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FULL PAPER

Adsorption of a Chiral Amine on Alginate Gel Beads and Evaluation of its Efficiency as Heterogeneous Enantioselective Catalyst

Daniel Antonio Aguilera,[a,b] Lisa Spinozzi Di Sante,[a] Asja Pettignano,[a,b] Riccardo Riccioli,[a] Joël Roeske,[a,c] Luce Albergati,[a,c] Vasco Corti,[a] Mariafrancesca Fochi,[a] Luca Bernardi,*[a] Françoise Quignard[b] and Nathalie Tanchoux*[b]

Dedication ((optional))

Abstract: A representative Lewis base organic catalyst (9-amino-9-deoxy *epi*-quinine, **QNA**) can be adsorbed in high yields onto acidic alginate gels (**AGs**) using a very simple and straightforward protocol. The resulting solvogel beads (**QNA@AGs**) are active as heterogeneous catalyst in the addition of aldehydes to nitroalkenes, affording the corresponding adducts in good yields and moderate to excellent diastereo- and enantio-selectivities. In these reactions, the carboxylic functions of the biopolymer act as both acidic co-catalyst and non-covalent anchoring site for the tertiary amine catalyst (as observed by IR spectroscopy). Use of heterocationic gels, derived from alkaline earth metal gels by proton exchange, provided materials with better mechanical properties and higher porosities, ultimately resulting in higher catalytic activities. This work represents the first utilization of alginates, abundant and renewable biopolymers, as gel supports/media for asymmetric organocatalytic processes.

Introduction

Alginates are natural polysaccharides extracted from brown macro-algae and available in very large amounts at low prices.[1] Structurally speaking, they are constituted by *β*-D-mannuronate (M) and *α*-L-guluronate (G) monomers, fixed in $^4C_1$ and $^1C_4$ conformations, respectively, and linked in a 1 → 4 fashion (see Scheme 1). The presence of a carboxylic functional group in each monomeric unit differentiates these biopolymers from other natural polysaccharides, such as cellulose, leading to unique properties and applications. Starting from aqueous sodium alginate solution, the preparation of hydrogel beads by proto- or iono-tropic dropping gelation processes is straightforward.[2] The thus obtained, easily manageable, hydrogel beads feature high surface areas (300-700 $m^2 \cdot g^{-1}$) and functional group (the carboxylate) density and availability (5.6 $mmol \cdot g^{-1}$). The properties of the hydrogel depend on the type of gelling agent, its concentration and the maturation time in the gelling bath.[3] Furthermore, the ratio between M and G units in the alginate, which derives from its natural source, plays a major role in the mechanical features of the gels; G rich alginates give stiffer and more resistant materials compared to M rich alginates,[4] enabling a fine-tuning of the gel properties. Importantly, the structure of the gel is nearly retained exchanging water with organic solvents (hydrogel → solvogel), or during a following supercritical drying (solvogel → aerogel).[2,5] Utilization of alginate gels is thus possible in different media. All these features make these renewable biomaterials highly attractive as heterogeneous supports in the frame of catalytic processes. In this context, a large number of metal based heterogeneous catalysts prepared by combining (transition) metals and nanoparticles with alginate gels have been reported.[6,7] Alginates can thus be considered an appealing alternative to oil based polymers and inorganic materials for supporting metal catalysts.[8]

Alginates are also being studied for water remediation purposes;[2c] we have recently demonstrated that acidified alginate foams are able to remove a basic dye (methylene blue) from aqueous solutions by adsorption.[9] This proficiency is mainly due to an acid-base interaction between the carboxylic acid functions of the biopolymer and the basic dye. We questioned whether such acid-base interaction could be leveraged to link an amine organic catalyst to alginic acid gels, providing the first example of the utilization of alginates as support for chiral organic catalysts.[10,11] Even if the retaining of catalyst activity and selectivity in the gel structure was considered challenging, literature encouragement to our working plan was given by few examples of non-covalent immobilization of amine catalysts to acidic supports.[12] These works demonstrated that, in aminocatalytic reactions, heterogeneous acids can act as both supports for the amine catalysts, and weakly acidic co-catalysts. The mild acidic nature of the carboxylic acid units of alginic acid (pK_a ca. 3.5 in water)[13] could fulfill these purposes. The non-covalent approach to catalyst immobilization[14] bears some obvious advantages in terms of simplicity and straightforwardness,

[a] D. A. Aguilera, L. Spinozzi Di Sante, Dr. A. Pettignano, R. Riccioli, J. Roeske, L. Albergati, V. Corti, Prof. M. Fochi, Prof. L. Bernardi
Department of Industrial Chemistry "Toso Montanari" & INSTM RU Bologna
Alma Mater Studiorum – University of Bologna
V. Risorgimento 4, 40136 Bologna (Italy)
E-mail: luca.bernardi2@unibo.it
https://www.unibo.it/sitoweb/luca.bernardi2/en

[b] D. A. Aguilera, Dr. A. Pettignano, Dr. F. Quignard, Dr. N. Tanchoux
Institut Charles Gerhardt
CNRS-ENSCM-UM
8, Rue Ecole Normale, 34296 Montpellier (France)
E-mail: nathalie.tanchoux@enscm.fr
https://www.icgm.fr/en/nathalie-tanchoux-en

[c] J. Roeske, L. Albergati
Haute Ecole d'Ingénierie et d'Architecture
Bd. de Pérolles 80, 1705 Fribourg (Switzerland)

