sub>3</sub> system, in which the acid sites were introduced by WO<sub>x</sub>, was successfully applied in the conversion of aq HMF, providing HHD in 59% GC yield.<sup>28</sup> Metal complexes such as [(η<sup>6</sup>-*p*-cymene)RuCl(8-aminoquinoline)]Cl with formic acid and [Cp\*Ir(2,2′-bipyridine)(H<sub>2</sub>O)]<sup>2+</sup>, which were able to generate acidity in situ through the heterolytic dissociation of H<sub>2</sub>, allowed the formation of HHD in GC yields in the range of 54–86%.<sup>29,30</sup> Yet, the product separation was tricky. The best result reported so far was achieved with the half-sandwich [Cp\*Ir(dpa)Cl]Cl (dpa = dipyridyl amine) catalytic complex, by which the reaction of aqueous HMF proceeded with full conversion and HHD was obtained in a 69% isolated yield.<sup>31</sup> This scenario led us to conclude that the setup of effective synthetic methods for HHD was still a largely unexplored area with major issues associated with the catalyst recovery and the product isolation/purification.

Based on our long-standing expertise on the chemical upgradation of bio-based molecules through multiphase (MP)-based protocols for the hydrogenation and reductive amination of levulinic acid,<sup>32,33</sup> hydrogenation of sugars and sugar-like substrates,<sup>34</sup> and oxidation of HMF,<sup>35</sup> we have recently demonstrated that the same MP conditions could be successfully used for the synthesis of HHD from HMF. At 100 °C and 50 bar of H<sub>2</sub>, in an MP system comprising water,

isooctane, methyltrioctylphosphonium bis(trifluoromethyl) sulfonimide ([P<sub>8881</sub>][NTf<sub>2</sub>]) as an ionic liquid (IL), and commercial 5 wt % Ru/C as the catalyst, HHD was achieved from HMF with 99% selectivity and 75% isolated yield.<sup>36</sup> No additional acids were necessary. Interphase phenomena in this configuration not only controlled the kinetics of the hydrogenation/hydrolysis of HMF and the product distribution but also allowed the segregation of the heterogeneous catalyst (Ru/C) in the IL phase. The catalyst acted in a phase different from water where the reaction took place, while the hydrocarbon solvent (*i*-octane), far from inconsequential, was necessary to improve phase separation. Particularly, the catalyst/product separation so achieved greatly facilitated the workup of the reaction mixture.

Notwithstanding the reliability and the good yield of the protocol, the productivity was moderate due to the long reaction time required for each batch test (up to 18 h), and Ru/C rapidly deactivated. Recycling experiments demonstrated that after each reaction, a thermal/reducing treatment was necessary to restore the catalyst performance. This was highly undesirable since the in situ reuse of both homogeneous and heterogeneous catalyst is one of the strongest advantages of the MP procedures. We were therefore prompted to look into the role and effects of the IL. Herein, a representative library of six onium salts, both ammonium and phosphonium, was investigated with the aim to improve both the reaction rate and the reuse of Ru/C.

Excellent results were achieved by the use of methyltrioctylammonium chloride ([N<sub>8881</sub>][Cl]), which was both ad hoc prepared and sourced by a commercial supplier. The corresponding MP system based on an aqueous solution of HMF, isooctane, [N<sub>8881</sub>][Cl], and 5% Ru/C is depicted in Figure 1 (center).

Under such conditions, at 100 °C and 40 bar of H<sub>2</sub>, the conversion of HMF was ca. 9 times faster compared to that observed in our previous studies, and the desired product (HHD) was obtained with a selectivity of 98% and an isolated yield of 85%, the best result so far obtained for this synthesis. Furthermore, the catalyst, which appeared fully suspended in the IL phase (Figure 1), preserved its performance over time: Ru/C was recycled for at least six times without having to be removed from the reactor and without any loss of activity. This allowed us to implement a semi-continuous procedure with a productivity of up to 9.7 mmol HHD (g<sub>cat</sub>·h)<sup>-1</sup> amenable for gram-scale syntheses. The metal leaching in the aqueous phase was negligible (<0.67 ppb, by ICP–MS). Overall, the screening of ILs proposed here was crucial to select one for the quantitative synthesis of HHD.

## RESULTS AND DISCUSSION

**General.** Carbon-supported Ru-based catalysts, even commercial samples, display features such as the surface area, the metal dispersion, and the thermal stability under non-oxidizing atmospheres, which often make them the best choice for the hydrogenation of water-soluble bio-based substrates including HMF or its derivatives.<sup>37–39</sup> Moreover, Ru is available at a relatively lower price (~4%) compared to other metals of comparable activity such as Au and Pt.<sup>40</sup> For these reasons and with the aim to design protocols as accessible as possible, commercial 5% Ru/C was exclusively used throughout this study. This catalyst was characterized for its structural, morphological, and acidic properties in recent papers by our group.<sup>32,35,36,41</sup>

Following the same rationale used in the selection of the catalyst, six easily available onium salts were chosen to implement a straightforward MP system for the synthesis of HHD. Halide-based (Cl, Br, and I) ammonium and phosphonium salts were employed, bearing C<sub>1</sub>, C<sub>4</sub>, and C<sub>8</sub> alkyl substituents. These included methyltetrabutylammonium chloride ([N<sub>4441</sub>][Cl]), tetrabutylammonium bromide ([N<sub>4444</sub>][Br]), tetrabutylammonium iodide ([N<sub>4444</sub>][I]), methyltrioctylammonium chloride ([N<sub>8881</sub>][Cl]), tetrabutylphosphonium chloride ([P<sub>4444</sub>][Cl]), and methyltrioctylphosphonium chloride ([P<sub>8881</sub>][Cl]). Commercial Aliquat 336 sourced by Aldrich was also used for this scope: this was a [N<sub>xxx1</sub>][Cl] salt comprising a mixture of C<sub>8</sub> and C<sub>10</sub> alkyl chains (x = 8 and 10) with C<sub>8</sub> predominating.<sup>42</sup> Regardless of the fact that [N<sub>4444</sub>][Br] and [N<sub>4444</sub>][I] have a melting point above 100 °C;<sup>43</sup> they are still ILs under the experimental conditions of this work.

