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Enantioselective Friedel-Crafts reaction catalysed by Alginate Aerogels

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Abstract

Alginates are polysaccharides derived from brown algae, available in nearly unlimited amounts at very low prices. In the presence of some divalent metals, these renewable biopolymers can readily form hydrogels, solvogels and aerogels, characterized by high surface areas, good mechanical properties, tolerance to different media, and easy manageability. For these reasons, alginates are nowadays being thoroughly studied in heterogeneous catalysis; several applications in supported metal catalysis and as heterogeneous Brønsted acids have emerged. However, none of these studies has given an answer to the following intriguing question: can we use the intrinsic chirality of alginates to induce enantioselectivity in a chemical reaction? In order to answer this question a representative reaction, the Friedel-Crafts alkylation of nitroalkenes with indoles, was tested in this master thesis. This study, which involved a large screening of a variety of alginate gels under different reaction conditions, showed that Cu^{2+} and Ba^{2+} are the best cross-linking metals to promote the Friedel-Crafts reaction. Indeed, good activity with moderate enantiomeric excesses were obtained under the optimized reaction conditions. Furthermore, these two metals allowed the access to both enantiomers of the products, an important aspect given that only one enantiomeric form of alginates is available. Finally, the heterogeneous nature of the catalysis by one of the two gels was proved, and a good recyclability was demonstrated, by showing that the same catalyst can be used at least five times with similar results.

KEYWORDS: Heterogeneous catalysis, metal catalysis, alginates, biopolymers, polysaccharides, aerogels, Friedel-Crafts alkylation, chirality, enantioselectivity, asymmetric synthesis, organic synthesis.

To my family and my friends, a real support in my life.

Science means constantly walking a tight rope between blind faith and curiosity; between expertise and creativity; between bias and openness; between experience and epiphany; between ambition and passion; and between arrogance and conviction – in short, between an old today and a new tomorrow.

Heinrich Rohrer.

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Doing the master Advanced Spectroscopy in Chemistry was my first choice for the topic but due to my level in English it was probably not the most pertinent of choices. After long discussions with Pr. Crystol Sylvain, I finally decided to try this specific program. Thus, firstly, I would like to thank Sylvain Crystol who was the first person to ever believe in my capacities and who allowed me to be a part of this amazing experience. Therefore, thank you for the time you spent to make this project possible and for your availability.

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Once I arrived in the organic chemistry laboratory, Luca Bernardi, my new supervisor welcomed me in his project and introduced me to the heterogeneous catalysis and the alginates which was a new domain for me. But thanks to his explanation and his project, it is clear that I have learned a lot with him. In this project I was also well supported by Daniel Antonio Aguilera, my co-worker.

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1. Introduction

Since several years, the concept of green chemistry has become an important area of chemistry. Indeed, the scientists change the way to make synthesis aiming at using nontoxic chemicals, heterogeneous catalytic processes, environmentally benign solvents and renewable resources in order to reduce the environmental impact of producing chemicals.[1] This new green synthetic strategy is really used in organic chemistry and obviously, in this perspective, take into account of trying to use renewable resources in the production of catalysts supports, catalysts and adsorbents. However, this is only possible if the materials intend to replace oil-derived or energy-intensive solids present adequate properties, like high surface area, appropriate surface chemistry and porosity, thermal and chemical stability, availability and low cost.[2]

This is why the use of natural polysaccharides, which are well known since several years to be supports for enzymatic catalysts, seems interesting. In fact, since few years the interest for these biopolymers has increased, and this interest can be explained by the following: there is nearly unlimited availability of polysaccharides materials in Nature; industrial processes of extraction are running at the plant scale; high binding ability of these materials for selected metals due to the presence of several and diverse functional groups; physical and chemical versatility of these materials; insolubility in most organic solvents; easy degradation of the organic material at the end of the life cycle and possible conformational effects.[2]

In this context, natural polysaccharides that can found use are those with anionic functions, like alginates (carboxylate groups) or carrageenans (sulfonate groups), but also with cationic functions such as chitosan (ammonium groups) (Figure 1-1).[3]