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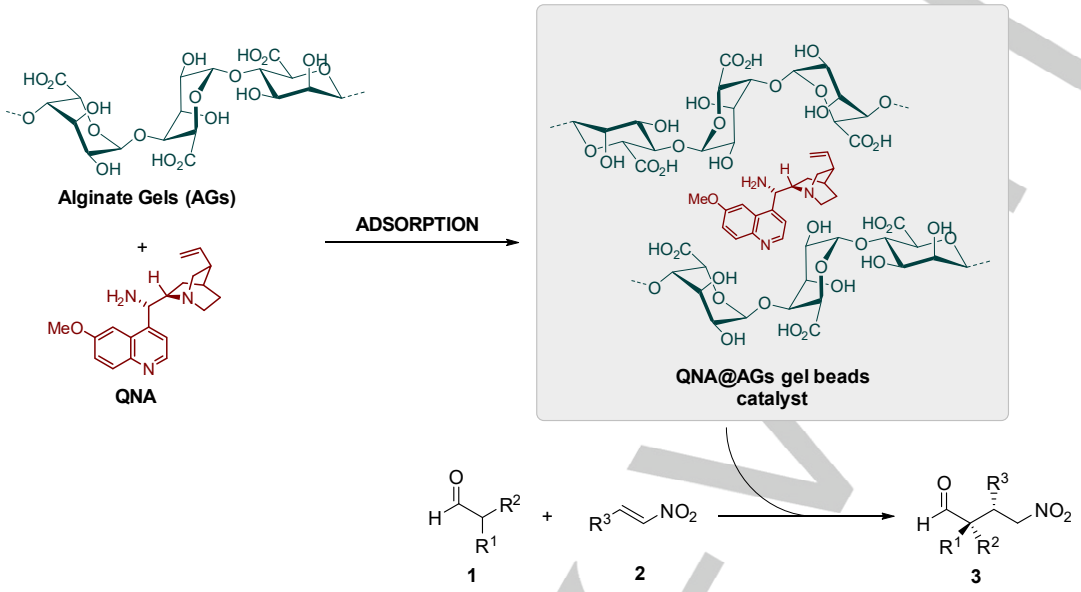

Scheme 1. Adsorption of an organic catalyst (**QNA**) on acidic alginate gels (**AGs**) and use of the resulting gel beads (**QNA@AGs**) as catalysts in a benchmark asymmetric Michael addition reaction.

compared to the more explored covalent anchoring of the catalyst to the support, which can lead to modifications of catalyst structure altering its performances.[10] The latter approach requires also multiple additional synthetic steps to prepare the heterogeneous catalyst, while being, on the other hand, less prone to catalyst leaching issues.

Herein, we present the optimization of the adsorption of a representative Lewis base organic catalyst (9-amino-9-deoxy *epi*-quinine, **QNA**),[15,16] onto acidic alginate gels (**AGs**), by varying the adsorption conditions and the characteristics of the material, rendering stable gel beads (**QNA@AGs**), which could be used as heterogeneous catalysts in the benchmark enantioselective Michael addition of aldehydes **1** to nitroalkenes **2**[17] (Scheme 1). Although the activity of this heterogeneous catalyst in subsequent reaction cycles was only moderate, the enantiomeric excesses of products **3** obtained with this heterogeneous system were generally very high.

Results and Discussion

We started our investigations by preliminarily testing the capability of alginic acid gel beads (**AG-H**) to adsorb and retain the catalyst **QNA**, while maintaining a stable gel structure. We studied guluronic-rich alginic acid (G/M 63:37), since these alginates feature better mechanical strength compared to other alginates more rich in mannuronic units. Taking advantage of using a dry aerogel material, different adsorption media were employed (Table 1). Considering the usually optimal ratio between acidic co-catalysts and Lewis base amines in the catalytic reactions,[15,16] the amount of biopolymer **AG-H** was tailored to reach 2 equiv. of carboxylic units per **QNA** catalyst. These tests were carried out by adding alginic acid aerogel beads (10 beads, corresponding to 0.028 mmol of carboxylic acid units) to a solution of **QNA** in the appropriate solvent (0.014 mmol in 300 µL), leaving the mixture under gentle magnetic stirring for 18-24 h. As shown in Table 1, entries 1-9, aprotic apolar solvents were not very efficient in **QNA** adsorption, leaving substantial amounts of **QNA** in solution at the end of the process. Experiments performed at different temperatures did not show any significant improvement (entries 2,3). A slight improvement was displayed by increasing the excess of carboxylic acid units (entry 4), which however was thought to be detrimental for catalytic activity and was thus not pursued further. While a protic but lipophilic alcohol such as *i*-PrOH (entry 10) behaved similarly to the aprotic solvents, much better adsorption results were obtained in EtOH as adsorption medium (entry 11). We rationalize these results on the bases of the swelling properties of the different solvents, with a polar protic solvent like ethanol enabling better interactions between **QNA** and the acidic protons of the polymer. We tend to exclude that the different adsorption values are due to the variation of the acidity of the polymer in the different media (i.e. to a thermodynamic phenomenon), since washing the **QNA@AG-H** beads several times with toluene and then placing them in fresh toluene did not cause any **QNA** desorption. This is a key important aspect as the beads have the right properties to be used as gel catalysts in different media. Moving to a more polar medium (water) was not feasible as the gel structure broke gelifying the whole solvent (entry 12). We believe that the interactions between the carboxylic groups and **QNA** are so strong in this medium that the alginic acid

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(a prototropic gel) hydrogel structure is not stable anymore. The carboxylic groups involved in **QNA** adsorption play, in fact, a fundamental role also in the formation of intramolecular H-bonds between the polymeric chains.[18] The competitive interaction with the **QNA** base could thus lead to a partial destabilization of the gel network.[19]

Table 1. Preliminary tests on the adsorption of **QNA** on **AG-H** aerogel beads in different media.[a]

