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Alginic acid aerogel: a heterogeneous Brønsted acid promoter for the direct Mannich reaction†

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We demonstrate that highly dispersed alginic acid aerogel beads can function as heterogeneous promoters for Brønsted acid catalyzed reactions. The activity displayed by alginic acid, benchmarked in the three-component direct Mannich reaction, depended on its morphology, with the aerogel formulation providing distinct advantages over other forms.

Alginates are polysaccharide biopolymers, available at extremely cheap prices and in virtually unlimited amounts by extraction mainly from brown algae. These biodegradable polymers are commonly encountered in daily life, being used both in the food industry and in textile printing as thickening agents, whereas their capability to serve as enzyme supports is exploited in brewing and laundry powders.[1] In the current vision of a necessary switch from fossil to non-depleting feed-stocks,[2] additional utilization of these biopolymers is arguably highly attractive and worth pursuing,[3] even for less mass-intensive applications.

Alginates are constituted by sequences of (1 → 4) linked β-D-mannuronate (M) and α-L-guluronate (G) residues (Fig. 1). In contrast to cellulose and starch but in common with other more expensive polysaccharides of marine origin (chitin/chitosan and carrageenan), alginates feature a functional group (a carboxylate moiety) in each monomeric unit of their backbone, and are thus polymers with an extremely high functional group density (5.6 mmol g^{-1}). In analogy with their natural structural function, alginates can be easily obtained as hydrogels.[4] However, recent findings have demonstrated their tremendous manipulability, well beyond the hydrogel form.[5] Appropriate treatments allow control of the shape, morphology, mechanical properties, porosity and surface area of metal alginates and alginic acids[6] (obtained by acidification), almost at will. In particular, the aerogel formulation renders a manageable macro-porous material with very high surface area (350–500 $m^2\ g^{-1}$), wherein all functional groups are exposed and available.[7] These features seem to be well suited for catalysis, and have already been exploited for the preparation of alginate-supported metallic catalysts.[8] Moreover, recent studies have suggested the possibility of easily obtaining highly shaped mesoporous materials from fresh macroalgae, allowing their exploitation for chromatography, catalyst supports and drug delivery systems.[9]

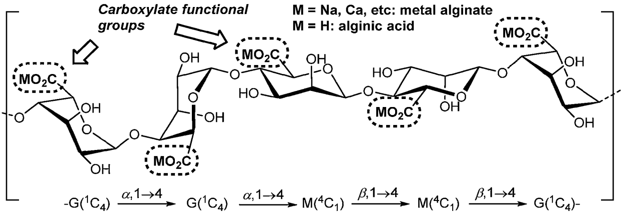

Fig. 1 Metal alginate and alginic acid structure.

Possibly prompted by the increasing attention to unconventional applications of renewable materials, the study of the capability of biopolymers in promoting simple reactions is a topic of current interest. Several unmodified biopolymers, such as chitosan,[10] calcium alginate,[11] polydopamine,[12] silk fibroin,[13] collagen and gelatin,[14] have been found to be active as Lewis or Brønsted base catalysts. Besides its potential in the frame of heterogeneous catalysis, interest in this peculiar research field is related to the intriguing hypothesis that these structural biopolymers, widely found in living systems and employed as passive supports/matrices in different settings (food and pharmaceutical industries, brewing, *etc.*), might not be as inert as they are thought to be. Whereas the above examples well demonstrate Lewis or Brønsted basic activation of substrates, the engagement of biopolymers in Brønsted acid catalysis has not been intensively studied. A single

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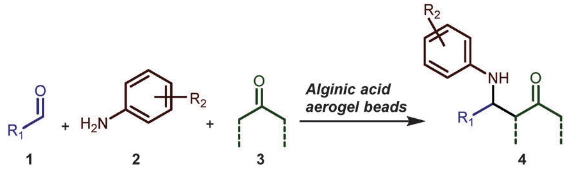
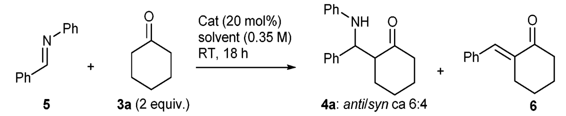
† Electronic supplementary information (ESI) available: Preparation of the gel materials, additional optimization results, kinetic studies, experimental details and product characterization, and copies of the ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c5nj00349k



Scheme 1 Alginic acid aerogel promoted 3C Mannich reaction.