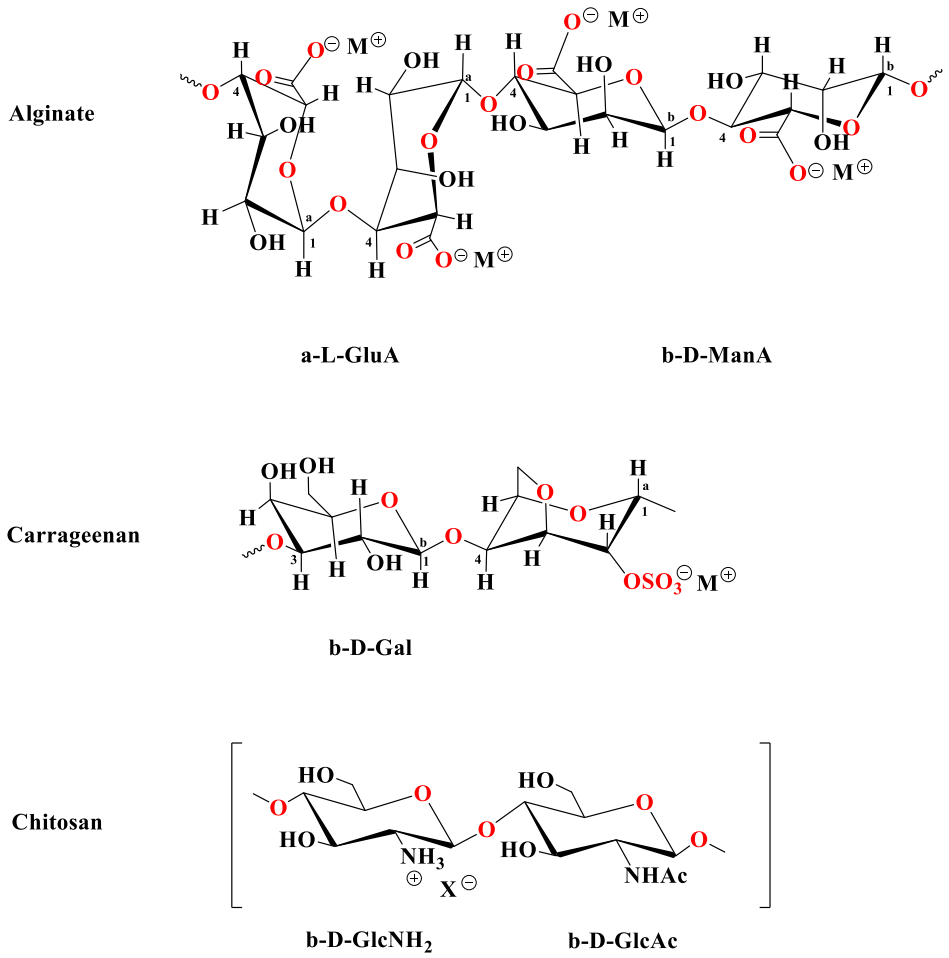


Figure 1-1 Polysaccharides with different chemical functions.

In this thesis, the focus was set on alginates.[4] The following chapter gives an overview on the properties and applications of these materials.

Alginates

Alginates belong to the family of polysaccharides obtained from brown algae, more specifically from the cell walls of algae, even if they can also be extracted from some bacteria like *Azotobacter* and *Pseudomonas*. The most common algae from which they are extracted are *Macrosystis pyrifera* (California) and *Ascophyllum nodosum* (North Atlantic). Currently, the alginates which are in the market, derive from algae in the form of sodium alginate (the salt form of alginic acid). Structurally speaking, alginate is a biopolymer formed by two monomers linked together: the mannuronic acid and guluronic acid. So, the alginic acid is a linear copolymer composed by the β-D-mannuronic (M)

and α-L-guluronic (G) linked in a (1 –> 4) fashion. They are covalently linked together following different way. We can have homogeneous sequences of the monomers constituted by M units (M-blocks), by G units (G-blocks) or have an alternance of M- and G- units (MG-blocks) with different lengths (Figure 1-2).[2,5]

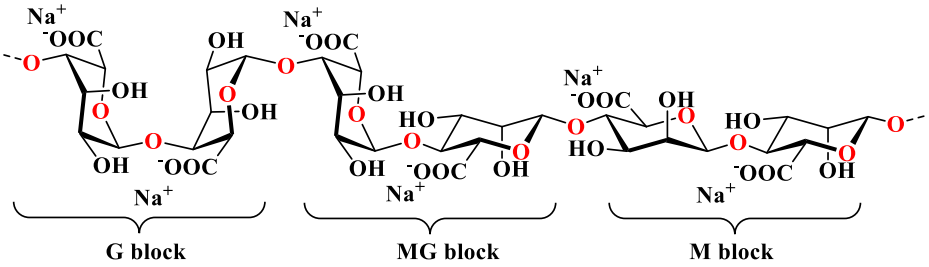


Figure 1-2 Sodium alginate chemical structure and its block distribution.

The ratio of M-units versus G-units and sequencing of uronic monomers affect the properties of the alginate gels. Indeed, we have the mannuronic acid forms (1–>4) linkages that give us a linear and flexible conformation, while the gluronic acid give us folded and rigid structural conformation which are responsible of the stiffness of the material. So, it is easy to see the importance of this ratio, especially of the contents of G-units, because when it is high, we will obtain more viscosity in the resulting gels. This ratio, as well as the length and the distribution in the polymeric chain of the different types of block are highly connected on the seaweed source, including the season, growth, conditions and age of the plant.[2,6]

As said previously, alginates possess a high density of functional groups in the polymeric structure (i.e. 5.6 mmol/g of carboxylate groups). The fact that these functional groups are stable in most organic solvents allows alginates to be considered as promising materials for catalytic application. Alginate as a versatile biopolymer for catalysis has been used for the enzymatic application with the immobilization of different biological precursors such as cells and organelles.[7,8,9,10,11] Since few years, alginate gels have been also used as supports for active low molecular weight species, especially for metal or organometallic catalysis; for these applications, alginate gels are in their dry or wet state.