Entry	Solvent	*T* [°C]	QNA_{ads}[b] [mol%]
1	Toluene	25	45
2	Toluene	0	45
3	Toluene	45	37
4[c]	Toluene	25	60
5	$CHCl_3$	25	38
6	CH_2Cl_2	25	50
7	EtOAc	25	32
8	CH_3CN	25	34
9	THF	25	31
10	*i*-PrOH	25	39
11	EtOH	25	86
12[d]	H_2O	25	-

[a] Conditions: **QNA** (0.014 mmol), **AG-H** (10 aerogel beads, corresponding to 0.028 mmol of carboxylic acid units), solvent (300 µL), 18-24 h. The solvent was then removed and the beads washed with fresh solvent 3-4 times. [b] Mol% of **QNA** adsorbed on **AG-H** compared to starting **QNA**. Determined by ^{1}H NMR using bibenzyl as internal standard after evaporation of the adsorption and washing solvents. [c] 20 beads of **AG-H** (corresponding to 0.56 mmol of carboxylic acid units) were used. [d] Beads broke.

To confirm the presence of **QNA** in the structure of the biopolymeric matrix of alginate, UV–Vis/DRS (Diffuse Reflectance Measurement) spectroscopy was performed (Figure 1). The blue line represents the UV–Vis/DRS spectra of the alginate beads after the adsorption test of **QNA** in EtOH (**QNA@AG-H**), and the red line represents the acidic alginate aerogel **AG-H** before the adsorption. Only the absorption spectrum of **QNA@AG-H** has a main band centered at ~333 nm, close to the maximum found in the UV-Vis spectrum in solution for **QNA** (~334 nm, spectrum not shown). This signal is associated to S0-S1 transition of the heterocyclic quinoline ring in *Cinchona* alkaloids.[20] All the above indicated that the **QNA** has been adsorbed on **AG-H** successfully.

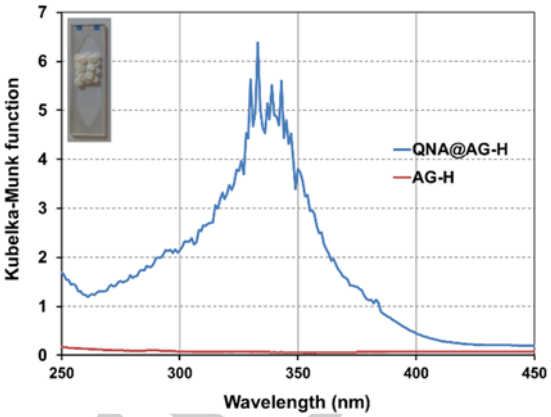

Figure 1. UV–Vis/DRS spectra of **QNA@AG-H** (blue line) and **AG-H** aerogel beads (red line).

Solid state FT-IR analysis of the **QNA@AG-H** beads confirmed that the main interaction between the biopolymer and **QNA** is at the carboxylic acid units (Figure 2). In more detail, the spectrum of **QNA@AG-H** (red line, Figure 2) shows a dramatic decrease of the signal of the carboxylic C=O stretching at 1730 cm^{-1} compared to the spectrum of **AG-H** (black line). Likewise, a new signal appeared at 1595 cm^{-1}. This signal can be assigned to the stretching of the carboxylate O-C=O group, and is not present in the parent **QNA** (blue line). This result indicates that **QNA** is, at least partially, deprotonating the carboxylic groups. Taking into account that in the adsorption process a molar excess of the carboxylic groups (COOH:**QNA** 2:1) is used, the disappearance of the signal of the carboxylic acid at 1730 cm^{-1} suggests that **QNA** interacts with more than one carboxylic groups of the support, presumably using both primary and tertiary amine groups.

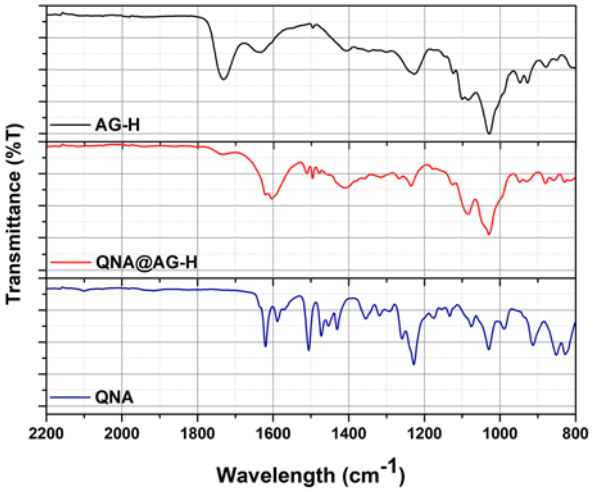

Figure 2. FT-IR spectra of **AG-H** (black line) **QNA@AG-H** (red line), and **QNA** (blue line).

Further refinement and optimization of the adsorption process led to a fully reproducible and robust protocol consisting

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in adding slowly a **QNA** solution to the **AG-H** beads (tailored to reach 2.5 equivalents of carboxylic acid units) soaked in EtOH. High dilution (8 x 10^{-3} M) was also beneficial to ensure preservation of the macroscopic properties (shape, size) of the gel material upon adsorption. On the other hand, in terms of material morphology, aerogel and ethanol alcogel beads could be indifferently employed with similar results.

