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Metal or ammonium alginates as Lewis base catalysts for the 1,2-addition of silyl nucleophiles to carbonyl compounds

Cécile Verrier [a,b], Sylvain Oudeyer [a,*], Isabelle Dez [b,*], Vincent Levacher [a]

[a] *Laboratoire de Chimie Organique Bio-organique Réactivité et Analyse (COBRA), CNRS UMR 6014 & FR 3038, Université et INSA de Rouen, Rue Tesnière, Mont-Saint-Aignan Cedex 76821-F, France*

[b] *Laboratoire de chimie moléculaire et thio-organique (LCMT), CNRS UMR 6507, INC3M, FR 3038, ENSICAEN, Université de Caen, 6 boulevard du Maréchal Juin, Caen 14050-F, France*

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ABSTRACT

Several metal (Na^+, Ca^{2+}) or ammonium (n-Bu_4N^+) derivatives of alginic acid, an abundant bio-polymer obtained from the cell walls of brown algae, were synthesized. Their potential to act as organocatalysts to catalyze the 1,2-addition of various silyl derivatives to carbonyl compounds was evaluated for the first time. Ammonium alginate **1h** is able to promote the reaction in modest to good isolated yields (up to 98%) affording access to a large range of substrates (β-cyano alcohols or ester, β-substituted methylacrylate or acrylonitrile, and cyanohydrin) by using only 5 mol % of catalyst.

In the actual economical context, the development of catalytic processes using cheap catalysts and the use of renewable feedstock or materials have become a challenging area for synthetic chemists. To this viewpoint, organocatalysis[1] can be considered as a method of choice and has therefore attracted a lot of attention since the early 2000's. Moreover, it is well known that the heterogenization of the catalysts provided advantages as it allows the rapid isolation of the product and easy recycling of the catalyst. In recent years, chemists have investigated the use of biopolymers such as polysaccharides, which are cheap and widely abundant in nature, as catalysts for organic transformations. As such, chitosan, a marine polysaccharide derived from chitin, was involved in organometallic chemistry[2] or organocatalytic[3] processes as catalyst support or as the catalyst itself. Surprisingly, alginate salts **1**, derived from alginic acid **2** which is another marine polysaccharide extracted from the cell walls of brown algae, have been less frequently used in catalytic processes than chitosan. Indeed, although the physical properties of metal alginates **1** have been extensively studied[4] for biological purposes,[5] their use in catalysis remains limited to metal catalyst support.[6] To the best of our knowledge, no application as organocatalyst has been reported in the literature to date. Sodium alginate **1a** constitutes of a sequence of two monomers (β-D mannuronate (M) and α-L guluronate (G)) randomly arranged in homogeneous (MM or GG) or heterogeneous blocks (GM) (Fig. 1).

In 2007, Mukaiyama[7] reported a cyanomethylation reaction[8] of carbonyl compounds **3** with (trimethylsilyl)acetonitrile **4a** catalyzed by alkali acetates used as Lewis bases. We postulated that the carboxylate function of the alginate could act as an efficient heterogeneous Lewis base catalyst for the addition of **4a** to carbonyl compounds **3**. To check our working hypothesis, we chose the addition of **4a** to benzaldehyde **3a** as the model reaction and commercially available sodium alginate **1a** was used as catalyst.[9] We were pleased to find out that under our heterogeneous conditions, the reaction proceeded to completion within 5 days but in a modest 35% isolated yield compared to the 66% yield obtained by using Mukaiyama's conditions (Scheme 1).

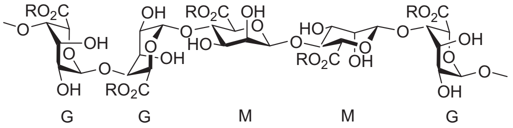
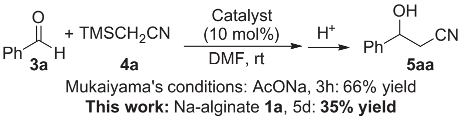


Figure 1. Polysaccharidic structure of Na alginate **1a** (R = Na) or alginic acid **2** (R = H).



Scheme 1. Na-alginate **1a** catalyzed cyanomethylation of **3a**: Preliminary results.

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* Corresponding authors. Fax: +33 (0) 235522962 (S.O.).
E-mail addresses: sylvain.oudeyer@univ-rouen.fr, sylvain.oudeyer@insa-rouen.fr (S. Oudeyer).

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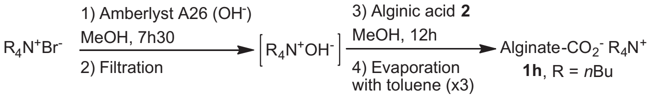
In an effort to optimize the reaction, we then turned our attention to the macromolecular structure of alginates. Thus, Ca-alginate hydrogel **1b** was prepared from **1a** and then dried under two different conditions, namely either by lyophilization or by supercritical CO_2 drying process to furnish Ca-alginates **1c** and **1d** respectively. Then, cross-linked Na-alginate (glutaraldehyde[10] as a cross-linker) was obtained and dried under the same conditions as those described previously to give **1e** and **1f**. Finally, a weak gel structure of Na-alginate was prepared by the precipitation of a solution of **1a** in acetone: this particular structure named Na-alginate acetogel **1g** was used without drying step. All these metal alginates were evaluated in the model reaction (Table 1).