Alginate hydrogels have a specific polymeric arrangement, their dispersed 3D arrangement favours the accessibility to the active functions, indispensable for the possible entrapment of the catalyst species and for the interaction with the substrates involved in the reaction. Unfortunately, it exists a

real issue of the use of dried polysaccharide gels, which is the diffusions limitations, because the surface area of the most commonly used dried materials, like xerogels or cryogels, is really low.[12] There is however a convenient tool to produce alginate gels without diffusion limitations; this technique is the supercritical drying of alginate gels, resulting in a high surface area, removing the diffusion limitations in their microporous network and allowing the development of high surface materials.[13]

We will discuss about this emergence of the use of alginates in the next following part with a focus on the effect of the catalyst formulation on its activity. We will focus, more specifically, on our specific subject on the use of alginate as a heterogeneous acidic catalyst.

1.1. Alginates as support in organometallic catalysis

The first use of alginate for non-enzymatic catalysis was as a support for the hydrosoluble trisulfonated triphenylphosphine palladium (0) complex $Pd(TPPTS)_3$, involved in heterogeneous allylic substitution of methyl-allylcarbonate with morpholine. In this case, the alginate was used under the form of alginate beads (Figure 1-3).[14]

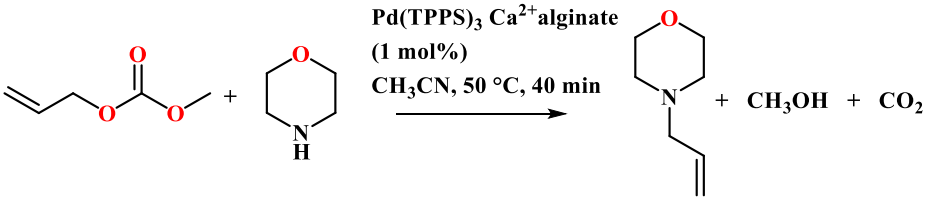


Figure 1-3 Heterogeneous allylic substitution of methyl-allylcarbonate with morpholine.

For this first non-enzymatic application, the authors used both aerogels and alcogels Ca- alginate beads. The reaction using these beads gave a complete yield in few minutes in both cases (aerogels and alcogels catalysts). However, the catalyst derived from the aerogel preparation showed a better stability, upon recycling, than the one from the alcogel.

It is worth noted that there was no catalyst activity when they used freeze-dried $Pd(TPPTS)_3$ supported alginate beads (BET surface area< $1 m^2 g^{-1}$) as catalysts. The fact that this catalyst was active in presence of water suggests that water allows the swelling of the material, making the catalytic units accessible. In contrast, for the aerogel beads, access to catalytic sites was guaranteed

regardless of the level of hydration. These results proved the importance of the formulation in the efficiency of alginate as catalyst support.[2]

1.2.Metal alginates as catalysts

The interaction between Cu^{2+} salts and alginates can give Cu^{2+} -alginate gel beads. The first use of this hydrogel formulation as catalyst was for the regioselective 1,3-cycloaddition of alkynes and azides in water, giving excellent conversion and good regioselectivity in all cases (Figure 1-4).[15]

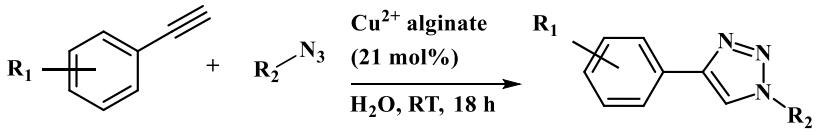


Figure 1-4 Regioselective synthesis of 1,4-disubstituted 1,2,3 triazoles.

The Cu^{2+} -alginate beads can be used also for the oxidative coupling of phenol and 2-naphthols in water, leading to a moderate to high yield for the product of interest. It can be used in powder and xerogel beads formulations, for the synthesis of hydroquinone and catechol by phenol hydroxylation with H_2O_2.[16] This reaction showed that Cu^{2+} -alginate was more effective than the alginates with other cations.[17] Finally, Cu^{2+} catalyst with Pd to form the so call Cu-Pd-alginate binary catalyst system [18] could be used giving higher turnover frequency (TOF) values and better selectivity, that proved the positive effect of the binary catalyst system.