With this new protocol, we studied in more detail the influence of water on the adsorption process, using EtOH/H_2O mixtures. The kinetics data (using UV-vis spectroscopy, Figure 3a) showed that the adsorptions proceed very fast for the first few hours, then reaching slowly the maximum value after around 24 h. The addition of 10% water to EtOH had a positive effect with a slight increase in the final amount of **QNA** adsorbed (Figure 3b). Lower percentages of water vs absolute EtOH did not have a significant effect on the adsorption process. The positive effect of water may be associated with the ability of the polysaccharides to swell in aqueous media, which leads to a more dispersed and accessible structure for the catalyst and therefore more efficient adsorption, as previously mentioned. On the other hand, the increase in the amount of water above 10%, led to a dramatic decrease in the **QNA** amount adsorbed. This decrease was associated with altering the structure of the gel of alginic acid, such as breaking of the beads and new gelation, which was observed at high water contents in the presence of the basic **QNA** (Figure 3c,d).

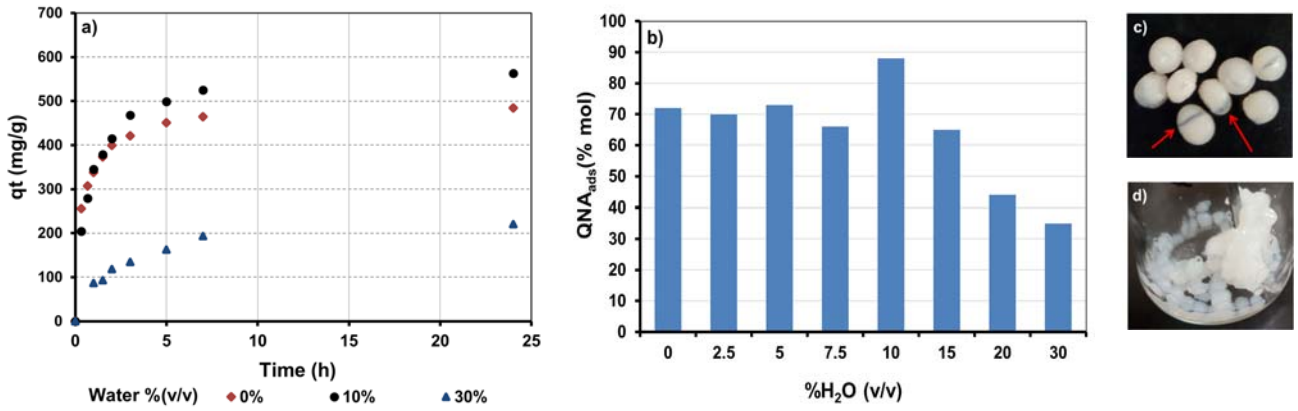
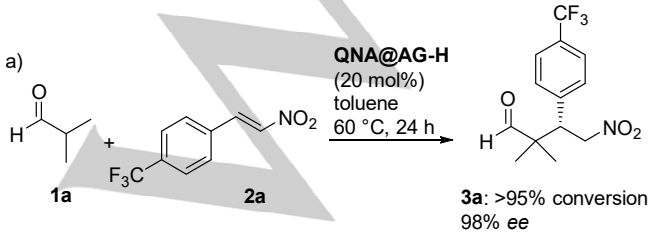
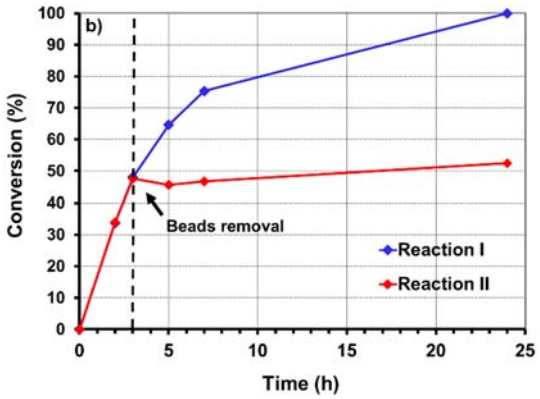


Figure 3. Adsorption data of **QNA** on **AG-H** obtained by UV-vis spectroscopy using appropriate calibration curves. (Conditions: solution of **QNA** added to **AG-H** beads (ratio COOH:**QNA** 2.5:1, **QNA** concentration 8 x 10^{-3} M) at 25 °C). a) Representative adsorption isotherms for the adsorption of **QNA** on **AG-H** at different percentages of water in EtOH at 25°C. b) Influence of the amount of water used as a co-solvent in the percentage of **QNA** adsorbed on **AG-H**. c) and d) Examples of beads breaking and new gelation at high percentages of water (> 10%).

The benchmark reaction between *iso*-butyraldehyde **1a** and 4-trifluoromethyl-*β*-nitrostyrene **2a** in the presence of **QNA@AG-H** as catalyst (prepared using the optimized protocol with EtOH/H_2O 9:1 as adsorption medium) was then studied and optimized (Scheme 2a). Working at 60 °C in toluene, we were delighted to observe that the gel beads were active in this reaction. The product **3a** was obtained with very good results in terms of conversion after 24 h. Enantioselectivity was also very good (*ee* 98%). The heterogeneity of the catalyst (used as toluene solvogel) was determined by a Sheldon test (Scheme 2b), which showed good heterogeneity as the reaction did not proceed to a considerable extent upon beads removal (compare reaction I *vs* reaction II), suggesting that catalyst leaching did not occur, and that the catalytic process takes place in the gel environment.





Scheme 2. a) Addition of **1a** to **2a** catalysed by **QNA@AG-H** (20 mol%). b) Reaction kinetics and Sheldon test. Conversion determined by ^{19}F NMR. In reaction II, **QNA@AG-H** beads were removed after 3 h.

