Ammonium Salts Catalyzed Acetalization Reactions in Green Ethereal Solvents

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Abstract: Cyclopentyl methyl ether and 2-methyltetrahydrofuran, low impact ethereal solvents forming a positive azeotrope with water, were successfully employed as solvents in the synthesis of a variety of acetals carried out under Dean–Stark conditions in the presence of heterogeneous acidic catalysts. Under these conditions, ammonium salts, either as such or supported on SiO_2, performed better or equally well than widely employed homogeneous and heterogeneous acidic catalysts such as *p*-toluenesulfonic acid, Amberlyst 15$^{®}$, or Montmorillonite K10. Several examples highlight the advantage of tuning the relative acidities of ammonium salts by appropriately selecting the counterion. Within one of these examples, our protocol clearly outweighs the classic *p*-toluenesulfonic acid/toluene protocol in terms of chemoselectivity. Silica-supported catalysts were characterized by SEM, TEM, and FTIR spectroscopies, as well as by N_2 physisorption. Such a characterization reveals an even distribution of ammonium salts on silica, thus confirming the formation of expected catalytic supports.

Keywords: heterogeneous catalysis; green solvents; acetals; ammonium salts; characterization of heterogeneous catalysts

1. Introduction

The setup of widely employed reactions under economical, practical, and environmentally friendly conditions is a challenge of wide interest in contemporary organic chemistry. From this point of view, great attention should be dedicated to the appropriate choice of solvents as they represent one of the major contributions to the environmental impact of fine chemical synthesis [1–6].

Acetals are widely employed in multistep organic synthesis for the protection of carbonyl compounds towards basic and nucleophilic reagents, due to their general stability to a wide range of reagents and ease of removal. Additionally, they have found application in everyday life as fragrances or profragrances [7–9].

Whilst a lot of work has been devoted to the search of low impact, heterogeneous, and recyclable catalysts to promote these reactions [10–18], much less attention has been dedicated to their employment in low impact solvents. Indeed, acid-catalyzed acetalization reactions are usually run under Dean–Stark conditions employing environmentally problematic hydrocarbon solvents, such as toluene or benzene [19].

Starting from these premises and following our interest in the development of reaction procedures in environmentally friendly solvents [20–23], we investigated the acetalization of aldehydes and ketones in well-known low impact ethereal solvents forming positive azeotropes with H_2O (Table 1), i.e., cyclopentyl methyl ether (CPME) [24–27] and 2-methyltetrahydrofuran (2-MeTHF) [28–31].

Table 1. Boiling points and percent composition of some organic solvent/H_2O azeotropes.

Organic Solvent	Bp (°C)	Composition (%) [1]
Toluene	85.0 [2]	79.8:20.2 [2]
Benzene	69.4 [2]	91.1:8.9 [2]
CPME	83 [3]	83.7:16.3 [3]
2-MeTHF	71 [4]	89.4:10.6 [4]

[1] Organic solvent/H_2O; *w/w*; [2] reference [32]; [3] reference [24]; [4] reference [31].

Besides being endowed with a relatively high stability towards acids and bases, both CPME and 2-MeTHF are characterized by low toxicity [33,34], relatively high boiling points, a narrow explosion range, hydrophobicity, easy drying and recovery, and appear as versatile green alternatives to ethereal solvents such as tetrahydrofuran, diethyl ether, or *tert*-butyl methyl ether. Additionally, CPME is produced via a 100% atom economical reaction [24], whilst 2-MeTHF is accessible from renewable resources [31].

In the meantime, we investigated the employment of ammonium salts and silica-supported ammonium salts as cheap, easily available, heterogeneous, and relatively mild acidic catalysts to promote the acetalization reaction. Moreover, ammonium salts offer the opportunity to evaluate how their catalytic activities vary as the counter ions change.

A preliminary communication concerning the protection of aldehydes and ketones under the abovementioned conditions has already been reported [22].

2. Results and Discussion

2.1. Synthesis of Acetals of Aldehydes and Ketones

As already reported in our previous communication [22], the reaction of acetophenone, **1a**, with an excess (1.1 to 2.0 equivalent) of 1,2-ethandiol, **2a**, was taken as a model reaction to evaluate the effectiveness of the combination of different solvents with ammonium salts as heterogeneous acidic catalysts. For comparison purposes, few reactions were run with a homogeneous acidic catalyst, i.e., *para*-toluenesulfonic acid (*p*-TSA), or with two widely employed, commercially available, heterogeneous acidic catalysts, i.e., Amberlyst 15® and Montmorillonite K10 (Mont K10).

Reactions were run by refluxing a 4 M solution of the ketone with **2a** (1.1 to 2.0 equivalent), under Dean–Stark conditions in the presence of the acidic catalysts (3 mol% relative to **1a**). Recovered reaction mixtures were very simply elaborated by filtering the catalyst followed by evaporation of the solvent in vacuo. Indeed, at variance with what was reported in our earlier communication [5c], we carefully checked that no neutralization of the reaction mixture was needed during the work-up procedure. However, the reactions run in the presence of the higher amounts of **2a** (1.5–2.0 equivalent) were additionally purified by aqueous work-up.

Our results, summarized in Table 2, show that by employing CPME as a solvent in the presence of a minimal excess of **2a** (1.1 equivalent), conversions ranging from 63% to 79% were obtained by performing reactions in the presence of different ammonium halides (Table 2, entries 1 and 2), or with glycine hydrochloride (HCl.Gly, Table 2, entry 3) [35], whilst a less satisfactory result was obtained by performing the reaction in the presence of $(NH_4)_2SO_4$ (Table 2, entry 4).

Table 2. Synthesis of dioxolane **3a** [1.]

Entry	2a (Equivalent)	Solvent	Catalyst	Product Distribution 1a/3a (%) [2]
1	1.1	CPME	NH_4Cl	35/65 [3]
2	1.1	CPME	NH_4Br	21/79 [3]
3	1.1	CPME	HCl.Gly	36/64 [3]
4	1.1	CPME	$(NH_4)_2SO_4$	68/32
5	1.1	CPME	$(NH_4)HSO_4$	10/90 [4]
6	1.5	CPME	$(NH_4)HSO_4$	5/95
7	2.0	CPME	$(NH_4)HSO_4$	<5/>95 [3,5]
8	2.0	Toluene	$(NH_4)HSO_4$	20/80
9	1.1	CPME	*p*-TSA	13/87
10	2.0	CPME	*p*-TSA	<5/>95
11	1.1	CPME	Amberlyst 15®	10/90 [6]
12	1.1	CPME	Mont K10 [7]	46/54
13	1.1	2-MeTHF	$(NH_4)HSO_4$	60/40
14	2.0	2-MeTHF	$(NH_4)HSO_4$	37/63 [5]
15	1.1	2-MeTHF	Amberlyst 15®	89/11 [6]
16	1.1	2-MeTHF	Mont K10 [7]	72/28

[1] All reactions were run at reflux for 6 h in the presence of 3 mol% of the catalyst, unless otherwise indicated; [2] Determined by ^{1}H-NMR analyses of crude reaction mixtures; no other reaction products were detected, unless otherwise indicated; [3] Comparable results were obtained recycling the recovered catalyst twice; [4] Comparable results were obtained when recycling the recovered catalyst four times; [5] Comparable results were obtained when recycling the solvent; [6] Unidentified by-products also formed; [7] 3% *w/w*.