Table 1 Solvent screening in the 2C Mannich reaction[a]



Entry	Solvent	Catalyst	**4a**-Yield[b] (%)	**4a** : **6**[c]
1	Toluene	AG-**1**	17	61 : 39
2	CH_2Cl_2	AG-**1**	13	52 : 48
3	EtOAc	AG-**1**	15	62 : 38
4	THF	AG-**1**	9	75 : 25
5	CH_3CN	AG-**1**	35	65 : 35
6	$CH_3CN–H_2O$ 8 : 2	AG-**1**	91[d]	>95 : 5
7	$CH_3CN–H_2O$ 8 : 2	—	24	>95 : 5
8	$CH_3CN–H_2O$ 8 : 2	AcOH	27	>95 : 5

[a] Conditions: imine **5** (0.15 mmol), ketone **3a** (0.30 mmol), cat. AG-**1** (20 mol%), RT, 18–24 h. [b] Yields were determined by ^{1}H NMR using bibenzyl as internal standard. [c] Determined by ^{1}H NMR. [d] Isolated yield after chromatography on the silica gel.

example, appeared while this work was in progress, showed moderate activity of alginic acid powder in a Hantzsch reaction,[15] without however reporting data on the dependency of the activity on the polymer morphology.

Herein, we present the evidence that alginic acid aerogel can act as a heterogeneous Brønsted acid promoter. In more detail, we disclose that the carboxylic moieties of the biopolymer can function as a mild catalyst for a three component (3C) Mannich addition reaction (Scheme 1), demonstrating the essential benefits of using the highly dispersed aerogel form of this material. Furthermore, upon acidification, even a seaweed commercialized for food purposes can be rendered catalytically active. For our studies, we chose the Mannich reaction as a benchmark not only for its known susceptibility to acidic (both Brønsted and Lewis) catalysis[16] but also for the typical challenges associated with this reaction, such as competing aldol addition, reversibility, formation of undesired α,β-unsaturated carbonyls, and the requirement of a water compatible reaction promoter.[17] These challenges render this 3C process a reliable test for demonstrating the efficiency of a Brønsted acid. Besides, the Mannich reaction is a fundamental transformation in organic chemistry, its 3C direct version provides a very straightforward access to structurally diverse β-amino carbonyl compounds (Mannich bases).[18]

At the outset, the capability of alginic acid to function as a Brønsted acid was assessed in a 2C Mannich reaction (Table 1), in order to simplify the system. The reaction between preformed imine **5** and cyclohexanone **3a** was investigated in different solvents, in the presence of guluronic-rich alginic acid (G/M 63 : 37)[19] in its aerogel bead formulation (aerogel AG-**1**, 20 mol% calculated on carboxylic functions). This preliminary solvent screening (Table 1, entries 1–5) suggested acetonitrile as a promising medium for the reaction, wherein a moderate conversion was observed (Table 1, entry 5). In all the solvents tested, the desired Mannich adduct **4a** was accompanied by considerable amounts of an undesired by-product **6**, derived from a retro-aza-Michael reaction also promoted by the heterogeneous acid.