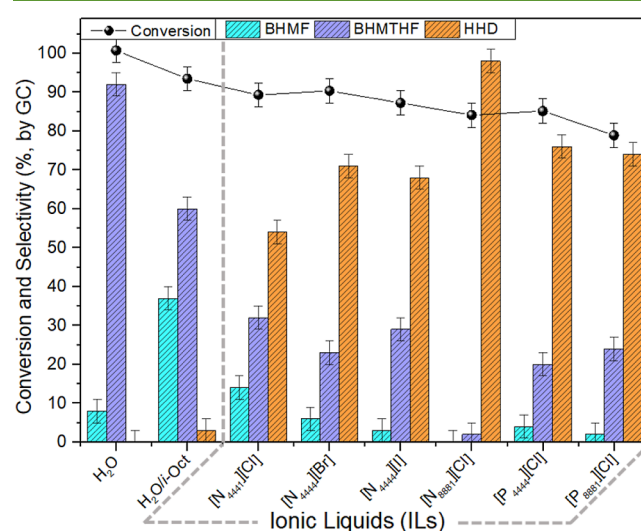
Based on our previous investigations,<sup>36</sup> if not otherwise indicated, MP experiments for the synthesis of HHD were run in a stainless-steel autoclave charged with an aqueous solution of HMF (HMF: 63 mg; H<sub>2</sub>O: 5 mL), 5% Ru/C (5 mol % with respect to HMF, 50 mg), isooctane (5 mL), and an IL (500 mg) selected among the above-quoted six onium salts. The reactor was heated at the desired temperature and pressurized with H<sub>2</sub> as described in the following sections. All the reported reactions were run in duplicate to ensure reproducibility: conversions, selectivities, and isolated yields differed by less than 5% from one test to another.

**Choice of IL-Based MP Systems for the Hydrogenation/Hydrolysis of 5-HMF to HHD.** MP experiments were carried out at 80 °C under 40 bar H<sub>2</sub> for 2 h, by systematically varying the IL chosen among [N<sub>4441</sub>][Cl], [N<sub>4444</sub>][Br], [N<sub>4444</sub>][I], [N<sub>8881</sub>][Cl], [P<sub>4444</sub>][Cl], and

[P<sub>8881</sub>][Cl]. For comparison, reference experiments were performed only in water and in a biphasic system comprising water and isooctane. NMR and GC/MS analyses of the reaction mixture confirmed the formation of the products of Scheme 1, while conversion and selectivity were determined by GC/flame ionization detector (FID). Given the interest for HHD, which was derived from both the hydrogenation and the hydrolysis of HMF, the product selectivity was defined according to eq 1

$$S_i = [\text{mol } i / \text{conv. HMF}] \times 100 \quad (1)$$

where S<sub>i</sub> is the selectivity [%] for compound *i* (i.e., BMHF, HHD, etc.), mol *i* stands for the total moles of compound *i* (by GC calibration), and conv. HMF is the converted moles of HMF (calibration curves are given in the Supporting Information, Figures S10–S12) in all the processes where it is consumed (hydrogenation and hydrolysis). Results are reported in Figure 2.

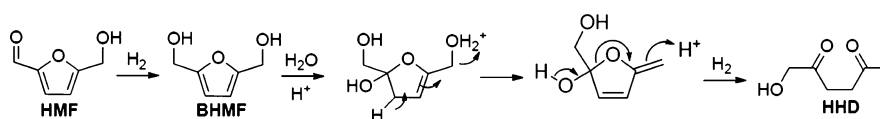


**Figure 2.** Effect of different ILs on the MP hydrogenation/hydrolysis of 5-HMF to HHD. Reaction conditions: HMF (0.5 mmol, 63 mg), Ru/C (5 mol % with respect to HMF, 50 mg), H<sub>2</sub>O (5 mL), isooctane (5 mL), IL (500 mg), 40 bar H<sub>2</sub>, 80 °C, 2 h. Conversion and selectivity were determined by GC.

In the absence of an IL, reactions proceeded with a very high conversion (90–100%) of HMF and the almost exclusive formation of products coming from the hydrogenation of both the carbonyl function and the furanic ring. More specifically, in water, the major product was BHMTHF (92%), while in water/isooctane, a mixture of BHMf (37%) and BHMTHF (60%) was achieved with only traces of HHD (<3%) (Figure 2: first two bars from left). These results were consistent with the partition of the hydrophobic catalyst in isooctane in the water/isooctane biphasic system (Figure 1, left). Such confinement of Ru/C out of the aqueous solution where the reactants and the products were soluble implied that an interfacial hydrogenation took place with slower kinetics compared to the reaction in water alone.<sup>36</sup> Accordingly, both a slightly lower conversion (90%) of HMF and a higher amount of the partially hydrogenated product, BHMf, were observed in the water/isooctane system.

The addition of an onium salt significantly changed the reaction outcome. Compared to the water/isooctane system, the conversion of HMF showed a general decrease, but at the

**Scheme 2. Mechanism for the formation of HHD via Hydrogenation of HMF and Hydrolytic Ring Opening of BHMF, from ref 36**



228 same time, a sizeable increase of the selectivity toward HHD  
229 was obtained. The latter result in particular indicated that ILs  
230 enhanced the acidity of the environment, in coherence with the  
231 most accepted mechanistic pathway for the formation of HHD  
232 (Scheme 2).<sup>36</sup>

233 After HMF hydrogenation, BHMF acted as the first  
234 intermediate for the acid-promoted ring opening sequence.  
235 On the other hand, once the fully hydrogenated derivative  
236 formed (BHMTF), the reaction could not proceed any  
237 further.

238 The occurrence of a weak acidity in ILs is well known,  
239 especially in the presence of a small amount of water, and  
240 highly appreciated in catalysis.<sup>44,45</sup> A recent paper has reported  
241 that even for simple ammonium salts, a residual content of  
242 water (0–7 wt %) could increase the cationic acidity by over  
243 10 orders of magnitude.<sup>46</sup> Under the MP conditions  
244 investigated here, an additional minor contribution to acidity  
245 could come also from the C support of the catalyst that from  
246 our previous characterization tests showed a total surface  
247 acidity of ca. 140  $\mu\text{equiv g}^{-1}$ .<sup>41</sup>

248 Figure 2, however, clearly highlighted how the structure of  
249 the onium salt was crucial in modifying the product  
250 distribution. Symmetrical cations with four C<sub>4</sub> substituents  
251 yielded apparently similar results, regardless of the N or P  
252 center and/or the halide anion: at conversions of 85–87%, the  
253 selectivity for HHD was 71, 68, and 76% for [N<sub>4444</sub>][Br],  
254 [N<sub>4444</sub>][I], and [P<sub>4444</sub>][Cl], respectively (Figure 2). On the  
255 other hand, unsymmetrically substituted onium salts showed  
256 larger differences with each other, even though they possessed  
257 the same anion. The most striking and best result was achieved  
258 with [N<sub>8881</sub>][Cl] in the presence of which HHD was almost  
259 exclusively formed (98%), at 81% conversion. Instead, other  
260 chloride-based salts, [N<sub>4441</sub>][Cl] and [P<sub>8881</sub>][Cl], allowed a  
261 conversion of 86 and 76% with a remarkably lower HHD  
262 selectivity of 54 and 74%, respectively. No products, other than  
263 BHMF and BHMTF, were detected in all cases.