Better results were obtained in the presence of NH_4HSO_4 (Table 2, entry 5), thus suggesting a correlation between the relative acidities of the ammonium salt [36] and their catalytic activities. Additionally, NH_4HSO_4 led to an almost quantitative conversion of **1a** to **3a** in the presence of 1.5–2.0 equivalents of **2a** (Table 2, entries 6 and 7), performing better in CPME than in toluene (Table 2, entry 7 versus entry 8). Interestingly, comparable results were obtained in the presence of a homogeneous acid catalyst, i.e., *p*-TSA (Table 2, entries 9 and 10). The above reported results could not be improved by employing Amberlyst 15® or Mont K10 as acidic catalysts (Table 2, entries 11 and 12) [37]. Indeed, although a relatively high conversion of the starting material was obtained with Amberlyst 15®, the reaction was accompanied by the formation of small amounts of unidentified by-products (Table 2, entry 11), whilst a poor conversion was obtained with Mont K10 (Table 2, entry 12).

Changing the solvent to 2-MeTHF and running the reactions in the presence of a catalytic amount of NH_4HSO_4 led to poor conversions of **1a**, even in the presence of 2.0 equivalents of **2a** (Table 2, entries 13 and 14). Poorer results were obtained when employing Amberlyst 15® or Mont K10 as acidic catalysts (Table 2, entries 15 and 16). Possible rationalizations of these results can be found in both the different boiling points of the CPME/H_2O versus 2-MeTHF/H_2O azeotropic mixtures, and in the different removability of H_2O from the reaction mixture by the different ethereal solvents (Table 1).

Finally, it is worth mentioning that both CPME and 2-MeTHF proved stable under these conditions, as established by the absence of any decomposition products within the reaction mixtures, as determined by ^{1}H-, ^{13}C-NMR and GLC analyses [38]. Accordingly, it was possible to realize an 80–85% mass recovery of both reaction solvents which were collected by evaporation of reaction mixtures, filtered over alumina, dried (KOH), and distilled. After stabilization with 2,6-di-*tert*-butyl-4-methylphenol (BHT), both solvents were successfully recycled to successive runs (Table 2, entries 7 and 14).

To assess the reusability of ammonium salts as acidic catalysts, selected reactions were submitted to a series of consecutive runs. After the end of each run, the reaction mixture was filtered and the recovered catalyst, washed on the filter with a few mL of the reaction solvent and dried in vacuo,

was reused for the next batch to find no significant loss of its catalytic activity (Table 2, entries 1–3, 5, and 7; for more details, see Table S1, Supplementary Materials).

It should be emphasized, however, that the recovery of the catalyst from the reaction mixtures performed in the presence of excess diol was problematic due to the deliquescent texture they assume under these conditions, thus requiring their exhaustive washing with THF (Table 2, entries 6, 7, and 14).

To overcome this problem and to improve our protocol, we investigated the efficiency of several SiO$_2$-supported ammonium salts (RNH$_3$X-SiO$_2$) as acidic catalysts.

To this end, 25% *w/w* dispersions of NH$_4$HSO$_4$ and NH$_4$Br and 17% *w/w* HCl.Gly on silica gel were prepared by wet impregnation and were successively employed as catalysts in our test reactions in CPME or 2-MeTHF [39].

Overall, the results in Table 3 show that the supported ammonium salts worked as efficient as their unsupported counterparts. Furthermore, they were particularly easy to handle and recover by filtration from reaction mixtures even in the presence of excess diol and were recycled without loss of their efficiencies (Table 3 entries 2–4; for more details, see Table S2, Supplementary Materials).

Table 3. Synthesis of dioxolane **3a** in the presence of SiO$_2$-supported ammonium salts [1].

Entry	2a (Equivalent)	Solvent	Catalyst	Product Distribution 1a/3a (%) [2]
1	1.1	CPME	NH$_4$Br-SiO$_2$	25/75
2	1.1	CPME	HCl.Gly-SiO$_2$	35/65 [3]
3	1.1	CPME	NH$_4$HSO$_4$-SiO$_2$	14/86 [4]
4	2.0	CPME	NH$_4$HSO$_4$-SiO$_2$	<5/>95 [4]
5	1.1	CPME	SiO$_2$	93/7
6	1.1	2-MeTHF	NH$_4$HSO$_4$-SiO$_2$	51/49
7	2.0	2-MeTHF	NH$_4$HSO$_4$-SiO$_2$	38/62

[1] All reactions were run at reflux for 6 h in the presence of 3 mol% of the catalyst, unless otherwise indicated; [2] Determined by ^{1}H-NMR analyses of crude react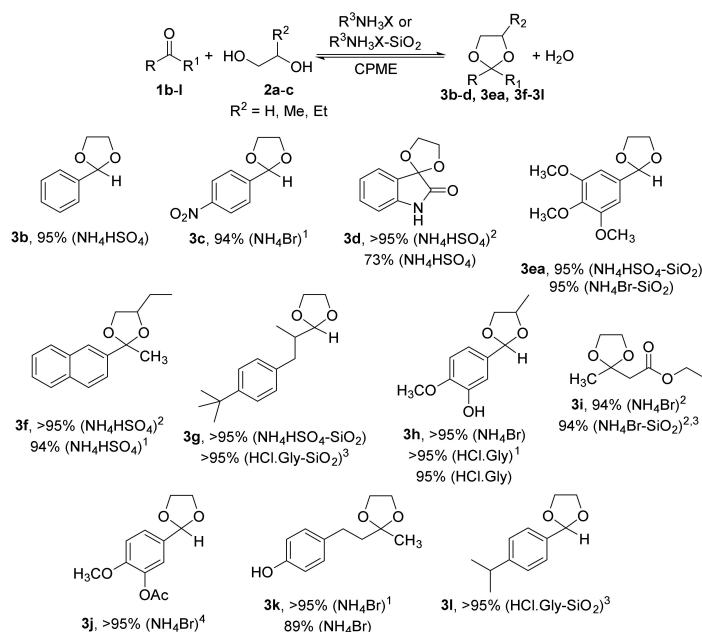ion mixtures; no other reaction products were detected; [3] Comparable results were obtained recycling the recovered catalyst twice; [4] Comparable results were obtained when recycling the recovered catalyst three times.