It was then found that a consistent improvement in reaction efficiency could be achieved by using $CH_3CN–H_2O$ mixtures as solvents instead of pure CH_3CN, which allowed increasing the productivity and completely suppressing the by-product (**6**) formation. To assess the influence of the amount of water, a series of experiments with different $CH_3CN–H_2O$ mixtures was performed (Fig. 2). Short reaction times (5 h) were used, to better appreciate variances in the activity displayed by AG-**1**. These experiments showed a steady increase in the yield of the Mannich adduct **4a** with the amount of water used. In particular, an 80 : 20 ratio between acetonitrile and water appeared to be optimal for studying and demonstrating the efficiency of AG-**1** as catalyst, since higher amounts of water promoted a non-negligible background uncatalyzed process, which would prevent the correct evaluation of the catalyst activity. This 80 : 20 ratio was thus employed throughout this study.[20] Monitoring by ^{1}H NMR spectroscopy the evolution of the yield with time (see ESI†), we were able to assess that the reaction follows approximately pseudo-first order kinetics and to choose 18–20 h as the best reaction time, as the reaction considerably slows down already after 9 h and it appears almost complete after 18 h, allowing the isolation of the pure Mannich product **4a** in 91% yield (Table 1, entry 6). Under these conditions (18 h reaction time), the low yield obtained performing the reaction in the absence of AG-**1** (Table 1, entry 7) clearly demonstrated the activity of alginic acid as a heterogeneous Brønsted acid promoter in the model reaction. Its effectiveness was further confirmed by comparison with a homogeneous carboxylic acid, such as AcOH, which showed a negligible yield (Table 1, entry 8), comparable with the background, uncatalysed reaction.

After having optimized the 2C reaction, implementation of its 3C version proved to be straightforward, allowing a short investigation of its scope by combining different aldehydes **1**,

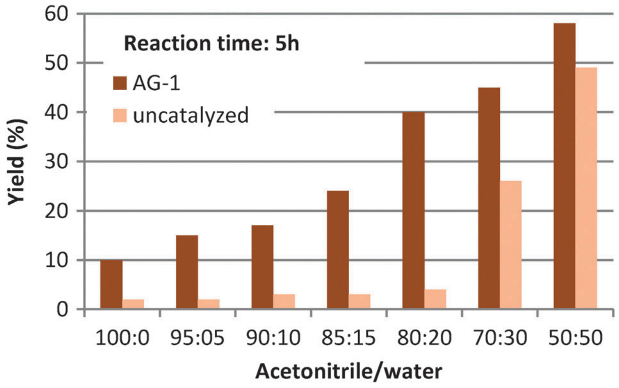
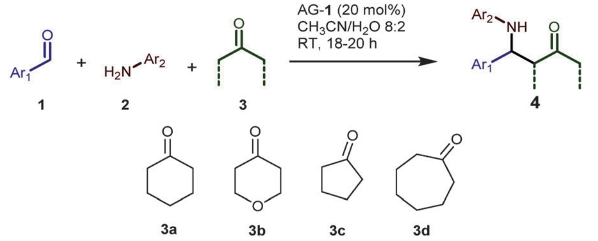


Fig. 2 Influence of the amount of water on the 2C Mannich reaction between **5** and **3a** (reaction time: 5 h). Yields were determined by ^{1}H NMR spectroscopy using bibenzyl as internal standard.

anilines **2** and cyclic ketone donors **3** (Table 2). Besides the Mannich adduct **4a** derived from benzaldehyde **1a** and aniline **2a**, a few other adducts **4b–h** were obtained in moderate to excellent yields from different aldehydes **1b–e** and electron-poor anilines **2b–d** (Table 2, entries 1–8).[21] Electron rich aldehydes **1f–g** and aniline **2e** could also be applied successfully to the reaction, even if the instability of adducts **4i–k** upon chromatographic purification on silica gel prevented the determination of the yield of isolated products (Table 2, entries 9–11). Other cyclic ketones **3b–d** were tested in the AG-**1** catalyzed reaction. While pyran-4-one **3b** and cyclopentanone **3c** performed well in the reaction (Table 2, entries 12 and 13), the 7-membered ring ketone **3d** did not afford the expected product **4n** (Table 2, entry 14), thus highlighting the limitation of the present catalytic protocol to more easily enolisable ketone substrates.