264 For comparison, an additional MP test was performed by  
265 using a non-halide anion-based IL; particularly [P<sub>8881</sub>][NTf<sub>2</sub>]  
266 was considered because it was previously investigated by some  
267 of us for the same reaction (see Introduction).<sup>36</sup> Under the  
268 condition of Figure 2 (HMF: 0.5 mmol, 63 mg; Ru/C: 5 mol  
269 % with respect to HMF, 50 mg; H<sub>2</sub>O: 5 mL; isooctane: 5 mL;  
270 IL: 500 mg; 40 bar H<sub>2</sub>; 80 °C; 2 h), the HMF conversion was  
271 77%, while the HHD selectivity did not exceed 80% due to the  
272 concurrent formation of BHMF (7%) and BHMTF (13%).  
273 This result further emphasized the superior performance of  
274 [N<sub>8881</sub>][Cl].

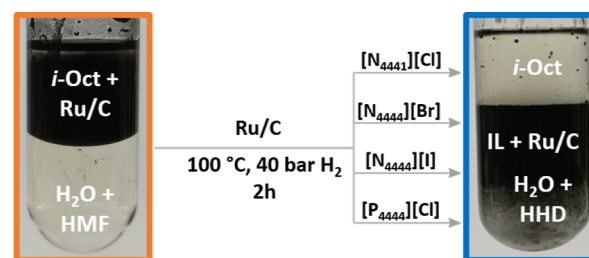
275 In line with these results, previous studies on catalytic MP  
276 reactions mediated by ILs indicated that the outcome (kinetics  
277 and selectivity) was largely dependent on the nature of the ILs  
278 themselves. For example, when an MP system comprising  
279 isooctane, water, and an IL was used for the Ru/C-catalyzed  
280 hydrogenation/dehydration of levulinic acid to  $\gamma$ -valerolactone  
281 (GVL, mentioned in the Introduction),<sup>32</sup> contrary to the MP  
282 conversion of HMF to HHD, it was noticed that [P<sub>8881</sub>][NTf<sub>2</sub>]

was better suited to the scope than [N<sub>8881</sub>][Cl]; the IL ensured  
283 a clean GVL separation in the aqueous phase and the catalyst  
284 recycle; it did not affect the reaction selectivity, but it  
285 substantially depressed the substrate conversion.<sup>286</sup>

In general, microscopic effects responsible for most  
287 interphase phenomena in mixtures of immiscible or partially  
288 miscible liquids and solids are very difficult to explain.<sup>47</sup> This  
289 holds truer in the presence of ILs because of their structural  
290 and reactivity complexity that makes it even harder to  
291 formulate (universal) models to describe such systems. Some  
292 aspects, however, were considered to discuss the results of  
293 Figure 2.<sup>294</sup>

First, the drop of conversion with the IL-mediated MP  
295 systems was taken into account. Polar/H-bonding interactions  
296 between cations/anions of the IL and polar groups on the  
297 surface of the C-support (carboxylic, phenolic, lactonic, and  
298 ether groups) were responsible for strong adsorption of the  
299 onium salts on Ru/C.<sup>48–50</sup> This adsorption associated with the  
300 high viscosity and surface tension of the onium salts likely  
301 limited the mass transport of both liquid and gaseous reagents  
302 and products from the liquid to the catalytic sites, thereby  
303 slowing the kinetics of all the involved reactions compared to  
304 water or even the isooctane/water biphasic.<sup>51,52</sup> The entity of  
305 these effects both on the reaction rate and on the product  
306 distribution was then further analyzed based on the visual  
307 inspection of the MP systems studied in this work. The use of  
308 less bulky onium salts with shorter C<sub>1</sub>–C<sub>4</sub> alkyl substituents  
309 [N<sub>4441</sub>][Cl], [N<sub>4444</sub>][Br], [N<sub>4444</sub>][I], and [P<sub>4444</sub>][Cl] did not  
310 result in the formation of a clear triphase reaction environment  
311 (water, isooctane, and IL) as that shown in Figure 1. Indeed,  
312 the moderate-to-good solubility of these organic salts in water  
313 (up to 20 g/L<sup>42</sup>) changed the liquid partitioning of the Ru/C  
314 catalyst that was mostly suspended in the IL/water solution  
315 with only a minimal part confined in a thin layer of the residual  
316 insoluble IL (Figure 3).<sup>317 f3</sup>

Both the hydrogenation and the hydrolytic ring opening of  
318 HMF were therefore affected not only by the adsorption of the  
319 onium salt on the catalyst but also by the water solvation of  
320 substrates/products. Water solvation was plausibly a predom-  
321



**Figure 3.** Effect of the addition of different onium salts on the formation of MP systems and Ru/C segregation. The picture on the right was taken after an MP reaction under the conditions of Figure 2: HMF (63 mg, 0.5 mmol), Ru/C (5 mol % with respect to HMF, 50 mg), IL (500 mg), H<sub>2</sub>O (5 mL), isooctane (5 mL), 100 °C, 40 bar H<sub>2</sub>, 2 h.

322 inating effect that tended to level off the conversion and the  
323 selectivity with these onium salts, as noticed in Figure 2.

324 A different situation emerged instead with  $[N_{8881}][Cl]$  and  
325  $[P_{8881}][Cl]$ . Both these onium salts were immiscible with water  
326 and were able to act as separate catalyst-phylic phases placed in  
327 between isoctane and the aqueous solution on the bottom, in  
328 which Ru/C was embodied via a selective strong adsorption  
329 (Figure 1, center). HMF (and the product HHD) was water  
330 soluble, while Ru/C catalyst was perfectly segregated in the IL  
331 medium owing to the presence of the organic phase, which  
332 prompted phase separation. At the phase boundary, reactions  
333 took place with kinetic/thermodynamic profiles that were  
334 largely influenced by the properties of the onium salt with only  
335 minimal water solvation. The cation acidity was also  
336 considered: a recent work has reported that the electron-  
337 donating effect of long alkyl substituents ( $C_{np}$ ,  $n \geq 8$ ) in  
338 imidazolium-based ILs reduced the acidity of the cationic  
339 headgroups and shielded the cation–anion couples.<sup>53</sup> Albeit  
340 effect(s) of ILs anion(s) did not clearly emerge from results of  
341 Figure 2, the comparison of the MP systems mediated by  
342  $[N_{8881}][Cl]$ ,  $[P_{8881}][Cl]$ , and  $[P_{8881}][NTf_2]$  (the latter from  
343 our previous study<sup>36</sup>) offered a clue in this respect. Among the  
344 three salts, the first one allowed the most active and selective  
345 system toward HHD. With a different cation in  $[P_{8881}][Cl]$ ,  
346 both activity and selectivity were partially lost, but by changing  
347 the anion in  $[P_{8881}][NTf_2]$ , the selectivity, not the activity, was  
348 completely recovered, thereby indicating how relevant the  
349 interactions of the cation–anion pair were for the role of the  
350 ILs in the MP reactions.