1.3. Heterogeneous Brønsted acid catalysts based on alginic acid

The chemists start to use more and more alternative green catalytic systems nowadays to replace the old catalytic system which have, most of the time, technical disadvantageous and environmental issues. In this perspective, mineral Brønsted acids tend to be replaced by greener alternatives. Even if the mineral Brønsted acids are the most used catalysts for science and technology, they possess also some disadvantages such as: corrosion, energy-inefficient processes for separation, recycling, and treatment of the spent acids, etc.[1] The use of unmodified biodegradable biopolymers involved in simple organic reaction receive more and more interests. Indeed, lot of unmodified biopolymers look like good candidates as Lewis or Brønsted bases: chitosan,[12] sodium and calcium alginates,[19,20,21] polydopamine,[22] silk fibroin,[23] collagen and gelatin.[24] However, the use of biopolymers in Brønsted acid catalysed reaction did not receive the same interest despite the advantages of using biodegradable

acid catalysts. In the few reports concerning the employment of biopolymers as Brønsted acids we can see that alginic acid, thanks to the fact it has several functional groups and to its mildly acidic character (pKa ~ 3.5)[25] made the alginic acid a good candidate for heterogeneous Brønsted acid catalysts.

Due to its advantages and its capacity to adsorb water, one article in 2014 used alginic acid to catalyse organic reaction.[26] They studied a one-pot pseudo-four components Hantzsch reaction which formed four equivalents of water delivering 1,4-dihydropyridine products. During this study, the solid alginic acid has been used in the quantity of 10 mol% catalyst respect to the carboxylic function and the optimization of the reaction showed that EtOH was the suitable reaction medium. Alginic acid swells with EtOH, allowing a good accessibility of the substrates/ intermediates to the carboxylic units. The reaction occurred under reflux conditions because under these conditions the reaction time was shorter (1h), leading to a study of the scope of the multicomponent reaction (Figure 1-5). They obtained really good yields in all cases and the solid alginic acid, after washing with ethyl acetate and drying at 60°C, can be reused for at least 6 more runs keeping good yields (above 90%) for the reaction between ethyl acetoacetate, 4-chlorobenzaldehyde, and ammonium acetate.

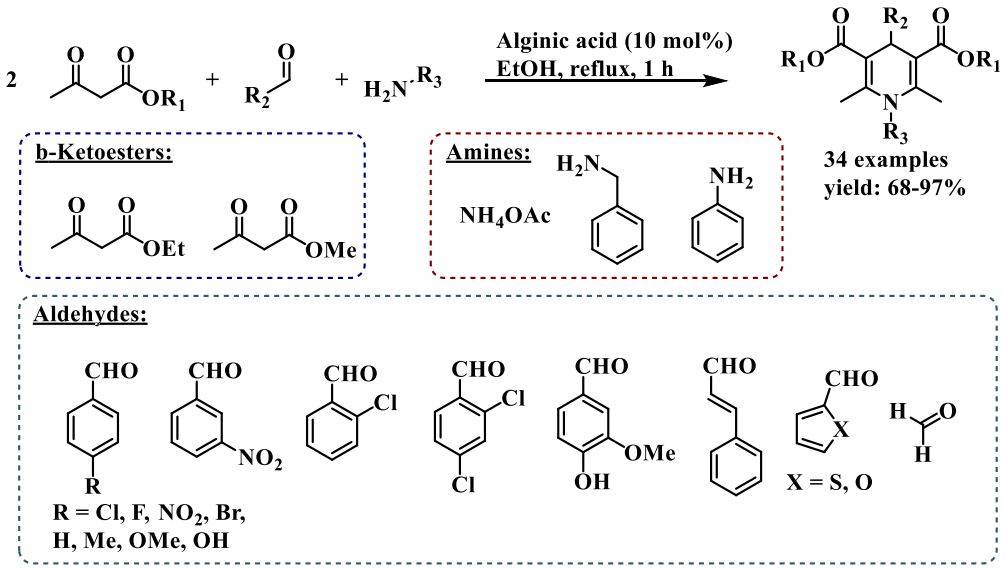


Figure 1-5 Alginic acid catalysed multicomponent Hantzsch reaction.

In 2015, a paper presented a Friedel-Crafts reaction between indoles and activated ketones (isoquinoline-1,3,4-triones) using a catalytic amount of alginic acid.[27] Both structures are relevant for biological purposes.[28,29] This reaction allowed us to see, under different conditions, the efficiency of alginic acid (commercial powder) as catalyst (Figure 1-6). The results obtained from this study show

that the best conditions for the reaction are: RT during 24h and using water as reaction medium (Method A).