While enantioselectivity was fully satisfactory and comparable to the homogeneous versions of this **QNA** catalysed reaction,[17] reaction rate was considerably lower. Furthermore,

some change in shape and size in the beads recovered after the reaction was observed. In order to improve the properties of the catalyst, some heterocationic alginate gels, that is gels featuring both carboxylic and metal carboxylate groups, were applied. The idea was to use a metal-cation for strengthening/improving the properties of the support while keeping the acidic moiety for anchoring the basic **QNA** catalyst. To this purpose, Ca^{2+} ion was first selected as a cross-linking agent based on the fact that it can generate alginate-based materials with better mechanical properties than the acidic ones.[21] The heterocationic gels were prepared from Ca^{2+} alginate hydrogels **AG-Ca** as starting materials, by exchanging some of the Ca^{2+} cations for H^+ by aq. HCl treatment at different concentrations. The thus obtained heterocationic hydrogels (**AG-Ca:nH**) were washed, then converted to the corresponding ethanol solvogels, which xerogels were characterized by TGA (thermogravimetric analysis) to determine the amount of Ca^{2+} remaining on the gel after the exchange, which was roughly inversely proportional to the amount of HCl used (see Supporting Information). The ratio between carboxylic and carboxylate units in the materials could thus be calculated (Table 2, entries 3-5). The cation exchange allowed the control of Ca^{2+} quantity in the final material by varying the initial concentration of HCl in solution. However, even with an excess of HCl (entry 5), a residual amount of Ca^{2+} in the **AG-Ca:4H** was observed. At the macroscopic level, all materials after the exchange conserved the initial spherical form of **AG-Ca**.

Table 2. Heterocationic **AG**s: H^+ content and **QNA** adsorption capability.

Entry	Alcogel[a]	-COOH[b] [%]	QNA_{ads}[c] [mol%]
1	**AG-H**	100	84
2	**AG-Ca**	0	16
3	**AG-Ca:0.5H**	27	85
4	**AG-Ca:2H**	79	90
5	**AG-Ca:4H**	95	91
6	**AG-Sr**	0	14
7	**AG-Ba**	0	13
8	**AG-Sr:2H**	67	93
9	**AG-Ba:2H**	66	87

[a] **AG-M:nH**: alcogels obtained from **AG-M** hydrogels by H^+ exchange: M refers to the metal ion while n refers to the molar ratio between HCl used in the exchange and the metal present in the hydrogel. [b] Ratio of -COOH vs overall -COOH + $-COO(M)^{1}/_{2}$ groups in the **AGs**, determined by TGA. [c] Adsorption performed at 25 °C by adding **QNA** solution in EtOH/H_2O 90:10 (0.014 mmol) to **AGs** beads (amount adjusted to have 0.035 mmol of carboxylic units) soaked in EtOH/H_2O 90:10 (**QNA** concentration 8 x 10^{-3} M). The solvent was then removed and the beads washed with fresh solvent 3-4 times. Mol% of **QNA** adsorbed on **AGs** compared to starting **QNA**. Determined by ^{1}H NMR using bibenzyl as internal standard after evaporation of the adsorption and washing solvents.

The thus obtained alcogels were then used for **QNA** adsorption (Table 2, entries 3-5), keeping the molar ratio between the carboxylic groups of the **AGs** and **QNA** fixed to 2.5. Initially, the adsorption of **QNA** using **AG-Ca** versus **AG-H** alcogels (entries 2 and 1) was compared, showing that the **AG-Ca** had a very low adsorption capability, as expected considering the lack of carboxylic acid groups in this gel. However, the partial replacement of Ca^{2+} by H^+ in **AG-Ca:0.5H**, **AG-Ca:2H** and **AG-Ca:4H** alcogels led to sharp increase of the adsorption of **QNA** (entries 3-5), which reached values comparable or even better than the adsorption featured by **AG-H**. The result obtained with **AG-Ca:0.5H** indicates that even a relatively large quantity of Ca^{2+} in the support does not compromise adsorption of **QNA** (entry 3).

The evaluation of the activity of **QNA** supported on this series of heterocationic gels (**QNA@AG-Ca:nH**) in the reaction between *iso*-butyraldehyde **1a** and nitroalkene **2a** is reported in Figure 4a.

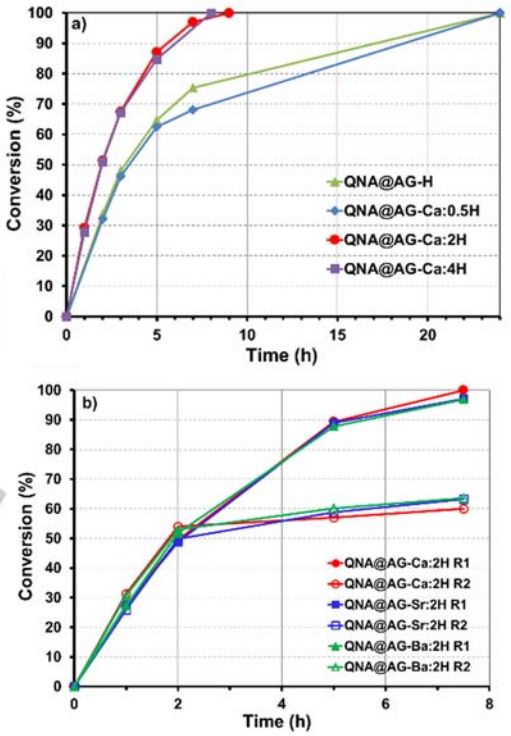


Figure 4. Kinetics of the reaction between **1a** and **2a**, performed in toluene at 60 °C and catalysed by **QNA@AG** at 20 mol% catalyst loading based on **QNA**. Conversion values were determined by ^{19}F NMR. Product **3a** was obtained in 98% *ee* in all cases. a) Kinetics of the reactions catalysed by **QNA@AG-H**, **QNA@AG-Ca:0.5H**, **QNA@AG-Ca:2H** and **QNA@AG-Ca:4H**. b) Kinetics of the reactions catalysed by **QNA@AG-Ca:2H**, **QNA@AG-Sr:2H**, **QNA@AG-Ba:2H** and their relative Sheldon tests: in R2, performed in parallel with R1, beads were removed after 2 h.