The effectiveness of our protocol was further confirmed by the synthesis of the series of acetals reported below (Schemes 1 and 2), thus expanding the scope of synthesized products reported in our previous communication (See Scheme SM1, Supplementary Materials).
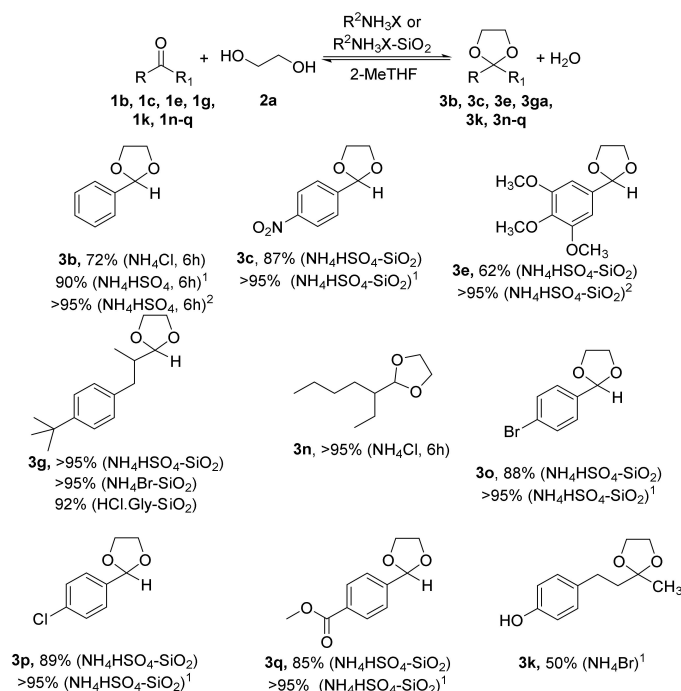
Scheme 1 shows new results performed in CPME leading, inter alia, to the synthesis of some known fragrances (**3f** [16], **3g** [40], **3h** [16,41], and **3i** [42]) or acetals of known fragrances (**3j** [43], **3k** [44], and **3l** [45]).

The reaction worked well with aliphatic and aromatic aldehydes in the presence of a minimal excess of diol (1.1–1.5 equivalent), whilst a relatively higher excess (1.5–2.0 equivalent) was required with less electrophilic ketones.
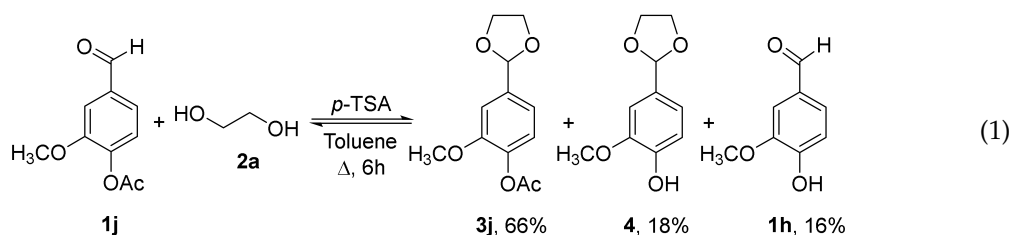
It is also worth noting that by employing NH$_4$Br as a catalyst, it was possible to realize the synthesis of **3i** and **3j** in a chemoselective way, i.e., avoiding hydrolysis of the ester moieties, most likely due to the employment of a catalyst endowed with appropriate acidity [36]. Indeed, under similar conditions but employing NH$_4$HSO$_4$ as an acidic catalyst, quantitative conversion of **1j** led to the formation of **3j** contaminated by trace amounts of **1h**, i.e., the product of acidic hydrolysis of the ester moiety of **1j** (not reported in Scheme 1). An even worse result was obtained when utilizing *p*-TSA, a stronger acid [46], as a catalyst and toluene as a solvent, as depicted in Equation (1). Under these conditions, 91% conversion of the starting material led to the formation of **3j**, **4** [47], and **1h** in a 66/18/16 ratio. In agreement with these findings, Corma et al. reported that the employment of strong acids and water formed during acetalization can cause the hydrolysis of the ester moiety of **1i/3i** [42].

Scheme 1. Synthesis of acetals in CPME. Reaction conditions: 4 M solution of **1** in CPME, 1.1 equivalent of **2a–c** (unless otherwise indicated), 3 mol% of RNH₃X or RNH₃X-SiO₂ (with respect to **1**), reflux (Dean–Stark conditions). Percentages represent conversion of the starting materials as determined by ^{1}H-NMR; no other products, besides starting materials, were detected. [1] In the presence of 1.5 equivalent of diol; [2] In the presence of 2.0 equivalent of diol. [3] Comparable results were obtained recycling the recovered catalyst three times. [4] Isolated yield 78%, see Supplementary Materials.
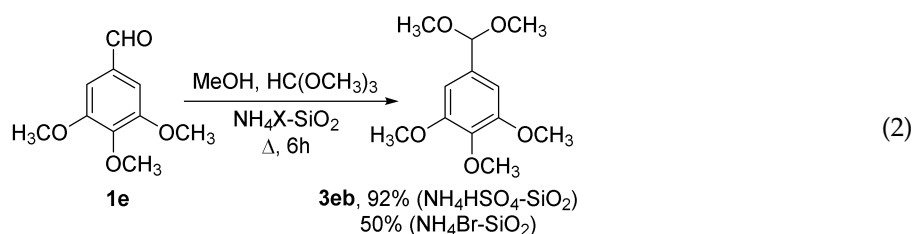

Scheme 2. Synthesis of acetals in 2-MeTHF. Reaction conditions: 4 M solution of **1** in CPME, 1.1 equivalent of **2a** (unless otherwise indicated), 3 mol% of RNH₃X or RNH₃X-SiO₂ (with respect to **1**), reflux (Dean–Stark conditions). Percentages represent conversion of the starting materials as determined by ^{1}H-NMR; no other products, besides starting materials, were detected. [1] In the presence of 1.5 equivalent of diol.; [2] In the presence of 2.0 equivalent of diol.
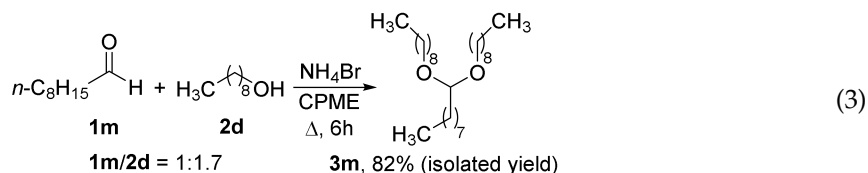
$$(1)$$

To widen the scope of our protocol, we slightly modified the above described experimental procedure to realize the synthesis of acetals of simple alcohols, such as methanol and nonanol.