351 All these aspects (phase separation, catalyst adsorption,  
352 cation acidity, ion pair interactions, poor water solvation)  
353 contributed in making the catalyst-IL layer a unique environ-  
354 ment where the formation of HHD could be enhanced with an  
355 outstanding selectivity, at least when  $[N_{8881}][Cl]$  was used  
356 (Figure 2). The reasons why  $[P_{8881}][Cl]$  did not perform  
357 equally well as its ammonium analogue (Figure 1) were not so  
358 obvious, though a starting point for further speculations was  
359 the analysis of  $H^+$  reduction potentials that showed how the  
360 P–H bond was more acidic compared to the N–H bond in  
361 protic ILs.<sup>54</sup> The use of a larger library of ILs could perhaps  
362 shed further light on the occurrence of a structure–  
363 performance correlation, if any, but this was far beyond the  
364 scope of the paper. Indeed, the combination of the property/  
365 structure of ILs and the multiphase reaction environment  
366 makes such a study hard enough to require a separated  
367 systematic analysis. This topic will be the object of future  
368 investigations in our labs.

369 The synthetic value of the finding of Figure 2 prompted us  
370 to design further experiments to explore the potential of the  
371 MP conditions, by focusing the investigation on the role of the  
372 major reaction parameters, such as temperature, time and  
373 hydrogen pressure, catalyst recycle, and the scale-up/  
374 productivity of the process.

375 **Parametric Analysis.** The effect(s) of temperature ( $T$ ),  
376 time ( $t$ ), and  $H_2$  pressure ( $p$ ) on the reaction of HMF in the  
377 water- $[N_{8881}][Cl]$ -isoctane MP system were investigated by  
378 changing (i)  $T$  from 25 to 100 °C, under 40 bar  $H_2$  for 2 h; (ii)  
379  $t$  from 0.5 to 2 h, at 100 °C under 40 bar  $H_2$ ; and (iii)  $p$  from  
380 10 to 40 bar  $H_2$ , at 100 °C for 2 h. All other conditions  
381 remained unaltered with respect to Figure 2 [HMF (0.5 mmol,  
382 63 mg), Ru/C (5 mol % with respect to HMF, 50 mg),  $H_2O$   
383 (5 mL), isoctane (5 mL),  $[N_{8881}][Cl]$  (500 mg)]. Results are  
384 reported in Figure 4a–c, respectively.

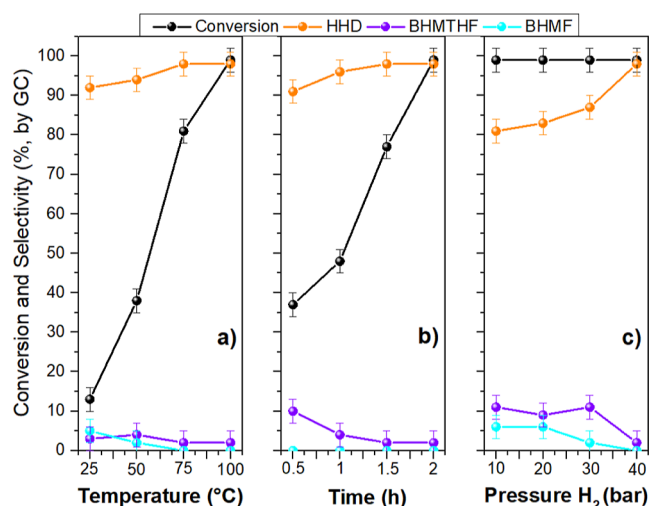


Figure 4. Effect of (a) temperature, (b) time, and (c)  $H_2$  pressure on the hydrogenation/hydrolysis of HMF to HHD. Reaction conditions: HMF (0.5 mmol, 63 mg), Ru/C (5 mol % with respect to HMF, 50 mg),  $H_2O$  (5 mL), isoctane (5 mL),  $[N_{8881}][Cl]$  (500 mg); (a) 40 bar, 2 h; (b) 100 °C, 40 bar; (c) 100 °C, 2 h; conversion and selectivity were determined by GC.

A gradual increase of the conversion from 13 to >99% was  
observed by increasing  $T$  from 25 to 100 °C, while the  
selectivity to HHD remained >92% in all cases. Interestingly,  
the higher the conversion, the better the selectivity, thanks to  
the total disappearance of the partially hydrogenated derivative  
BHMF (Figure 4a). This result was consistent with the  
mechanism of Scheme 2, in which the formation of BHMF  
(from HMF) was followed by its consumption through an  
acid-catalyzed aperture of the furan ring yielding HHD.<sup>22,55</sup> A  
similar trend was noticed by investigating the effect of the  
reaction time. When the reaction was prolonged from 0.5 to 2  
h, the HMF conversion increased from 37 to >99% and the  
HHD selectivity was slightly improved from 91 to 98% due to  
transformation of the BHMF intermediate into the desired  
product (Figure 4b).

The variation in the hydrogen pressure brought about non-  
negligible changes in the product distribution, while the  
conversion remained steady to a quantitative value. At the  
lowest investigated pressure (10 bar), HHD was achieved in an  
81% amount only, with considerable quantities of both BHMF  
(6%) and BHMTFH (11%). Thereafter, a progressive  
improvement of the HHD selectivity up to 98% was obtained  
by increasing  $p$  from 20 to 30 and 40 bar (Figure 4c). This was  
consistent with an increase of the hydrogenation rate of both  
HMF and its (intermediate) derivatives for the formation of  
HHD (Scheme 2), determined by a gradual larger availability  
of  $H_2$  solubilized in the multiple liquid phases where the  
reaction took place.

Compared to our previous studies on the MP synthesis of  
HHD, the result reported under optimized conditions (100 °C,  
40 bar  $H_2$ , 2 h) was a remarkable improvement not only in  
terms of conversion and HHD selectivity (>99 and 98%,  
respectively) but particularly for the reaction rate which was  
increased by approximately 1 order of magnitude; more  
specifically the conversion of HMF was ca. 9 times faster  
compared to that achieved in our previous studies with the use  
of  $[P_{8881}][NTf_2]$  (see also other sections later in this paper).<sup>36</sup>

422 This confirmed the suitability of  $[N_{8881}][Cl]$  to mediate the  
423 investigated interfacial processes.

424 **Catalyst Recycling and Leaching Tests.** The cost of the  
425 catalyst in a liquid-phase reaction may represent up to one  
426 third of the total cost of the process, implying that its loss by  
427 leaching or other reasons is critical and its recovery and reuse  
428 are crucial.<sup>56</sup> In this study, recycle experiments were designed  
429 under the conditions of Figure 4a [HMF (0.5 mmol, 63 mg),  
430 Ru/C (5 mol % with respect to HMF, 50 mg), H<sub>2</sub>O (5 mL),  
431 isooctane (5 mL),  $[N_{8881}][Cl]$  (500 mg), 100 °C, 40 bar H<sub>2</sub>, 2  
432 h]. A schematic description of recycle tests is illustrated in  
433 Figure 5.