An improvement in the activity by using as support heterocationic gels with low content of Ca^{2+} could be clearly observed, as the reactions catalyzed by **QNA@AG-Ca:2H** and **QNA@AG-Ca:4H** went to completion in less than 8 h, compared to the reaction with **QNA@AG-H** which required around 24 h. This improvement can be rationalized considering an increase of surface area and thus accessibility to substrates for these heterocationic materials, related to the conservation of the more

disperse initial structure of **AG-Ca** even after the exchange. In fact, the surface areas of **AG-H** and **AG-Ca** aerogels were measured to be close to 250 $m^2 \cdot g^{-1}$ and 350-500 $m^2 \cdot g^{-1}$, respectively.[2b,22] The catalyst with higher quantity of Ca^{2+} (**QNA@AG-Ca:0.5H**) performed worse under these reaction conditions, albeit comparably to the previously applied **QNA@AG-H**. In all cases, the reactions afforded product **3a** in nearly enantiopure form. Furthermore, **QNA** leaching was not observed as beads removal in parallel experiments halted the reactions.

In order to discriminate whether there were differences between the use of the calcium *vs* other alkaline earth metals, heterocationic gels starting from **AG-Sr** and **AG-Ba** were prepared (Table 2, entries 8,9). Perhaps due to the higher affinity of these cations for polyuronates,[23] exchange with H^+ left larger amounts of Ba^{2+} and Sr^{2+} in the gels, compared to **AG-Ca** (Table 2, compare entry 4 with entries 8,9). Nevertheless, both cations behaved very similarly to calcium in terms of both adsorption of **QNA** (entries 6-9) and catalytic performances. **QNA@AG-Sr:2H** and **QNA@AG-Ba:2H** gave kinetics essentially superimposable to **QNA@AG-Ca:2H** in the reaction between **1a** and **2a** (Figure 4b). Heterogeneity was also comparable.

Unfortunately, recovery of the heterogeneous catalysts after reaction and use in subsequent reaction cycles showed a considerable loss of activity (from full conversion to 75% for **QNA@AG-Ca:2H**). Excluding catalyst leaching as the major factor, we attribute these results to the combination of two elements, with the second one likely prevailing:

i) **QNA** deactivation/degradation, which has been observed in all polymer-supported versions of this catalyst preventing its use for more than just few cycles;[16]

ii) pore occlusion by reaction of alginate functionalities with aldehyde **1a**, which is used in excess (5 equiv.) in the reaction.

In fact, control experiments (see Supporting Information) showed a slow deactivation of the heterogeneous catalyst over the course of the reaction and a dramatic loss of activity upon pre-treatment of **QNA@-AG** catalysts with the aldehyde **1a** prior to the reaction. In contrast, **QNA@-AG** catalysts appeared to be perfectly intact upon prolonged heating (60 °C, overnight) in toluene, even in the presence of nitroalkene **2a**. Unfortunately, reducing the amount of aldehyde donor **1a** was not practical, while all attempts to restore the activity of the catalyst after the reaction by acidic ($EtOH:HCO_2H$ 9:1), basic (EtOH/aq. NH_4OH 9:1), aqueous or thermal (60 °C, overnight) treatments were not successful. Similarly negative results were obtained by i) changing reaction solvent to dichloromethane, THF, EtOH, EtOAc or acetonitrile; ii) increasing or decreasing reaction temperature to 40 °C or 80 °C; iii) using an inert atmosphere, degassed or dry toluene; iv) applying different additives, such as drying agents, or adding water in different amounts (from water saturated toluene to biphasic mixtures). Nevertheless, it must be noted that the enantioinduction furnished by all **QNA@AG** catalysts in subsequent cycles was always identical to the one displayed in the first cycle (98% *ee*).

Using the **QNA@AG-Ca:2H** catalyst, we verified the tolerance of this heterogeneous system to substrate variations (Scheme 3). By adjusting the reaction time case by case (see Supporting Information), aromatic and one aliphatic nitroalkenes **2a-e** reacted well with *iso*-butyraldehyde **1a**, delivering the corresponding products **3a-e** in good yields and excellent enantioselectivities. Variations at the aldehyde partner were also explored.[24] Other α,α-disubstituted aldehydes (cyclopentane carbaldehyde **2b** and 2-phenylpropionaldehyde **2c**), rendered products **3f** and **3g** with good results. High diastereoselectivity was obtained in product **3g** bearing a quaternary stereocentre at the α-position of the aldehyde. In contrast, a linear monosubstituted aldehyde (*n*-hexanal **2c**) afforded the corresponding product **3h** with moderate diastereoselectivity. However, enantioselectivity was fully satisfactory. In fact, despite the moderate activity displayed by this heterogeneous **QNA@AG-Ca:2H** catalyst system, high enantioselectivities were observed in most cases, even at 60 °C. The intrinsic chirality of alginates does not seem to have an effect in these reactions; 9-amino-9-deoxy *epi*-quinidine **QDA** behaves very similarly to **QNA** both in terms of adsorption behaviour and catalytic results (see product *ent*-**3a** in Scheme 3, for reaction kinetics see Supporting Information).