Accordingly, we synthesized the dimethyl acetal of 3,4,5-trimethoxybenzaldehyde, **3eb**, by warming **1e** at 65 °C for 6 h with 1.1 equivalents of MeOH and 1.1 equivalents of $HC(OCH_3)_3$ as a scavenger of water. Under the new conditions, the most acidic catalyst, i.e., NH_4HSO_4-SiO_2 proved more efficient as compared to NH_4Br-SiO_2 (Equation (2)).
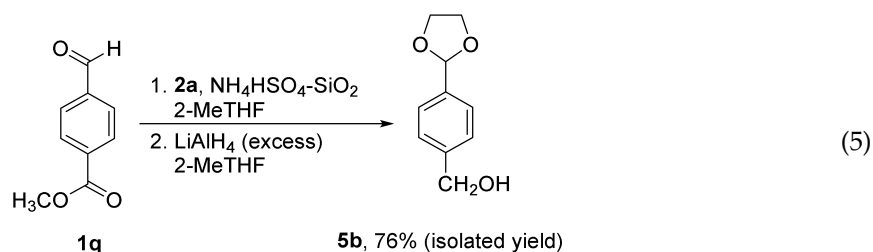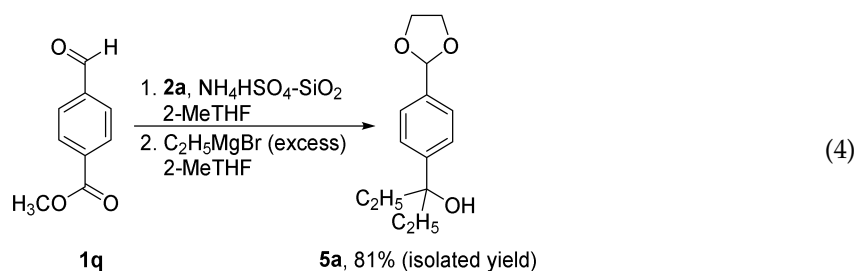

$$(2)$$

A good result was obtained in the synthesis of the dinonyl acetal of nonanal, **3m**, employing a lower than stochiometric amount of **2d** to allow an easier separation of the reaction product from the unreacted starting material(s) by vacuum fractional distillation (Equation (3)).

$$(3)$$

An additional set of reactions was run by employing 2-MeTHF as a solvent (Scheme 2). Aliphatic aldehydes were almost completely converted into the corresponding acetals even in the presence of 1.1 equivalent of **2a** and of the relatively less acidic catalysts, HCl.Gly-SiO_2 or NH_4Br-SiO_2 for the synthesis of **3g** or NH_4Cl for the synthesis of **3n**.

At variance with these results, a higher excess of **2a** (1.5 to 2.0 equivalents) and the employment of NH_4HSO_4 or NH_4HSO_4-SiO_2 as catalyst were required for the less electrophilic aromatic aldehydes **1b**, **1c**, **1e**, and **1o–q**. Poorer conversions were achieved with less electrophilic aromatic and aliphatic ketones such as **1k**, thus representing a limitation to the employment of 2-MeTHF as a solvent in the present methodology.

It is nonetheless worth noting that 2-MeTHF is particularly well suited for reactions involving highly polar nucleophilic reagents, such as organomagnesium [29,48,49] or organolithium compounds [29], i.e., for multistep reactions where the temporary protection of an aldehyde as an acetal is required. Accordingly, and in agreement with what already achieved for telescopic reactions run in CPME (see Equations (S1)–(S3) Supplementary Materials) [22], acetalization of **1q** followed by reaction of the crude acetal with excess ethylmagnesium bromide employing 2-MeTHF as a solvent under two-steps in one-pot reaction conditions, as depicted in Equation (4), led to the formation of the tertiary alcohol **5a** in 81% overall yield. Under related conditions, reduction in the crude acetal with $LiAlH_4$ afforded the corresponding benzyl alcohol, **5b**, in 76% overall yield (Equation (5)).

$$(4)$$

1q　　　　　　　　　　　　　**5a**, 81% (isolated yield)

$$(5)$$

1q　　　　　　　　　　　　　**5b**, 76% (isolated yield)

2.2. Preparation and Characterization of SiO$_2$-Supported Ammonium Salts

SiO$_2$-supported ammonium salts, namely NH$_4$Br-SiO$_2$, HCl.Gly-SiO$_2$, and NH$_4$HSO$_4$-SiO$_2$ were prepared by wet impregnation [50]. The resulting products were characterized by means of Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM) coupled with energy-dispersive X-ray (EDX) spectroscopy, N$_2$ physisorption, and IR spectroscopy.

The microstructural, surface morphology, and elemental analysis of the samples were characterized by TEM and SEM. In Figure 1, representative SEM images of granular silica gel particles, after impregnation with the three above mentioned ammonium salts, are reported.

For all samples, the as-embedded silica particles are not regular in shape and are characterized experimentally by an average diameter of ca. 58 μm, in line with the dimension of the as-received SiO$_2$.

Therefore, the treatment to which the raw silica particles are subjected appears to have an influence on their size and shape. Additionally, from the SEM images of surface, it is clear that the functionalized surface exhibits more roughness, with respect to the original (see Figure S1, Supplementary Materials), which is indicative of the anchoring ammonium salt components to the surface of silica gel.

To further confirm the effectiveness of the impregnation step, considering the amorphous nature of NH$_4$HSO$_4$-SiO$_2$ and HCl.Gly-SiO$_2$ provided by X-ray powder diffraction (see Figure S2, Supplementary Materials), FTIR was used to characterize the major chemical groups in the silica gel after impregnation. The FTIR spectra are depicted in Figure 2.

For all three samples, the characteristic and peak positions of the FTIR spectra of the as-modified silica gel match with those of commercial silica which was reported by Zhang and coauthors [51]. The broad peak centered at 3500 cm^{-1} is due to the silanol OH group and the adsorbed water bonding to the silica surface by the hydrogen bond. The peaks at 1100, 800, and 490 cm^{-1} can be assigned to asymmetric Si-O-Si stretching, symmetric Si-O-Si stretching, and to the O-Si-O bending vibrations, respectively (as example see Figure 2B).