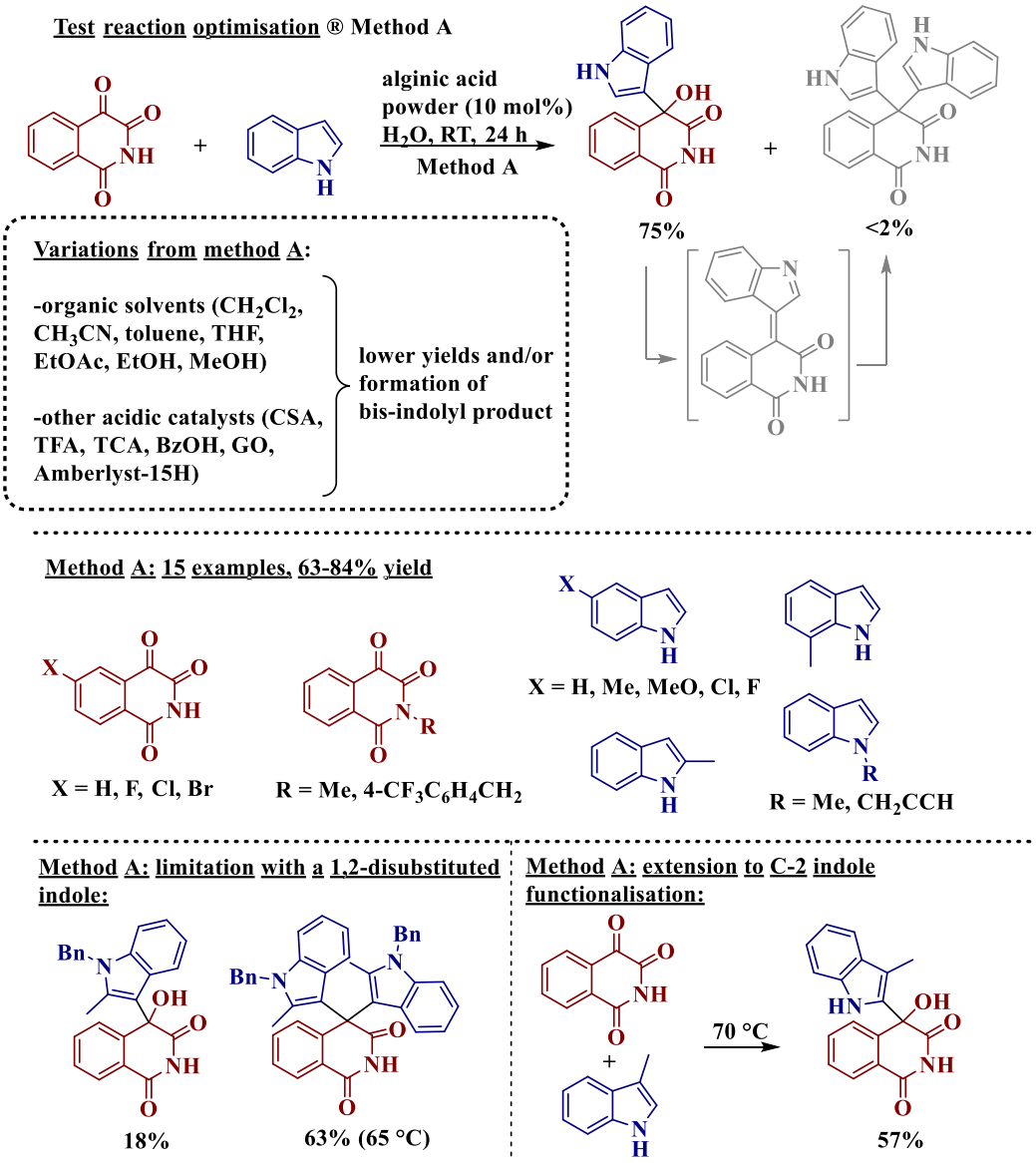


Figure 1-6 Alginic acid powder catalysed Friedel-Crafts reaction between isoquinoline-1,3,4-triones and indoles: method A.

As you can see, the fact to use organic solvents with different polarity (dichloromethane, acetonitrile, toluene, tetrahydrofuran, ethylacetate, ethanol, and methanol) gave a lower selectivity due to the formation of a by-product which is formed via a dehydrated alkylideneindolenine intermediate. It is worth to be noted also that the selectivity of alginic acid was compared with acidic catalysts which are commonly used ((±)-camphor sulfonic acid (CSA), trifluoro and trichloroacetic acid (TFA and TCA), benzoic acid (BzOH), GO, Amberlist-15H), taking into account that, in contrast with the Hantzsch reaction, these particular Friedel-Crafts reactions had never appeared in the literature

before. Finally, this study allowed to say that alginic acid as catalyst is sometimes more efficient than the more common acidic catalysts. But also, thanks to these results and to the properties of the alginic acid we can consider that the role of alginic acid might go further, not just as a Brønsted acid activation of the substrates, but also for example as a dehydrating agent. Method A was used with a wide range of isoquinoline-1,3,4-trione and indole substrates giving, in most cases, good yields.