Among all the alginates tested, Na alginate acetogel **1g** furnishes the best yield with a catalytic amount of catalyst (entry 6). The catalyst can be recovered and reused twice without any loss of catalytic activity nevertheless a drop of the yield is observed after 3 cycles (entry 6, 29% vs 44%). One could expect some chiral induction from alginates which display a chiral backbone. Unfortunately, only racemic products were formed whatever the catalyst used. It is noteworthy that despite a quantitative transformation of the starting materials observed in most cases, only poor isolated yield not exceeding 54% was obtained (even when 3 equivalents of benzaldehyde where used) probably due to a possible trapping of the aldehyde within the polymeric matrix. Accordingly, this phenomenon severely hampers the potential use of metal alginates as heterogeneous Lewis base catalysts.

It is well known that quaternary ammonium salts are an efficient phase transfer catalysts (PTC) able to improve the rate or the efficiency of a solid/liquid reaction.[11] We thus postulated that the association of the insoluble polymeric alginate matrix with a soluble organic quaternary ammonium could have a positive effect in terms of catalytic activity by making the resulting ammonium alginate more soluble. This higher solubility of the catalyst could have a positive impact on both the rate and the efficiency of the reaction. A similar strategy has already been successfully applied to the alkylation of glycine derivatives catalyzed by polymer supported chiral quaternary ammonium sulfonates or carboxylates.[12] First, we synthesized tetra-*n*-butylammonium alginate **1h** by using a resin exchange process previously reported by Mukaiyama for the preparation of chiral ammonium phenoxides[13] (Scheme 2).

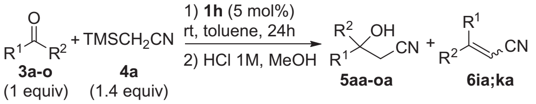
Ammonium alginate **1h** was used as an organocatalyst in our model reaction (see Table 1) at rt in DMF and we were pleased to observe the formation of the desired product **5aa** in higher yield (ie 77%) than those that could be obtained previously with metal alginates **1a–g** (Table 1). After the optimization of the reaction parameters, we were able to reach 88% isolated yield by performing the reaction at rt in toluene. Then, the scope and limitation of this method was studied using the following general conditions at room temperature (Table 2).



Scheme 2. Preparation of tetra-*n*- butylammonium alginate **1h**.

The general trend regarding the different substrates **3a–o** evaluated reveals that aromatic aldehydes **3a–k** furnished higher

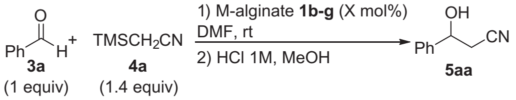
Table 2
1,2-addition of **4a** to carbonyl compounds **3a–o** catalyzed by **1h**



Entry	3	R^1	R^2	**5:** Yield (%)[a]
1	**3a**	C_6H_5	H	**5aa:**88
2	**3b**	4-NC-C_6H_4	H	**5ba:**95
3	**3c**	2-NC-C_6H_4	H	**5ca:**58
4	**3d**	4-F_3C-C_6H_4	H	**5da:**64
5	**3e**	4-MeO_2C-C_6H_4	H	**5ea:**75
6	**3f**	4-Cl-C_6H_4	H	**5fa:**80
7	**3g**	4-F-C_6H_4	H	**5ga:**63
8	**3h**	4-MeO-C_6H_4	H	**5ha:**65
9[b]	**3i**	2,4,6-$(MeO)_3$-C_6H_2	H	**5ia:**5[c]
10	**3j**	3-Pyridyl	H	**5ja:**76
11	**3k**	2-Thiophenyl	H	**5ka:**75[d]
12	**3l**	$-(CH_2)_2-C_6H_5$	H	**5la:**25
13	**3m**	–*t*Bu	H	**5ma:**35
14	**3n**	C_6H_5	CH_3	**5na:**22
15	**3o**	C_6H_5	(*E*)-CH=CH-C_6H_5	**5oa:**26[e]

[a] Unless otherwise stated, only the addition product **5** was observed.
[b] A maximum 70% conversion was reached.
[c] The compound **6ia** was obtained in a 57% yield as a *E/Z* ratio of 21/79 (determined by ^1H NMR analysis).
[d] The compound **6ka** was obtained in a 17% yield as a *E/Z* ratio of 70/30 (determined by ^1H NMR analysis).
[e] The 1,4-addition product was isolated in a 12% yield.