All these peaks are common characteristics of the three samples analyzed, as better highlighted by the blue dashed lines in Figure 2. Additionally, the spectrum related to the sample NH$_4$HSO$_4$-SiO$_2$ (Figure 2A) presents four further signals, which can be associated with the vibrational modes of NH$_4^+$ (3170 and 1400 cm^{-1}), HSO$_4^-$ (1190 cm^{-1}), and SO$_4^{2-}$ (600 cm^{-1}) species in NH$_4$HSO$_4$, as also reported in other studies [22,52–54].
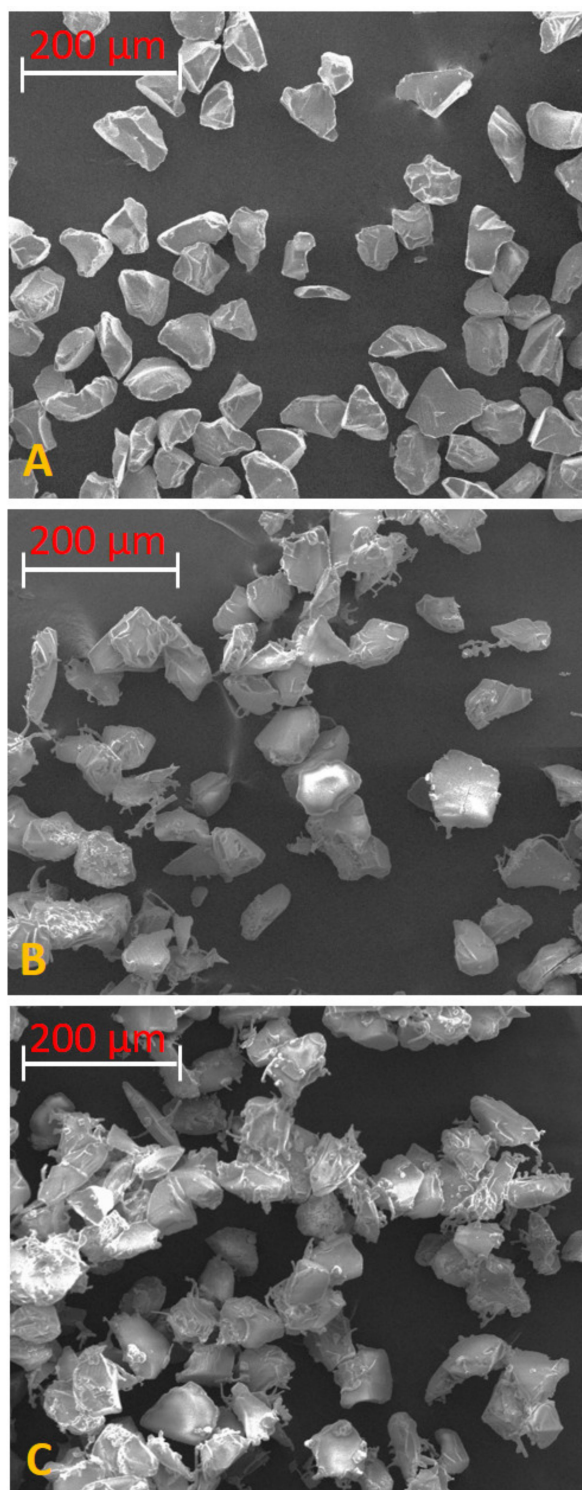
Figure 1. SEM image of silica gel beads impregnated with (**A**) NH$_4$HSO$_4$, (**B**) HCl.Gly, and (**C**) NH$_4$Br.
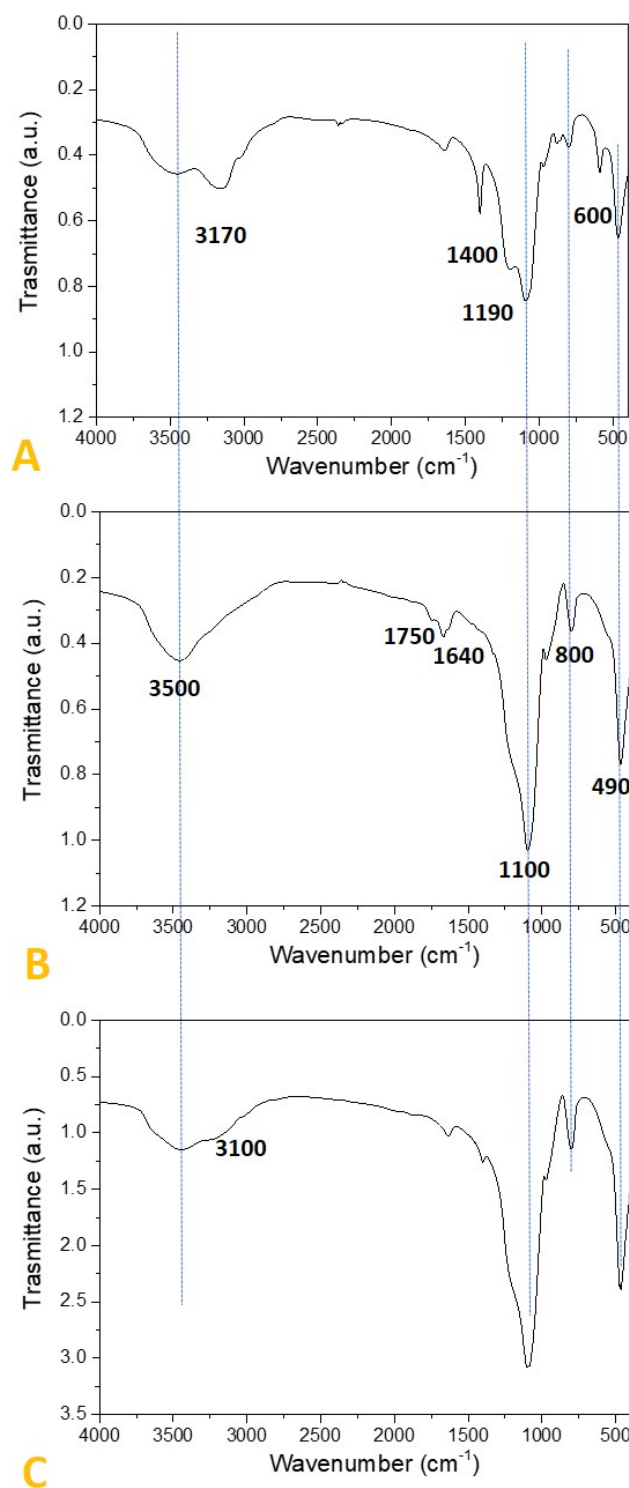
Figure 2. FTIR spectra of silica gel impregnated with (**A**) NH_4HSO_4, (**B**) HCl.Gly, and (**C**) NH_4Br ammonium salts.

Evidence of glycine hydrochloride (HCl.Gly) has been confirmed by the characteristic peaks at 1750 and 1643 cm^{-1} (Figure 2B) assigned to the CO stretch and CO_2 asymmetric stretches, respectively [55]. The appearance of a new peak at 3100 in Figure 2C can be attributed to NH^+ symmetric and asymmetric vibrations modes of NH_4Br [56]. It is also important that FTIR spectra, acquired after several catalytic

cycles, presented the same features reported in Figure 2. FTIR analysis performed on the exhausted solution, recovered after catalytic tests, did not reveal trace of ammonium salts.

In accordance with the high reproducibility of the catalytic performance as showed by these supported catalysts (see Table 3), this seems to confirm the effective immobilization of the ammonium salts on the SiO_2.