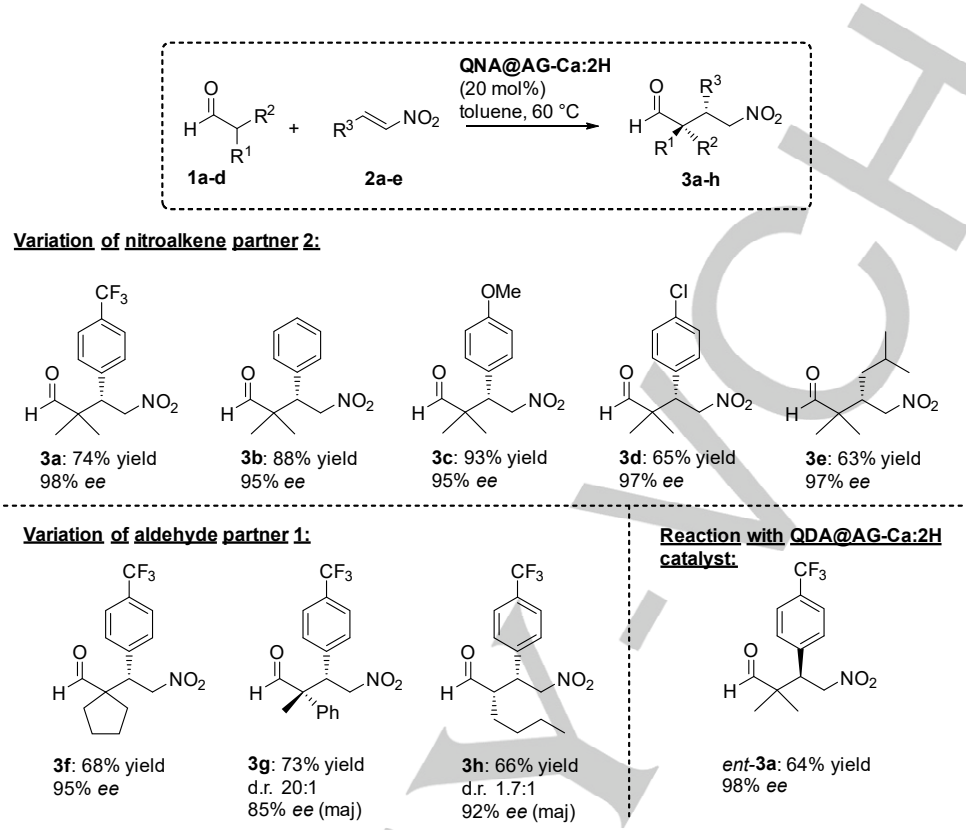
Conclusions

We demonstrated the possibility of using cheap and renewable alginate gels (**AGs**) as support for a model organocatalyst, (9-amino-9-deoxy *epi*-quinine **QNA**), by means of a simple and efficient adsorption protocol. The adsorption conditions were optimized, leading to nearly full adsorption of **QNA** on alginic acid alcogels using $EtOH:H_2O$ 9:1 as adsorption medium under high dilution (8×10^{-3} M). Crucial parameters, allowing the production of stable **QNA@AG-H** gel beads, were found to be the type of alginate (guluronic rich), the addition order and the amount of water in the adsorption mixture. IR studies showed that the interaction between **QNA** and **AG-H** takes place mainly between the basic groups of the alkaloid and the carboxylic groups of the biopolymer. Heterocationic alginate gels of type M^{2+}-H^+ based on alkaline earth metals (Ca, Sr, Ba) also showed a remarkable adsorption of the **QNA**, even with high metal contents. The new catalytic **QNA@AGs** systems are fully heterogeneous and promote efficiently the asymmetric addition of aldehydes (α-substituted and α,α-disubstituted) to nitroalkenes. The activity was improved using heterocationic type supports compared to simple alginic acid (e.g. **QNA@AG-Ca:2H** *vs* **QNA@AG-H**) showing good yields (up to 93%) for a significant range of substrates. Although the recyclability is moderate (up to 2 cycles), the enantioselectivity is high in most products. Forthcoming studies will assess the influence, if any, of the gel chiral environment[25] on reaction outcome, with the ultimate goal of developing uniquely selective systems in this and related reactions.

Experimental Section

Preparation of alginic acid gel (AG-H).[8b] A 2% w/V solution of sodium alginate was prepared, adding 2 g of sodium alginate (Protanal 200S; G/M 63:37) to 100 mL of distilled water and stirring it until a clear and viscous solution was obtained. The thus prepared solution was added dropwise (using a dropping funnel) to 400 mL of 1 mol/L HCl kept under magnetic

10.1002/ejoc.201900247



Scheme 3. Conditions: Aldehyde **1** (1.05 mmol), nitroalkene **2** (0.21 mmol), **QNA@AG-Ca:2H** (30 beads, corresponding to 20 mol% **QNA** catalyst loading), toluene (0.90 mL), 60 °C. Yields of products **3** after purification by chromatography on silica gel. *ee* determined by chiral stationary phase HPLC. D.r. of **3g** and **3h** determined by ^{19}F NMR spectroscopy on the crude mixtures.

stirring at RT. The resulting mixture was slowly stirred overnight to allow the maturation of the beads, whose formation is immediately evident. After filtration, the beads were carefully rinsed with distilled water and dehydrated by immersion in a series of EtOH/H_2O baths, with increasing alcohol content (10, 30, 50, 70, 90% and absolute EtOH), for 15 min each [**AG-H** sample].

Preparation of M^{2+} alginate gels (AG-M).[8b] 50 mL of a solution of sodium alginate (2% w/V) was added dropwise (using a dropping funnel) to 100 mL of a 0.1 mol/L solution of metal chloride ($CaCl_2$, $SrCl_2$, $BaCl_2$) kept under magnetic stirring at RT. The amount of metal chlorides correspond to an excess of cations (4 equivalents, considering two uronic units for complexation of an ion). The resulting mixture was stirred gently overnight to allow the maturation of the beads, which were then washed carefully with water. The beads were divided in two groups. The first one for the preparation of heterocationic gels (see protocol below) and the second group was exchanged with EtOH following the same protocol used for **AG-H** [**AG-Ca**, **AG-Sr** and **AG-Ba** samples].