During this test, they also looked at the recyclability of the alginic acid catalyst. And after using the following protocol: recover the alginic acid powder from the mixture by centrifugation, washing with diethyl ether and drying, the catalysts can be re used at least five times with a small decrease of the yields (75%, 73%, 70%, 71%, and 67% yield values for the five runs).

Moreover, the by-product formed during the previous method (Method A) can be useful also due to one of its derivatives: bis-(indol-3-yl) methane, which is also interesting for biology purposes.[30] Knowing that, the authors decided to go further and they demonstrated the bis-indolyl derivatives can also form with good results, by Friedel-Crafts reaction catalysed by alginic acid (Figure 1-7). Taking into account the fact that these reactants were the by-product resulting from the first mono-indolyl Friedel-Crafts reaction, for some of them they had to do supplementary alginic acid powder catalysed reactions with indoles under stronger conditions. The fact that the process is in two steps allowed to obtain an unsymmetrical bis-indolyl products (i.e. products with two distinct indole groups). They used two different conditions of reaction (Method B and C), and both conditions were useful for the second step and both methods needed the presence of 10mol% alginic acidic as catalyst.

The only differences between these two methods were for the solvents and the temperature (water at 65°C for method B, ethanol at 55°C for method C) and obviously the reaction time has to be adjusted according on the substrates. As you can see on the Figure 1-7, both methods gave the right unsymmetrical product with very good results.

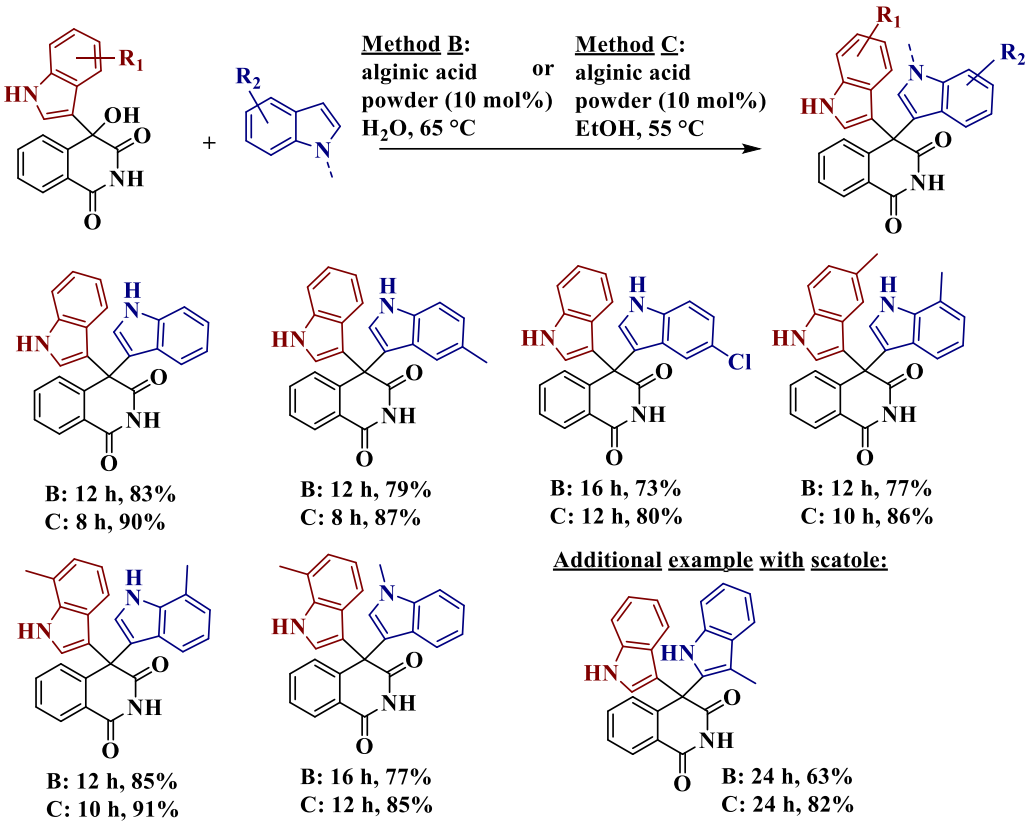


Figure 1-7 Alginic acid powder catalysed synthesis of bis-indolyl products from the primary Friedel-Crafts adducts: method B and method C.

Finally, we know that the alginate gels are really versatile in terms of texture, the understanding of the effects of this parameter on the catalytic activity is potentially very useful. For this parameter a complete study on the relation between the alginic acid formulation and its catalytic behaviour has been done recently.[31] First of all, the authors demonstrated the capacity of the guluronic rich (G/M 63:37), highly dispersed alginic acid aerogel (AG1) to promote the two and three-component Mannich addition reaction. In the first time, the capacity of AG1 to promote at 20mol% with respect to its carboxylic functions, was estimated for the two components Mannich reaction between N-phenylbenzylidene imine and cyclohexanone; then, this reaction was done under different conditions. As you can see on the figure 1.8, the optimal condition, for this reaction, is when they used 80:20 acetonitrile/water mixture (Figure 1-8). In these conditions, the product of interest could be isolated in 91% yield.