Taking into consideration the nanoporous nature of SiO_2, it should be clarified if the ammonium salts were immobilized on the surface and/or into the porous channels of SiO_2. To shed light on this aspect, TEM characterization of the three samples was performed. Representative TEM micrographs of the as-prepared systems are shown in Figure 3.
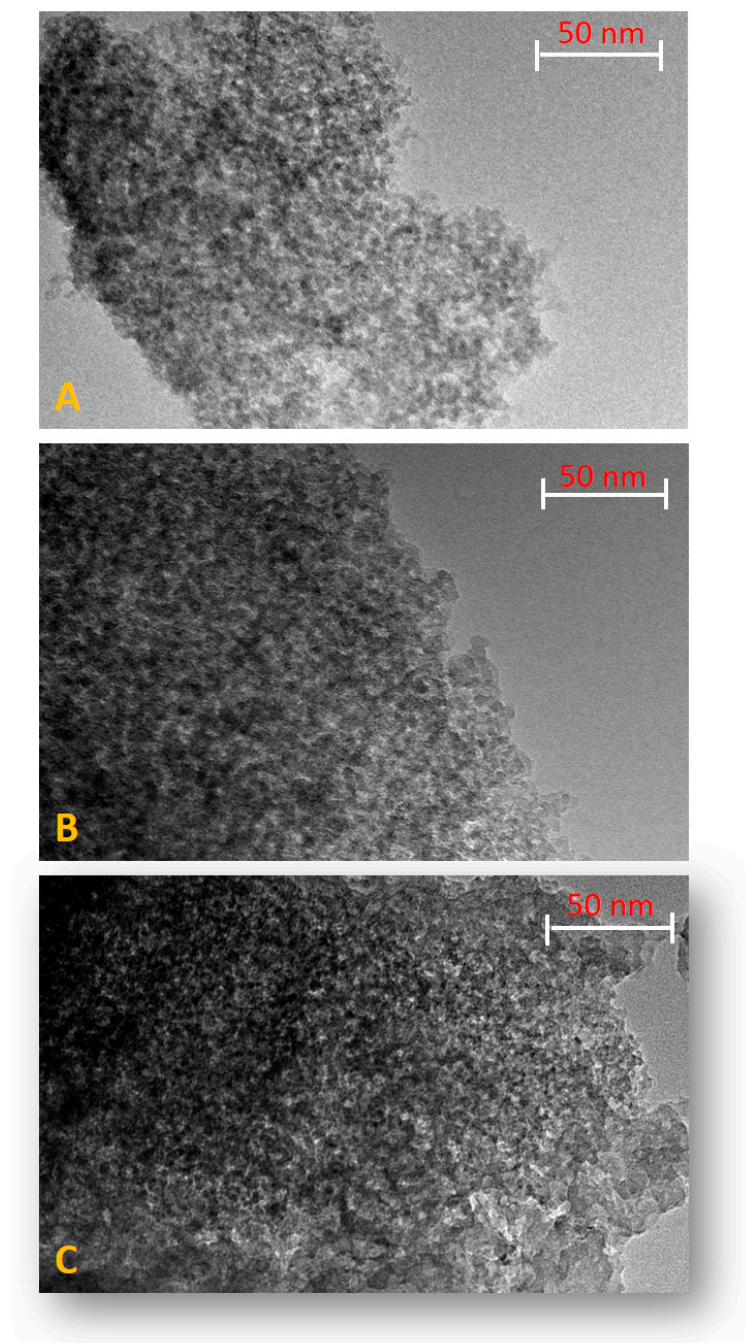

Figure 3. TEM spectra of the silica gel product impregnated with (**A**) NH_4HSO_4, (**B**) HCl.Gly, and (**C**) NH_4Br.

As emerged from all the analysis, after the impregnation step, the porosity of the SiO_2 matrix is characterized by a larger distribution of porous diameter (4–9 nm) with respect to the untreated SiO_2, while pore shape seems to be preserved. EDX analysis (see Figures S3–S5, Supplementary Materials) performed on the TEM images areas revealed that the specific elements, Cl, S, and Br, existed over a significant percentage, although light elements are difficult to quantify due to limited sensitivity. Furthermore, the presence of ammonium salts into the pores cannot be directly confirmed because they are characterized by low contrast with respect to the amorphous carbon support.

Specific surface area and pore distribution were calculated from N_2 sorption isotherms according to Brunauer, Emmett, and Teller (BET) and Barrett–Joyner–Halenda (BJH) approaches, respectively. N_2 physisorption isotherms and the pore size distribution plots of all the synthesized samples are depicted in Figure 4A–F.
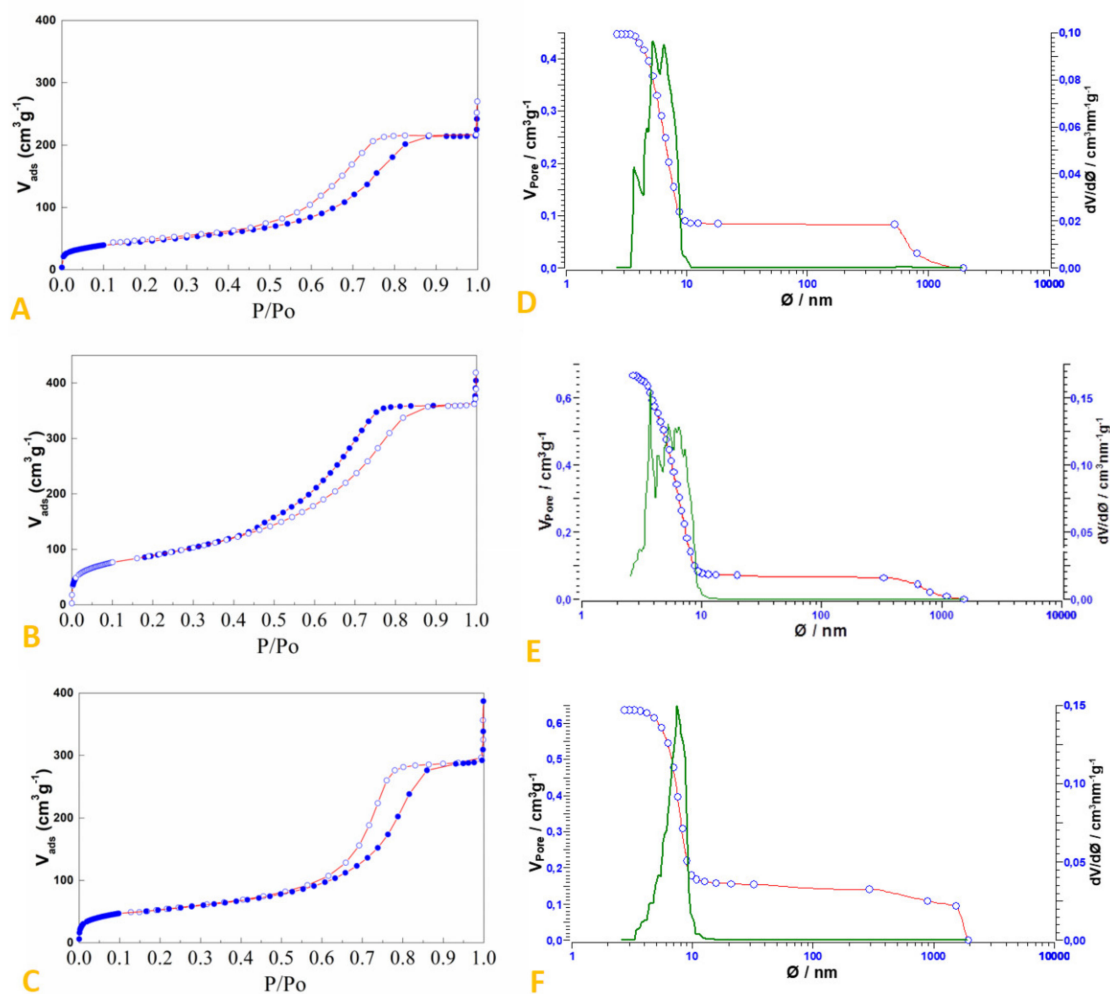