Preparation of heterocationic gels (AG-M:nH). The heterocationic gels of M^{2+}-H^+ (M^{2+}: Ca^{2+}, Sr^{2+}, Ba^{2+}) were prepared starting with M^{2+} alginate hydrogels obtained after maturation and washing with water. The exchange of the M^{2+} in the gels with H^+ was performed using aq. HCl at different concentrations (5.2, 21.0, 42.0 mM). The quantity of H^+ was calculated assuming that two moles of H^+ are necessary for the exchange of each mole of M^{2+} in the gel. For each solution, the system was stirred gently overnight to allow the exchange. Next, the hydrogels were converted to alginate alcogels following the same protocol used for **AG-H**. The final materials were labelled as **AG-Ca:0.5H**, **AG-Ca:2H**, **AG-Ca:4H**, **AG-Sr:2H** and **AG-Ba:2H** where nH refers to the molar ratio between the metal in the gels and the H^+ used during the exchange process.

Preparation of gel catalysts QNA@AGs: optimised adsorption protocol. The gel catalysts **QNA@AGs** were prepared using the optimized condition for the adsorption of **QNA**[26] on alginate gels (EtOH/H_2O 9:1 as adsorption medium, native pH, room temperature, and initial concentration of **QNA** in the adsorption mixture equal to ca. 8×10^{-3} M). A **QNA** solution (8×10^{-3} M in EtOH/H_2O 9:1) was added dropwise under gentle stirring to the alcogel beads soaked in EtOH (number of beads calculated in order to have molar ratio of COOH : **QNA** of 2.5:1). The mixture was left overnight under gentle stirring. Then, the beads where washed twice with EtOH and then exchanged twice with toluene. The remnant solutions after adsorption, washing and exchange solvents were combined and evaporated, and the mol% of **QNA** adsorbed on **AGs** was determined by ^1H NMR using bibenzyl as internal standard. [**QNA@AG-H** and **QNA@AG-M:nH** samples].

Catalytic tests with QNA@AGs catalysts in the addition reaction of isobutyraldehyde 1a to nitrostyrene 2a. 14-15 Solvogel beads of **QNA@AGs** (which correspond to ca. 0.021 mmol of **QNA**), were added to a reaction tube equipped with a magnetic stirring bar, followed by 450 µL of toluene, 22.8 mg (0.105 mmol) of nitrostyrene **2a** and 48 µL (0.525

10.1002/ejoc.201900247

mmol) of freshly distilled isobutyraldehyde **1a**. The mixture was then heated to 60 °C with gentle (200 rpm) stirring. The reaction evolution was followed by ^{19}F NMR analysis on reaction samples. In order to study the heterogeneity of the catalyst, two reactions (**I** and **II**) were carried out in parallel. As the conversion reaches 20-40%, the catalyst beads were removed from reactions **II**; in case of heterogeneity, the reactions stop right after beads removal. Once complete, the beads of reactions **I** were washed three times with 1 mL of toluene, to be ready to be employed in new reaction cycles. The enantiomeric excess of product **3a** was determined after purification by chromatography on silica gel (7:3 *n*-hexane/diethyl ether) by chiral stationary phase HPLC analysis (Chiralcel OD, *n*-hexane/*i*-PrOH 80:20, flow 0.75 mL/min, t_{maj} = 25.7 min; t_{min} = 14.2 min, 98% *ee*).

General procedure for the addition of aldehydes 1 to nitroalkenes 2 catalysed by QNA@AG-Ca:2H gel catalyst. Thirty solvogel beads of **QNA@AG-Ca:2H** (which correspond to 0.044 mmol of **QNA**), were added to a reaction tube containing a stirring bar. Then, 900 µL of toluene, 0.21 mmol of appropriate nitroalkene **2** and 1.05 mmol of aldehyde **1** were added in the reaction tube and the system closed. The reaction was performed at 60 °C under 200 rpm. In the case of adducts **3g** and **3h**, the mixture was filtered on a plug of silica gel, the plug flushed with Et_2O, the solvents evaporated and the residue analysed by ^{19}F NMR to determine the diastereomeric ratio of **3g** and **3h**, which were then purified by chromatography on silica gel (7:3 *n*-hexane/diethyl ether). In all other cases, products **3** were purified directly from the mixture by chromatography on silica gel (7:3 n-hexane/diethyl ether). The enantiomeric excess of the products **3** was determined by HPLC analysis on a chiral stationary phase.

Supporting Information

Additional experimental details, control experiments and product characterization can be found in the Supporting Information.

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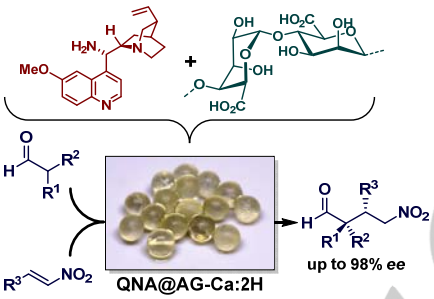
FULL PAPER

Gel catalyst. An organic catalyst derived from quinine can be adsorbed on alginate gels with a simple protocol. The resulting solvogel beads are competent and highly stereoselective catalysts for an asymmetric Michael reaction.



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Page No. – Page No.

Adsorption of a Chiral Amine on Alginate Gel Beads and Evaluation of its Efficiency as Heterogeneous Enantioselective Catalyst