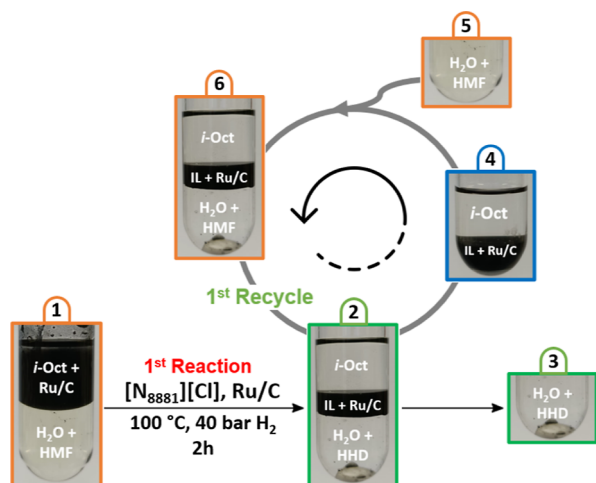


Figure 5. Semi-continuous catalytic hydrogenation/hydrolysis of 5-HMF under MP conditions, with integrated recovery and recycling of the catalyst.

434 The protocol involved a number of steps labeled 1–6. After  
435 the multiphase hydrogenation/hydrolysis of HMF (1st step: 1  
436 → 2), the water solution containing the product, HDD, was  
437 removed from the bottom of the reactor (2 → 3). To the  
438 biphasic isooctane/IL mixture with the suspended catalyst (2  
439 → 4) was added a fresh aqueous solution of the reactant  
440 (HMF: 63 mg; H<sub>2</sub>O: 5 mL) to restore the initial reaction

conditions (4 + 5 → 6). Finally, the 1st recycle was 441  
implemented (6 → 2), and the entire sequence was repeated. 442  
The overall arrangement proved perfectly suited to operate in a 443  
semi-continuous mode. The recycling procedure was repeated 444  
six times, and the whole set of reactions was run twice to 445  
ensure reproducibility. The results are reported in Figure 6A 446  
(left). 447

The HHD selectivity remained unaltered and very high 448  
(>98%) in all cases, but the conversion remarkably dropped 449  
from >99% (first run) to ca. 45–50% in the second run (1st 450  
recycle), and it then remained substantially steady up to the 451  
sixth run (5th recycle). If a catalyst deactivation was 452  
responsible for this behavior, one would have expected a 453  
progressive decrease of the conversion, which instead was not 454  
observed. The trend of Figure 6A was apparently inconsistent. 455

A residual acidity in the IL (methyltrioctyl ammonium 456  
chloride was prepared by a metathesis process involving 457  
HCl<sup>57</sup>) was initially suspected to play a role. However, this was 458  
not verified since an additional set of recycle experiments 459  
carried out at a controlled pH (ca. 2 by added HCl) provided 460  
the same results of Figure 6A. Details are reported in Table S1, 461  
Supporting Information. 462

A close visual inspection of the water- $[N_{8881}][Cl]$ -isooctane 463  
MP system showed that before the first reaction, Ru/C was not 464  
yet fully sequestered by the IL. It was then plausible that 465  
during the first test only, the catalyst remained partitioned 466  
between water and the IL. On the contrary, from the second 467  
run on, Ru/C was perfectly confined in the IL, implying that 468  
catalysis was less productive because it must operate at the 469  
water–IL interphase. If this reasoning was correct, the results 470  
of Figure 6A were due to a difference in the reaction kinetics: 471  
the first reaction was faster because the catalyst was partially 472  
available in water, while the subsequent runs were slower 473  
because of the embodiment of the catalyst in the IL (compare 474  
Figure 2). 475

This explanation was corroborated by an additional (third) 476  
set of recycling experiments carried out by increasing the 477  
catalyst amount from 5 to 10 mol % with respect to HMF, 478  
while other conditions were not changed compared to Figure 479  
6A. In this case, a higher number of reactions up to 8 480  
subsequent ones were performed. Results, shown in Figure 6B, 481

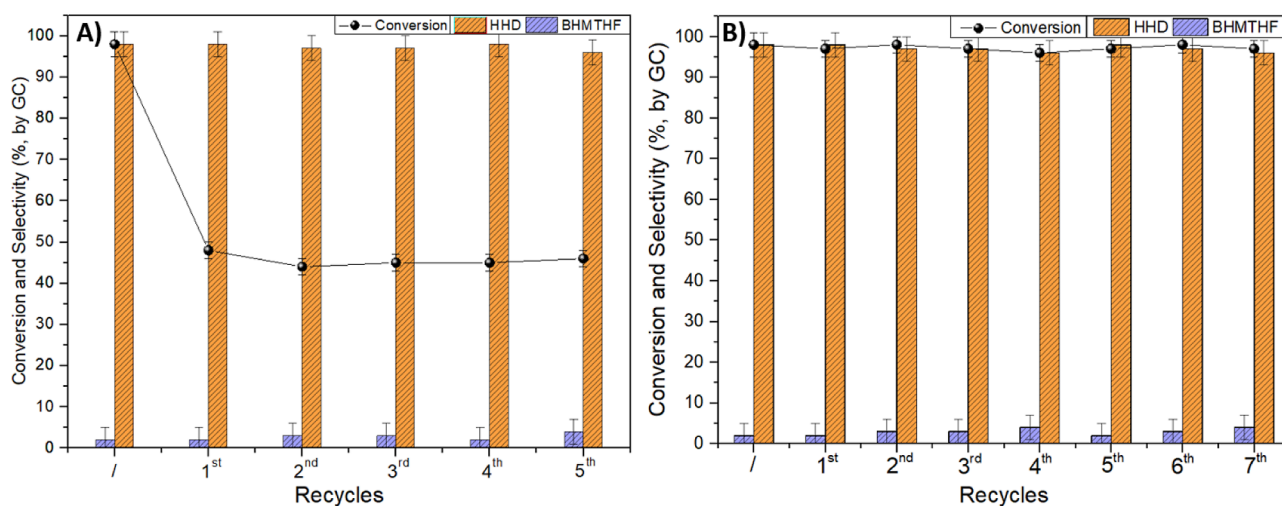


Figure 6. Recycling of Ru/C in six subsequent runs in the conversion of 5-HMF to HDD. (A) Ru/C: 5 mol % with respect to HMF (50 mg); (B) Ru/C: 10 mol % with respect to HMF (100 mg). Other reaction conditions: HMF (0.5 mmol, 63 mg), H<sub>2</sub>O (5 mL), isooctane (5 mL),  $[N_{8881}][Cl]$  (500 mg), 100 °C, 40 bar H<sub>2</sub>, 2 h. Conversion and selectivity were determined by GC.