Table 1
1,2-addition of **4a**–**3a** catalyzed by metal alginates **1b–g**

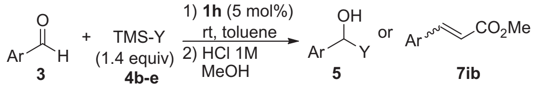


Entry	Alginate (Metal)	Form	X (mol %)	Time	Conv[a] (%)	**5aa** Yield (%)
1	**1c (Ca)**	Freeze-dried	100	3d	100	38
			10	3d	100	26
2	**1d (Ca)**	SC–CO_2 dried	10	3d	93	10
3	**1b (Ca)**	Hydrogel	100	2d	13	–
4	**1e**[b] **(Na)**	Freeze dried	100	6d	100	51
5	**1f**[b] **(Na)**	SC–CO_2 dried	100	4d	–	–
6	**1g (Na)**	Acetogel	100	2d	100	22
			10	2d	100	44
						29[c]
						54[d] (27)[e]

[a] Measured by GC and/or ^1H NMR analyses.
[b] Alginate was cross-linked with glutaraldehyde.
[c] Yield obtained after 3 cycles.
[d] 10% Vol. of acetone in DMF was used.
[e] Reaction performed with 3 equiv of PhCHO.

Table 3

1,2-addition of various silyl derivatives **4b**–**e** to aromatic aldehydes **3** catalyzed by **1h**



Entry	**3:** Ar	**4:**Y	**5:** Yield (%)	**7:**Yield (%)
1	**3a:**C_6H_5	**4b:**CH_2CO_2Me	**5ab:**49	–
2	**3i:**2,4,6-$(MeO)_3$-C_6H_2	**4b:**CH_2CO_2Me	–	**7ib:**69[a]
3	**3a:**C_6H_5	**4c:**CN	**5ac:**98	–
4	**3b:** 4-NC-C_6H_4	**4c:**CN	**5bc:**78	–
5	**3h:** 4-MeO-C_6H_4	**4c:**CN	**5hc:**61	–
6	**3p:** 2-MeO-C_6H_4	**4c:**CN	**5pc:**96	–
7	**3a:**C_6H_5	**4d:**CF_3	**5ad:**42[b]	–
8	**3a:**C_6H_5	**4e:**2-furanyloxy	**5ae:**65[c]	–

[a] A *E/Z* ratio of 88/12 was determined by ^1H NMR analysis of the crude product.

[b] Reaction performed in DMF.

[c] A *anti/syn* ratio of 75/25 was determined by the comparison of the chemical shift of H-3 with the ^1H NMR data reported in the literature.[14]

isolated yields than aliphatic aldehydes **3l–m** and ketones **3h–o** (entries 1–11 vs 12–15). It is worth noting that aromatic aldehydes bearing both electron-withdrawing and -donating groups afforded the various addition products **5** in good to excellent yields, except for the more sterically hindered aldehyde **3i** (entry 9) for which the desired product **5ia** was obtained in a rather low yield along with the formation of the acrylonitrile derivative **6ia** resulting from an addition-elimination sequence. Heteroaromatic aldehydes **3j–k** gave the corresponding addition products **5j–k** in 76% and 75% yields respectively (entries 10–11).

The addition of various silyl derivatives **4b–e** to aromatic aldehydes **3** was also assessed under the conditions reported in Table 3.

When methyl(trimethysilyl)acetate **4b** was allowed to react with **3a**, the addition product **5ab** was obtained in modest yield (entry 1). More interestingly, the use of **3i** instead of **3a** leads exclusively to the formation of methyl cinnamate derivative **7ib** in a 69% yield (entry 2). The synthesis of cyanohydrins **5ac;bc;hc;pc** was also achieved in good to quantitative yields by using TMSCN **4c** as pro-nucleophile (entries 3–6). The trifluoromethylation of **3a** using the Ruppert-Prakash reagent **4d** afforded the corresponding addition product **5ad** in a modest 42% yield (entry 4). At last, a vinylogous Mukaiyama aldol reaction was performed by using 2-trimethylsilyloxyfuran (TMSOF) **4e**. The addition product **5ae** was obtained in a 65% yield as a 75/25 mixture of anti/syn diastereomers.

In summary, we have reported the first use of metal or ammonium alginates **1a–h** as efficient Lewis base catalysts. Their catalytic abilities were demonstrated in the course of the 1,2-addition of several silyl nucleophiles **4a–e** to carbonyl compounds **3a–p**. Among all the alginates tested, tetra-*n*-butylammonium alginate **1h** revealed to be an efficient organocatalyst (only 5 mol % of catalyst) for the formation of various addition products **5** or addition-elimination products **6** and **7** in modest to good yields. These promising results show the great potential of such natural-occurring catalysts to be a plausible alternative to usual synthetic catalysts. Further investigations on the use of alginate derivatives as chiral organocatalysts or support of chiral organocatalysts are under way in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data (general informations, procedure for the preparation of alginate materials **1**, spectral data for tetra-*n*-butylammonium alginate **1h**, general procedures and copies of NMR spectra for compounds **5**, **6** and **7**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.012.

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