Given the heterogeneous nature of the catalyst, its recovery and reuse were preliminarily investigated. At the end of the reaction between benzaldehyde **1a**, aniline **2a** and cyclohexanone **3a**, performed using the optimized conditions, the catalyst was separated from the solution and carefully washed with the $CH_3CN–H_2O$ 8 : 2 mixture, before application in the next cycle. After the first recycle, the yield dropped to 77% of that obtained in the first run (Y**4a**: 65%). In the next two cycles, the yield stabilized at a moderate value (Y**4a**: 50%), falling further upon the fourth recycle (Y**4a**: 40%). Attempts to restore the catalytic activity by acidic washings were unfruitful. Since the macroscopic nature of the beads seemed to be unchanged, and the carboxylic functions were clearly visible by IR spectroscopy analysis, we speculate that pore occlusion by the reactants/products was the main reason for this partial loss of activity.

Table 2 Scope and limitations of the 3C Mannich reaction between different aldehydes **1**, anilines **2** and ketones **3** catalyzed by AG-**1**[a]



Entry	**1**: Ar_1	**2**: Ar_2	**3**	**4**-Yield[b] (%)	*anti*/*syn*[c]
1	**1a**: C_6H_5	**2a**: C_6H_5	**3a**	**4a**-90	61 : 39
2	**1b**: 4-ClC_6H_4	**2a**: C_6H_5	**3a**	**4b**-68	63 : 37
3	**1c**: 4-$NO_2C_6H_4$	**2a**: C_6H_5	**3a**	**4c**-76	64 : 36
4	**1d**: 2-naphth	**2a**: C_6H_5	**3a**	**4d**-60	61 : 39
5	**1e**: 4-FC_6H_4	**2a**: C_6H_5	**3a**	**4e**-61	64 : 36
6[d]	**1b**: 4-ClC_6H_4	**2b**: 4-ClC_6H_4	**3a**	**4f**-57	53 : 47
7[d]	**1b**: 4-ClC_6H_4	**2c**: 4-BrC_6H_4	**3a**	**4g**-95	50 : 50
8[d]	**1b**: 4-ClC_6H_4	**2d**: 3,4-$Cl_2C_6H_4$	**3a**	**4h**-90	65 : 35
9	**1f**: 4-$MeOC_6H_4$	**1a**: C_6H_5	**3a**	**4i**-76[e]	61 : 39
10	**1g**: 3,4-$(MeO)_2C_6H_3$	**2a**: C_6H_5	**3a**	**4j**-60[e]	64 : 36
11[d]	**1b**: 4-ClC_6H_4	**2e**: 4-$MeOC_6H_4$	**3a**	**4k**-72[e]	64 : 36
12	**1b**: 4-ClC_6H_4	**2a**: C_6H_4	**3b**	**4l**: 92	65 : 35
13	**1b**: 4-ClC_6H_4	**2b**: 4-ClC_6H_4	**3c**	**4m**: 50	61 : 39
14	**1b**: 4-ClC_6H_4	**2b**: 4-ClC_6H_4	**3d**	**4n**: <10	—

[a] Conditions: aldehyde **1** (0.15 mmol), aniline **2** (0.15 mmol), ketone **3** (0.30 mmol), AG-**1** (20 mol%), $CH_3CN–H_2O$ 8 : 2 (480 μL), RT, 18–20 h. [b] Isolated yield after chromatography on the silica gel. [c] Determined by ^1H NMR on the crude mixture. [d] 5 equiv. of ketone (0.75 mmol) were used. [e] Product unstable upon chromatography. Yield determined by ^1H NMR spectroscopy on the crude with an internal standard (bibenzyl).

Different formulations of alginic acid (xerogel XG, solvogel SG, and, for the sake of comparison, commercial alginic powder C) were then tested. Using pure acetonitrile as a solvent, the obtained results (Fig. 3) clearly indicated the requirement of a polysaccharide material with high porosity and surface area for the promotion of the reaction, with solvogel SG giving results comparable to AG-**1**, while xerogel XG and the commercial powder C hardly showing any reactivity. Different results were obtained using the usual $CH_3CN–H_2O$ 8 : 2 mixture, where all the formulations showed an increased activity, with all gels leading to similar yields. To better understand this different behaviour the reaction was repeated using a protic solvent (EtOH) instead of water, so as to verify if it has to be ascribed to a swelling or a proton transfer effect of water. The results clearly showed that the AG-**1** and SG formulations, in which all the active sites are accessible, maintain almost the same activity in the presence of EtOH, while XG and C are essentially unable to promote the reaction. Thus, the activity featured by XG and C in the presence of water is simply due to the swelling of the polysaccharide structures leading to a higher amount of exposed catalytic sites.