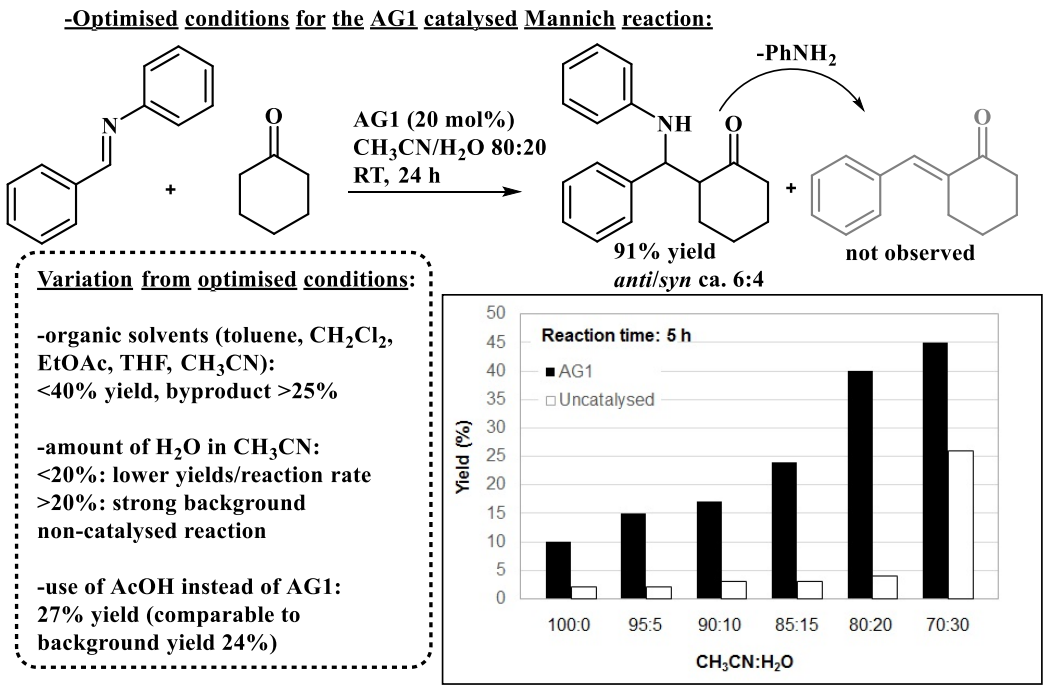


Figure 1-8 Alginic acid aerogel AG1 catalysed Mannich reaction between N-phenylbenzylidene imine and cyclohexanone. Optimized conditions and variations thereof.

In order to understand and see the effects of the textural properties on its catalytic activity, they decided to compare the efficient AG1 catalyst with different alginic acid formulations (xerogel XG, solvogel SG, and, for the sake of comparison, commercial alginic powder C), with different dispersion of the polymeric chains.[32] Indeed, AG1 and SG are highly dispersed structure while XG and C are denser and less accessible structure as show the values of the surface area (<2m^2 g^{-1} for XG and C vs. 250m^2 g^{-1} for AG1). The fact that there are such differences between these alginic acid formulations influence the accessibility to functional groups which can change the catalytical activity of the material.[21] The main effect of alginic acid texture was found when they used pure acetonitrile as solvent with the different formulations. The results of this comparison are shown in the Figure 1-9, and as you can see the better result were obtained by the most dispersed and accessible formulations (AG1 and SG); in these cases they obtained a moderate yield between 35% to 45% while XG and C showed almost any reactivity (Figure 1-9). Furthermore, the mixture CH_3CN/ H_2O 8:2 showed an increase of the yield in all cases (85% - 95%); this increase, especially for XG and C, can be explained by the use of water that facilitates the proton transfer but also to facilitate the access to the functional groups.[33]