**Table 1.** Effect of the Ru/HMF Molar Ratio ( $Q$ ) on the MP Hydrogenation/Hydrolysis of 5-HMF to HHD Ru/C (100 mg)<sup>a</sup>

entry	HMF (mmol)	Ru/HMF ( $Q$ , mol/mol)	conversion (%) <sup>b</sup>	selectivity (%) <sup>b</sup>			productivity (mmol HHD/g <sub>cat</sub> h) <sup>b</sup>
				HHD (3)	BHMF (1)	BHMTHF (2)	
1	0.5	0.1	>99	98		2	2.5
2	1	0.05	>99	97 (85) <sup>c</sup>		3	9.7
3	3	0.02	79	98		2	11.6
4	5	0.01	49	99		1	12.1

<sup>a</sup>Reaction conditions: Ru/C (100 mg), H<sub>2</sub>O (5 mL), isooctane (5 mL), [N<sub>8881</sub>][Cl] (500 mg), 100 °C, 40 bar H<sub>2</sub>, 2 h. <sup>b</sup>Conversion, selectivity, and mmol HHD were determined by GC, and mesitylene was used as the internal standard. <sup>c</sup>Isolated yield.

demonstrated that the HMF conversion and the HHD selectivity were constant from one run to another, both >99 and >97%, respectively, thereby meaning that once the catalyst was available in a sufficient amount in the IL phase, each recycle test proceeded to completion. Under such conditions, Ru/C became less effective when suspended in [N<sub>8881</sub>][Cl] than in water or isooctane, but its overall performance was preserved. Further details on the catalyst activity/recycle are available in the Supporting Information, Figure S1.

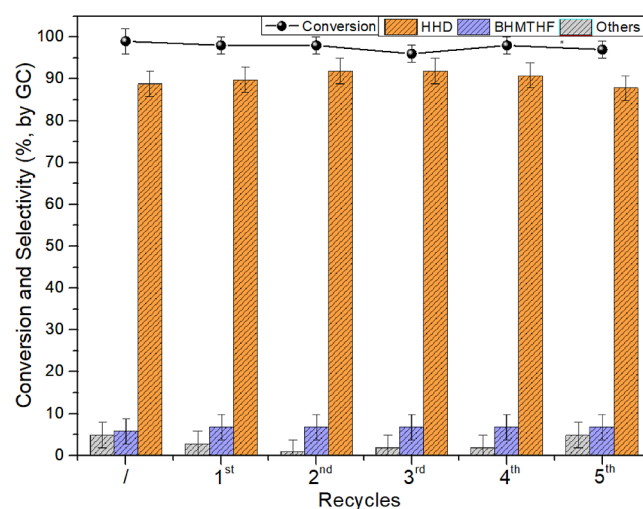
This exclusive catalyst partitioning in the IL phase was also reflected in the absence of metal leaching as confirmed by ICP–MS analyses carried out in the aqueous solutions recovered at the end of each recycling run. The amount of Ru dissolved in water was negligible (0.67 ppb), less than 0.01% with respect to the metal loading in the catalyst used for the reactivity tests (details of ICP–MS measurements are given in Table S3).

**Reaction Scale-Up/Productivity.** The scale-up of the reaction and the optimization of the Ru/substrate molar ratio ( $Q$ ) were investigated by experiments carried out under the conditions of Figure 4B [Ru/C (100 mg), H<sub>2</sub>O (5 mL), isooctane (5 mL), [N<sub>8881</sub>][Cl] (500 mg), 100 °C, 40 bar H<sub>2</sub>, 2 h], except for the amount of the reagent (HMF) that was progressively increased from 0.5 mmol (63 mg) up to 5 mmol (630 mg). The  $Q$  ratio was reduced from 0.1 to 0.01, respectively. Results are reported in Table 1. The table also shows the reaction productivity ( $P$ ) expressed as the mmol HHD produced per hour and per mass unit (g) of catalyst [ $P = \text{mmol HHD}/(\text{g}_{\text{cat}} \text{h})$ ].

The MP hydrogenation/hydrolysis reaction of HMF proceeded with quantitative conversion and selectivity of >97% to HHD, when the  $Q$  ratio was halved. The resulting productivity was almost quadrupled from 2.5 to 9.7 mmol HHD/(g<sub>cat</sub> h) (entries 1–2). A further decrease of  $Q$  to 0.02 and 0.01 (and increase of the reagent amount) brought about a drop of the conversion to 79 and 49%, respectively, while the selectivity was steady at 98–99%. Compared to the previous tests ( $Q = 0.05$ – $0.1$ ), the corresponding  $P$  increased, though it tended to level off at ca. 12 mmol HHD·(g<sub>cat</sub>·h)<sup>-1</sup> (entries 3–4). Experiments proved that the process could be successfully intensified, and the catalyst segregation was observed in all cases, confirming that the semi-continuous protocol of Figure 3 was equally efficient regardless of the catalyst/substrate molar ratio. Under the reaction conditions of entry 2, where the highest conversion was observed, HHD was isolated in an 85% yield, the best result so far reported for the synthesis of this product. Further tests on the reaction scale-up were carried out with a halved amount of catalyst (conditions of Figure 4A; Ru/C: 50 mg). An upper limit for the reaction productivity in the range of 11–13 mmol HHD·(g<sub>cat</sub>·h)<sup>-1</sup> was confirmed. Details are given in Table S2 of the Supporting Information. These

results further corroborated the robustness of the MP protocol and its flexibility toward process intensification.

**Use of Commercial Aliquat 336 in the MP Conversion of 5-HMF to HHD.** The MP hydrogenation/hydrolysis of HMF was investigated in the presence of Aliquat 336, known as Starks' catalyst, which is a well-known IL/phase-transfer agent commercialized by Sigma-Aldrich.<sup>58</sup> As anticipated, Aliquat 336 is nominally described as methyltrioctylammonium chloride, but it is in fact a mixture of [N<sub>8881</sub>][Cl] with variable amounts of C<sub>10</sub> (decyl) alkyl substituents at the N cation. An MP experiment followed by 5 recycling tests were run under the same conditions of Figure 4B [HMF (0.5 mmol, 63 mg), Ru/C (10 mol % with respect to HMF, 100 mg), H<sub>2</sub>O (5 mL), isooctane (5 mL), 40 bar H<sub>2</sub>, 2 h], except by replacing [N<sub>8881</sub>][Cl] with an equal amount of Aliquat 336 (500 mg). The results are reported in Figure 7.



**Figure 7.** Recycling of Ru/C in the conversion of 5-HMF to HHD carried out in the presence of commercial Aliquat 336 (500 mg). Reaction conditions: HMF (0.5 mmol, 63 mg), Ru/C (10 mol % with respect to HMF, 100 mg), H<sub>2</sub>O (5 mL), isooctane (5 mL), 40 bar H<sub>2</sub>, 2 h. Conversion and selectivity were determined by GC.