Then, the effect of natural variability in terms of the alginic acid composition on the reaction was verified by comparing the performance of the guluronic rich AG-**1** (G/M 63 : 37) with a mannuronic-rich alginic acid aerogel,[22] AG-**2** (G/M 33 : 67).[19] The G/M ratio influences the mechanical properties of the gels, their strength increases with the guluronic content.[23] As expected, the use of the weaker AG-**2** led to a poorer yield (Y-**4a**: 66% *vs.* 91%), presumably due to the partial disruption of the gel structure of AG-**2** during the reaction. Finally, our model reaction was performed using a commercial seaweed (S), Laminaria Digitata (G/M 41 : 59),[24] conveniently pre-treated to obtain an acid seaweed aerogel (Fig. 4 and ESI†). The result of

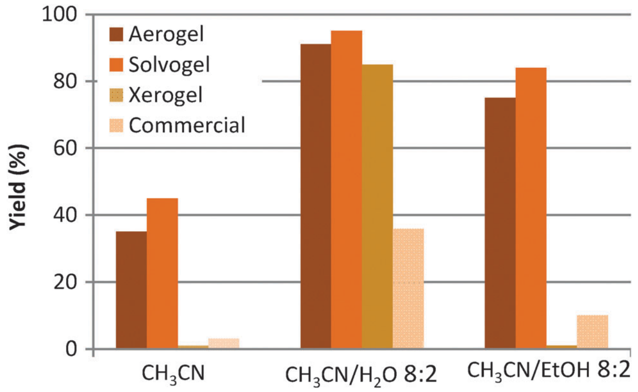


Fig. 3 Effect of the solvent on the activity displayed by the different alginic acid formulations in the reaction (RT, 18–20 h) between preformed imine **5** and cyclohexanone **2a** (2 equiv.). Yields determined by ^1H NMR spectroscopy using bibenzyl as internal standard.

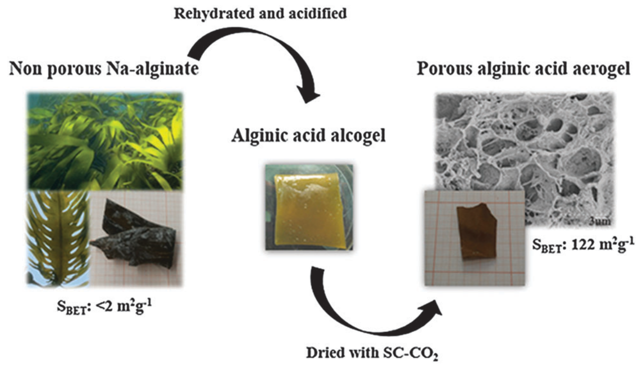


Fig. 4 Preparation of the acidified seaweed aerogel (S).

the benchmark 2C reaction between **5** and **3a** (Y-**4a**: 85%) is comparable to that obtained using AG-**1**; thus, this result suggests that the carboxylic acid functionalities can be made available directly from seaweed without any extraction or purification of the polysaccharide.

In conclusion, we have demonstrated that alginic acid can function as a mild Brønsted acid catalyst for a three component Mannich reaction. Thus, the present report offers prospects in the frame of heterogeneous catalysis based on renewable resources. Besides, the capability of unmodified alginic acid in promoting a chemical transformation provides additional support to the provoking suggestion that biopolymers featuring structural functions, widely found in living systems and used in the food and other industries as additives, might not be as innocent as they are thought to be.[12–14]

Acknowledgements

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substrates, in the presence of SDS there was no evidence of **AG-1** catalytic activity. See ESI†.

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