Figure 4. N_2 physisorption isotherms and the corresponding pore size distribution of (**A**), (**D**) NH_4HSO_4-SiO_2, (**B**), (**E**) HCl.Gly-SiO_2 and (**C**), (**F**) NH_4Br-SiO_2.

BET surface areas vary from 161 to 185 $m^2 g^{-1}$ except for the sample impregnated with HCl.Gly, which exhibits a surface area of 319 $m^2 g^{-1}$ (see Table 4). All the samples show a type IV isotherm (Figure 4A–C) characteristic of mesoporous materials [57], in accordance with TEM analysis, with a H2(b) type hysteresis loop associated with pore blocking, typical of mesocellular silica foams and certain mesoporous ordered silicas [57,58]. The BJH pore size distributions of the impregnated SiO_2 matrices are illustrated in Figure 4D–F and show pores between 4 and 10 nm for all products.

Table 4. Parameters of porous structure of the as-prepared catalyst and commercial silica gel support.

System	Surface Area (m^2/g)	Pore Volume (cm^3/g)	Median Pore Width (nm)
Silica Gel (60 Å, 230–240 mesh)	550 [1]	≈0.8 [1]	6.0 [1]
HCl.Gly-SiO$_2$	319	0.555	5.2
NH$_4$Br-SiO$_2$	185	0.444	5.5
NH$_4$HSO$_4$-SiO$_2$	161	0.331	5.6

[1] Reference [59].

Nitrogen adsorption data are summarized in Table 4. The values of BET surface area, BJH average pore diameter, and cumulative volume of pores for silica gel decreased significantly for the three functionalized catalysts relative to the unreacted SiO$_2$ support, which can be ascribable to the fact that ammonium salts are present both on the surface and in the pores, as already suggested by SEM and TEM characterization.

2.3. Green Chemistry Metrics

Finally, in order to evaluate the sustainability of our procedure, we calculated and compared some green chemistry metrics for the synthesis of several acetals run with our green solvent/heterogeneous catalyst protocol with literature data for reactions run employing an aromatic solvent in the presence of *p*-TSA [60–65].

In addition to the reaction yield (better specified in Table 5), we chose to report Reaction Mass Efficiency (RME) [66] as a measure to show the usage of stoichiometric reactants and Process Mass Intensity (PMI) [67] to include the contribution of all materials used in the procedure. Indeed, PMI, is a metric of choice in industry because of its comprehensive nature and straightforward calculation [68,69]. The results, as reported in Table 5, concern the synthesis of acetals **3c**, **3d**, and **3o**, and the different methodologies employed in this work to synthesize acetal **3j**.

Table 5. Comparisons of green chemistry metrics for the synthesis of selected acetals.

Compound	Procedure [Ref]	Yield (%)	RME (%)	PMI
3c	This work	95 [1]	65	4.6
3c	Yang et al. [60]	100 [1]	70	20.5
3c	Wang et al. [61]	100 [1]	61	12.4
3d	This work	95 [1]	67	3.9
3d	Cliffe et al. [62]	99 [2]	48	63.4
3d	Wenkert et al. [63]	90 [2]	82	44.7
3o	This work	95 [2]	78	3.3
3o	Xu et al. [64]	100 [2]	28	37.4
3o	Nishi et al. [65]	95 [2]	25	20.4
3j	This work Toluene/*p*-TSA	69 [2]	62	6.0
3j	This work CPME/NH$_4$HSO$_4$	63 [2]	57	3.2
3j	This work CPME/NH$_4$Br	78 [2]	71	2.6

[1] Crude reaction product. [2] Purified by recrystallization.

Taken as a whole, RME values show how, with our procedure, the reactants are used with an efficiency that compares well with literature procedures, while PMI highlights the advantages due to the straightforward work-up and efficient use of solvents and catalysts of our protocol (for methods of calculations and additional information, see Supplementary Materials).

3. Materials and Methods

Starting materials, solvents and reagents were of the highest commercial quality and were employed as received, including silica gel (60 Å, 230–400 mesh) (Alfa Aesar, Kandel, Germany). FTIR and TEM characterization of commercial silica gel can be provided by the following manuscripts [70,71]. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded with a Ascend 400 spectrometer

(Bruker, Billerica, MA, USA) in $CDCl_3$ (99.8% D content) solution with the residual peak of $CHCl_3$ as the internal standard. $CDCl_3$ was stored in a refrigerator under K_2CO_3 to avoid deacetalization during spectra recording. FTIR spectra of reaction products were recorded from KBr pellets on a Fourier Transform Infrared Spectrophotometer FT/IR-480 Plus (Jasco, Tokyo, Japan). Gas chromatographic analyses were recorded on an 6890N Network GC System (Agilent, Santa Clara, CA, USA). The HRMS spectra were acquired on a Thermo Finnigan Q Exactive instrument (Thermo Instrument Systems Inc, Waltham, MA, USA) with an API-HESI source. Samples were introduced as 0.1 mg/L solutions in MS grade methanol with a 5 μL/min flow and the following source parameters: positive polarity; sheath gas flow rate: 5 a.u.; aux gas flow rate: 3 a.u.; sweep gas flow rate: 0 a.u.; spray voltage: 3.50 kV; capillary temperature: 250 °C; S-lens RF level: 60.0 V; aux gas heater temperature: 0 °C. The peroxide content of the solvents was tested employing semi-quantitative test-strips Quantofix®(Macherey-Nagel, Düren, Germany), measuring range 0.5–25 mg/L H_2O_2, in agreement with the general indications provided by the producer.