The use of Aliquat 336 allowed an equally good conversion compared to [N<sub>8881</sub>][Cl] but a slightly lower HHD selectivity (on average, 88–92%) in favor of the formation of the fully hydrogenated derivative BHMTHF and other by-products (as 2,5-dimethylfuran, methylfurfural, identified by GC–MS). Overall, the MP procedure was still satisfactory from the synthetic standpoint and with the additional advantage that Aliquat 336 was far cheaper than pure [N<sub>8881</sub>][Cl] and attractive for large-scale preparations. Additional experiments with Aliquat 336 were performed under the conditions of Figure 6A with results consistent with those achieved with pure

Table 2. Conversion of HMF to HHD: Complete *E*-Factor (cE) Calculated Based on the Reaction and Purification Steps

entry	reaction mode	catalyst	<i>T</i> , <i>p</i> , <i>t</i> (°C, bar, h)	conv., sel. (%) <sup>a</sup>	HHD, isolated yield (%)	consumption of reagents, catalysts, solvents, others (g/g product)						cE g <sup>-1c</sup>	ref
						reaction step			purification step <sup>b</sup>				
						catalyst	water	IL/i-oct	solvent	eluant	silica		
1	single batch	Ir-complex <sup>d</sup>	120, 10, 2	>99, - <sup>e</sup>	69	2.61	200	none	324	902	59.8	1501	31
2	single batch (MP)	Ru/C	100, 50, 18	>99, 99	75	0.25	100	41	142	807	59.8	1150	36
3	single batch (MP)	Ru/C	100, 40, 2	>99, 98	85	0.5	50	39.5	none	807	59.8	956	this work
4	one recycle (MP)			98, 98	83	none	50	none	none	807	59.8	917	

<sup>a</sup>Conversion of HMF and selectivity toward HHD. <sup>b</sup>If not otherwise specified in refs 27 and 31, the amounts of eluant (AcOEt/Et<sub>2</sub>O in a 1:1 v/v ratio) and silica gel were defined according to the standard quantities reported for separation/purification by column chromatography (*R<sub>f</sub>* for HHD was 0.2).<sup>60,61</sup> <sup>c</sup>Complete *E*-factor was calculated by including all solvents and water as a waste. <sup>d</sup>Catalyst: bipyridine coordinated Cp-Ir(III) half-sandwich complex (Cp = 1,2,3,4,5-pentamethylcyclopenta-1,3-diene). <sup>e</sup>HHD selectivity not available.

560 [N<sub>8881</sub>][Cl]. Details are reported in Figure S2, Supporting  
561 Information.

562 **Comparison of the MP Hydrogenation/Hydrolysis of**  
563 **HMF to Literature Results.** A comparative assessment of the  
564 proposed MP protocol against other methods available for  
565 HMF hydrogenation/hydrolysis was carried out by selecting  
566 papers from the literature that reported not only the reaction  
567 but also a procedure for the purification of HHD and its  
568 isolated yield. The product isolation is indeed a tricky step of  
569 the sequence, and, to the best of our knowledge, this has been  
570 detailed in only two papers both already cited in the  
571 introduction, one coming from our group.<sup>31,36</sup> To make the  
572 analysis consistent, beyond the comparison of the catalyst, the  
573 reaction conditions (temperature, hydrogen pressure, and  
574 time), the conversion of HMF, the selectivity to HHD, and the  
575 isolated yields were considered, and the complete *E*-factor (cE)  
576 associated with each of the processes was calculated.<sup>59</sup> cE  
577 included all solvents and water as a waste, in both the reaction  
578 and the purification steps. Table 2 describes the results.

579 In the first seminal study summarized in entry 1,<sup>31</sup> the  
580 authors described the formation of an insoluble polymeric solid  
581 as a major by-product, presumably humins, which implied a  
582 multistep HHD purification sequence (entry 1). This  
583 comprised a liquid/liquid extraction using an undesirable  
584 solvent (dichloromethane, DCM: ca. 300 mL/g product),  
585 followed by column chromatography and further treatment  
586 with DCM and pentane. Not to mention that the Ir-based  
587 homogeneous catalyst used in that study was not recyclable. A  
588 considerably high cE of 1501 g g<sup>-1</sup> resulted.

589 The second work reported by our group (entry 2)<sup>36</sup>  
590 described the first successful MP synthesis of HHD. Albeit  
591 with excellent conversion and selectivity (both >99%), the  
592 reaction was slow (18 h at 100 °C), and the catalyst suffered  
593 from poisoning which not only required a post-reaction  
594 activation step to restore its performance but also complicated  
595 the product purification step. The isolation of HHD was  
596 achieved by a procedure similar, though simpler, to that of  
597 entry 1. The corresponding (isolated) yield was 75%, and the  
598 corresponding cE was 1150 g g<sup>-1</sup>.

599 In the present work, a new design of the MP system allowed  
600 a much faster reaction, successful catalyst recycling, and easier  
601 product separation by a straightforward column chromatog-  
602 raphy (details are in the Experimental Section). Thus, HHD  
603 was obtained in an 85% yield and 99% purity (by GC), the  
604 best result reported to date for this reaction. Attempts to

isolate HHD by liquid–liquid extraction failed because the by- 605  
product BHMTHF (ca. 3%) was co-extracted and present as 606  
an impurity in all cases. The cE was 956 g g<sup>-1</sup> for a single 607  
reaction without any recovery of catalyst, IL, and isooctane, 608  
while it lowered to 917 g g<sup>-1</sup> after a recycle, reclaiming all the 609  
MP components except for the aqueous solution (entries 3 and 610  
4). It should also be noted that in additional purification tests, 611  
the eluant used for column chromatography (mixture of 612  
AcOEt and Et<sub>2</sub>O in a 1:1 v/v ratio) was quantitatively 613  
recovered by distillation at atmospheric pressure and could be 614  
reused, thereby further lowering the cE. This distillation/reuse 615  
was likely possible also for other procedures of Table 2, 616  
thereby suggesting that this operation would have decreased 617  
the cE of the different methods by the same quantity, with no 618  
impact on their final comparison. This reason along with the 619  
evidence that the recovery of the eluant was not reported or 620  
experimentally verified in all cases lead us to not calculate a 621  
new set of (reduced) cE. 622

The following aspects emerged from Table 2: (i) in all cases, 623  
a far higher contribution to cE, ranging from 85 to 95%, was 624  
due to the purification rather than the reaction step, confirming 625  
the negative impact of the isolation of HHD on the carbon 626  
footprint of the synthetic procedure; (ii) the MP protocols of 627  
entries 2–4 were advantageous to significantly reduce cE by 628  
approximately 25–40% compared to the value calculated for 629  
the homogeneously catalyzed process of entry 1; (iii) a 630  
literature analysis proved that the cE of MP reactions—though 631  
apparently high—were of the same order of magnitude as 632  
those typically reported for early-stage syntheses. In this 633  
respect, a recent assessment of the relative process greenness 634  
averaged over 64 processes for drug manufacturing demon- 635  
strated that the associated cE value dropped from 709 to 352 636  
and to 155 kg kg<sup>-1</sup> once the synthetic sequences were 637  
optimized from an early-stage to an advanced development 638  
and, finally, to a commercial application, respectively.<sup>62</sup> 639