3.1. General Procedure for the Acetalization Reaction

In a 50 mL flask fitted with a Dean–Stark distiller and bubble condenser provided with a $CaCl_2$ valve (for reactions in CPME or toluene) or under an Ar atmosphere (for reactions run in 2-MeTHF), the starting material (**1**, 80 mmol) was dissolved in the appropriate solvent (20 mL) together with the amount of the required diol (**2**, 88 to 160 mmol, 1.1 to 2.0 equivalent), as reported in Tables 2 and 3, Schemes 1 and 2, and Equations (1)–(5). After addition of the appropriate catalyst (2.4 mmol, 3 mol% of the starting material), the reaction mixture was heated in an oil bath under vigorous stirring and allowed to reflux for 6 h, then cooled to rt, and the reaction mixture was filtered. The reaction run in the presence of 1.5 to 2.0 equivalents of diol were then washed with H_2O (3 × 5 mL) and dried over anhydrous Na_2SO_4. The resulting solution was evaporated under reduced pressure and the crude product was analyzed by ^{1}H-NMR spectroscopy. No other products, besides starting material, were detected, unless otherwise indicated (Tables 2 and 3, Schemes 1 and 2, and Equations (1)–(5)).

Recovery of the catalyst (washed twice with the reaction solvent and dried in vacuo) usually exceeded 90%.

Reaction products were identified by comparison with the literature data and/or with authentic samples synthesized according to the literature. For more details, see Supplementary Materials.

2-Methyl-2-phenyl-1,3-dioxolane, **3a**: Colorless oil, which solidifies upon standing; white crystals, mp 61–62 °C (CPME) [5c]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.48 (2 H, d, *J* = 7.6 Hz), 7.35 (2 H, t, *J* = 7.6 Hz), 7.29 (2 H, t, *J* = 7.6 Hz), 4.09–3.99 (m, 2 H), 3.83–3.73 (m, 2 H), 1.66 (3 H, s); ^{13}C NMR ($CDCl_3$; 100 MHz) = 143.2, 128.1, 127.8, 125.2, 108.8, 64.4, 27.6.

3.2. Preparation and Characterization of the SiO_2-Supported Ammonium Salts

Silica-supported ammonium salts (25% *w/w* for NH_4HSO_4 and NH_4Br, 17% for HCl.Gly) were prepared by wet impregnation. A total of 20.0 g of SiO_2 (column chromatographic grade, 60 Å, 200–400 mesh) was added to a stirred solution of the appropriate amount of ammonium salt dissolved in 30 mL of H_2O. The resulting suspension was stirred at 50 °C for 1 h, followed by solvent evaporation under reduced pressure. The resulting white powder was dried at 120 °C for 48 h, then transferred and stored in a desiccator over anhydrous $CaCl_2$.

The microstructural, surface morphology, and elemental analysis of the samples were characterized by X-ray powder diffraction with a SmartLab diffractometer (Rigaku, Tokyo, Japan), transmission electron microscopy with a FEI TECNAI 200kV (Thermo Fisher Scientific, Waltham, MA, USA), and by scanning electron microscopy with a FEI QUANTA 200 (Thermo Fisher Scientific, Waltham, MA, USA). For TEM measurements, samples were prepared by dispersing a few milligrams in ethanol followed by the deposition of two drops of the suspension on an amorphous carbon-supported grid. For SEM imaging, a small amount of powder was deposited onto carbon tapes mounted on aluminum supports.

Fourier transform infrared spectroscopy (FTIR) measurements were performed with a FT/IR-480 Plus (Jasco, Tokyo, Japan) and all spectra were acquired with a resolution of 1 cm^{-1}. Each sample (0.01 g) was finely mixed with ultra-dry KBr and pressed into pellets.

N_2 sorption isotherms were collected with a Sorptomatic 1990 instrument (Fisons Instruments, Thermo Instrument Systems Inc., Waltham, MA, USA) and the specific surface area and pore distribution were calculated according BET and BJH approaches, respectively. Before measurements, 200 mg of each sample were put in a quartz tube and degassed under dynamic vacuum (1×10^{-3} bar) at 423 K for 24 h. The dead volume was evaluated through helium measurements.

4. Conclusions

Our results underline the scope and limitations of an environmentally friendly protocol aimed at the acetalization of aldehydes and ketones in green ethereal solvents, namely CPME and 2-MeTHF, in the presence of ammonium salts as environmentally friendly, cheap, easily available, and relatively mild heterogeneous acidic catalysts.

Interestingly, whilst CPME efficiently promoted the acetalization of a wide array of aldehydes and ketones both with diols and, under appropriate conditions, with monohydric alcohols, reactions in 2-MeTHF led to satisfactory results only for the acetalization of aldehydes. Nonetheless, it is worth mentioning that, as already reported for CPME [22], 2-MeTHF effectively promoted multistep reactions, requiring the temporary protection of the aldehyde moiety towards strong nucleophilic reagents.

Both solvents proved stable under the reported conditions and their employment in the presence of heterogeneous catalysts allowed their easy recovery and recycling through an efficient work-up procedure, leading to a reduced amount of wastes.

In our test reactions, ammonium salts, either as such or supported on SiO_2, performed better or equally well of widely employed homogeneous and heterogeneous acidic catalysts such as *p*-TSA, Amberlyst 15®, or Mont K10. Several examples highlight the advantage of tuning the relative acidities of ammonium salts by appropriately selecting the counterion, as in the synthesis of compounds **3a**, **3eb**, **3i**, and **3j**. In the last example, the proposed ammonium salts/green ethereal solvent protocol clearly outweighed the classical *p*-TSA/toluene protocol in terms of chemoselectivity.

Furthermore, ammonium salts were easily recovered by filtration, particularly when supported on SiO_2, and recycled several times with no significant loss of their catalytic activities. Silica-supported catalysts were characterized by SEM, TEM, and FTIR spectroscopies, as well as by N_2 physisorption, revealing an even distribution of HCl.Gly-OH, NH_4Br, and NH_4HSO_4 on the silica, whilst EDX analyses display the presence of specific elements Cl, Br, and S, respectively, thus confirming the formation of the expected supported catalysts. Taken as a whole, the characterization results strongly suggest that ammonium salts are present both on the surface and in the pores of silica, thus providing supported catalysts endowed with relatively high stabilities.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/10/10/1108/s1, General method, synthetic procedures, characterization data of all compounds including copies of ^{1}H and ^{13}C NMR spectra of previously not completely described compounds and of recycled solvents. Table S1: Performance of the recycled catalysts in the synthesis of dioxolane **3a**. Table S2. Performance of the recycled catalysts in the synthesis of dioxolane **3a** in the presence of SiO_2-supported ammonium salts. Figure S1: Representative SEM micrograph of the as-received SiO_2 support. Figure S2: Wide-angle XRD patterns of the as-received SiO_2, $(NH_4)HSO_4$, HCl Gly and NH_4Br supported systems. Figure S3: EDX spectrum of NH_4HSO_4-SiO_2. Figure S4: EDX spectrum of NH_4Br-SiO_2. Figure S5: EDX spectrum of HCl.Gly-SiO_2. Green Metrics. Scheme SM1: Previous synthesis of acetals and aminals in CPME. Equations (S1)–(S3): Two-step one-pot reactions in CPME. Literature references for the characterization of all reaction products. Literature references to Green Metrics.

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