This analysis led us to conclude that if the design of new 640  
catalytic routes to improve kinetics and productivity of the 641  
conversion of HMF to that of HHD was crucial, the search for 642  
effective product purification solutions was equally, if not 643  
more, important for the sustainability of the overall process. 644

## EXPERIMENTAL SECTION 645

**Materials and Equipment.** HMF, 5% Ru/C, isooctane, BHMF, 646  
and Aliquat 336 were commercially available compounds sourced 647  
from Sigma-Aldrich. If not otherwise specified, reagents and solvents 648



649 were employed without further purification. ILs such as methyl-  
650 tetrabutyl ammonium chloride ( $[N_{444}][Cl]$ ), tetrabutyl ammonium  
651 bromide ( $[N_{444}][Br]$ ), tetrabutyl ammonium iodide ( $[N_{444}][I]$ ),  
652 methyltrioctyl ammonium chloride ( $[N_{888}][Cl]$ ), tetrabutyl phos-  
653 phonium chloride ( $[P_{444}][Cl]$ ), and methyltrioctyl phosphonium  
654 chloride ( $[P_{888}][Cl]$ ) were prepared according to a method  
655 described by our research group.<sup>53</sup> Water was Milli-Q grade. H<sub>2</sub>  
656 was purchased from SIAD, Italy. GC–MS (EI, 70 eV) analyses were  
657 performed on an HP5-MS capillary column ( $L = 30$  m,  $\varnothing = 0.32$   
658 mm, film = 0.25 mm). GC (FID) analyses were performed with an  
659 Elite-624 capillary column ( $L = 30$  m,  $\varnothing = 0.32$  mm, film = 1.8 mm).  
660 <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in a Bruker Avance III HD  
661 400 WB equipped with a 4 mm CP/MAS probe, at 400 and 101  
662 MHz, respectively. Chemical shifts were reported downfield from  
663 tetramethylsilane, and CDCl<sub>3</sub> or MeOD was used as the solvent.  
664 ICP–MS analyses were performed using a PerkinElmer Optima  
665 5300DV. All reactions were performed in duplicate to verify  
666 reproducibility.

667 **Typical Hydrogenation–Hydrolysis Reaction Procedure**  
668 **and Product Analysis.** Experiments were performed in a 25 mL  
669 tubular reactor of borosilicate glass (Pyrex) charged with HMF (0.5  
670 mmol, 63 mg), Ru/C (5 mol % with respect to HMF, 50 mg), H<sub>2</sub>O,  
671 (5 mL), isooctane (5 mL), and the desired IL. The reactor was then  
672 placed in a jacketed stainless-steel autoclave equipped with a  
673 manometer and two needle valves. The autoclave was pressurized  
674 with H<sub>2</sub> (40 bar) and heated by oil circulation at the desired  
675 temperature. The mixture was kept under magnetic stirring at a rate of  
676 1500 rpm. At the end of the tests, the autoclave was cooled to room  
677 temperature and gently purged. The lower aqueous product solution  
678 was withdrawn by a syringe, analyzed by GC/FID to determine the  
679 reaction conversion and selectivity, and rotary-evaporated (60 °C, 15  
680 mbar). The obtained dried sample was analyzed by GC–MS and  
681 NMR in CDCl<sub>3</sub> or MeOD solvent. Characterization data of HHD,  
682 BHMF, and BHMTHF are available in the Supporting Information,  
683 Figures S3–S9.

684 **HHD Isolation and Purification.** Under conditions of Table 2  
685 [HMF (1 mmol, 126 mg), Ru/C (10 mol % with respect to HMF,  
686 100 mg), H<sub>2</sub>O, (5 mL), isooctane (5 mL),  $[N_{888}][Cl]$  (500 mg), 100  
687 °C, 40 bar H<sub>2</sub>, 2 h], HHD was achieved with 98% selectivity at  
688 quantitative conversion (by GC/FID). The aqueous product solution  
689 was rotary-evaporated (60 °C, 15 mbar) and directly purified by flash  
690 column chromatography on silica gel (230–400 mesh; diethyl ether  
691 and ethyl acetate (1:1) were used as eluents) to afford HHD in 85%  
692 isolated yield (110 mg).

## 693 ■ CONCLUSIONS

694 The use of MPs for the chemical valorization of biomass-  
695 derived compounds represents an alternative strategy with  
696 respect to the classic single-liquid-phase processes. In MP  
697 systems, the confinement of a heterogeneous catalyst in a  
698 liquid different from the one containing the reagents and the  
699 products is advantageous not only for catalyst/product  
700 separation but also to steer the reaction selectivity by  
701 exploiting interfacial effects. In this work, the potential of IL-  
702 based MP systems has been highlighted by upgrading 5-HMF  
703 through a selective hydrogenation/hydrolysis pathway yielding  
704 HHD as an exclusive product. By tuning the experimental  
705 conditions, particularly the structure of the IL, an MP  
706 comprising water, isooctane, methyltrioctylammonium chlor-  
707 ide, and Ru/C as a catalyst allowed us to achieve HHD in  
708 >98% selectivity and 85% isolated yield, at quantitative  
709 conversion of HMF. Several aspects, most plausibly the  
710 phase separation, the catalyst adsorption on the IL, the acidity  
711 of the IL cation, and the poor water solvation, contributed to  
712 such a result.

713 No less significant is the recycling of Ru/C that was carried  
714 out under MP conditions in a robust semi-continuous mode.

The catalyst did not alter its performance after six successive  
715 runs without ever being removed from the system and with a  
716 negligible metal leaching of 0.67 ppb in the aqueous solution.  
717 This improved the efficiency of the downstream reaction  
718 processing by avoiding any handling and/or losses of the  
719 catalyst due to filtration, centrifugation, washing, and drying or  
720 thermal treatments for the re-activation and restoration of the  
721 catalyst in the reactor.

The investigated MP procedure discloses new scenarios for  
723 scalable applications, with a high degree of process  
724 intensification. The (non-optimized) productivity of HHD  
725 has been increased by a factor of ca. 5, from 2.5 up to 12 mmol  
726 HHD·(g<sub>cat</sub>·h)<sup>-1</sup>, by increasing the concentration of the  
727 reactant solution without any variation in the batch reactor  
728 size and the volumes of the liquid MP components.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at  
732 <https://pubs.acs.org/doi/10.1021/acssuschemeng.2c06692>.

Effect of pH on recycling tests, effect of reaction time on  
734 Ru/C recycling, effect of catalyst amount on scale-up/  
735 productivity, effect of the catalyst amount with  
736 Aliquat336, leaching tests, characterization data, and  
737 calibration curve (PDF)

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### Author Contributions

D.P.: conceptualization, investigation, methodology, and  
758 writing—original draft preparation; A.P.: writing—reviewing  
759 and funding acquisition; I.E.M.: investigation and analytical  
760 methodology; M.S.: conceptualization, supervision, writing—  
761 reviewing and editing, and funding acquisition.

### Notes

The authors declare no competing financial interest.

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