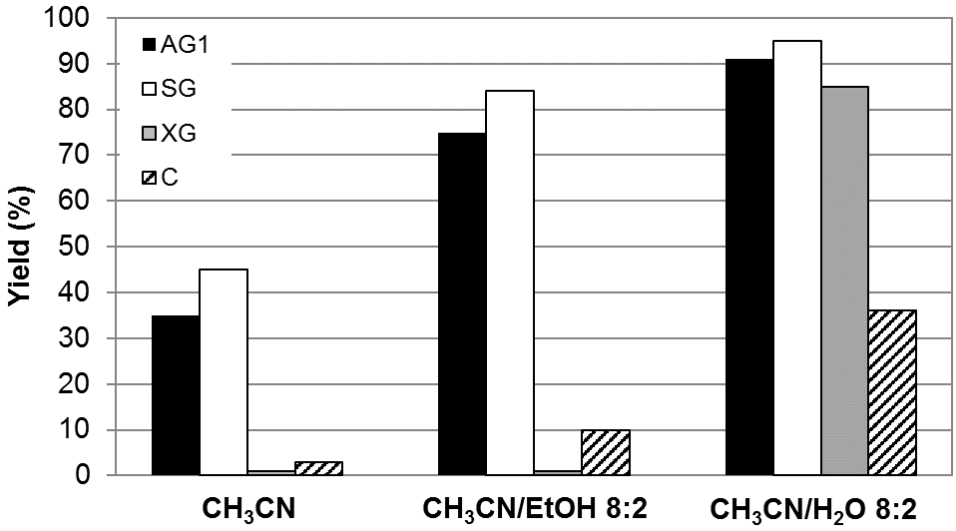


Figure 1-9 Effect of the formulation on the activity displayed by alginic acid in the reaction between N-phenylbenzylidene imine and cyclohexanone in different reaction solvents. Optimized reaction conditions.

2. Aim of my Master Thesis

The introduction has shown the utility of alginate biopolymers as versatile, highly dispersed supports for metal catalysed reactions and as heterogeneous Brønsted acids, without mentioning the stereoselectivity of the processes, which was not an object of those studies. This thesis aims instead at giving a preliminary answer to a provocative question: can we use the intrinsic chirality of these biopolymeric materials to induce asymmetry in a chemical transformation? A positive answer to this fundamental question would open new avenues on the full exploitation of these natural materials, which chiral information has never been exploited for asymmetric catalytic purposes.

Such work inserts itself in the growing field of heterogeneous asymmetric catalysis. Based on the publication of Tanaka et al, describing the Friedel–Crafts alkylation of electron-rich N-heterocycles with trans-β-nitrostyrene using chiral Cu-MOF,[34] the main point of my master thesis is to study the reaction between nitroalkene **2** and indole **1** catalysed by metal alginates aerogel, to prove that these materials can indeed induce stereoselectivity in the reaction (Figure 2-1).

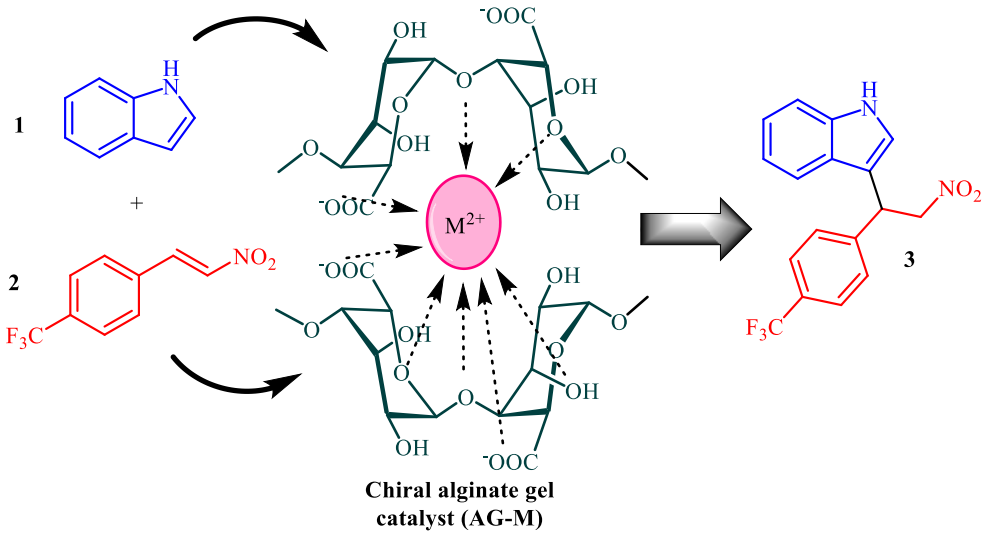


Figure 2-1 Asymmetric Friedel-Crafts alkylation using AeG-M catalysts.

In order to do that, we focused on different specific points of the synthesis which are:

- Screening different type of X^{n+}-alginate gels (X^{n+}: Cu^{2+}, Ba^{2+} and Ni^{2+}), by changing both metal and alginate type.
- Screening different type of acceptors, different from nitroalkenes, in the reaction.

- Screening different type of donors (1-methylindole; 3-methoxy-N,N-dimethylaniline and N,N-dimethylaniline) in the reaction.
- The effects of the solvents on the reaction by using organic solvents with different polarity.
- The effects of the Temperature on the reaction.
- The effects of the amount of catalysts used.
- The heterogeneity and recyclability of the catalyst.

3. Experimental Part

In this part, we will see the general methods that I used to prepare my samples with the catalysts, the technique of characterisations, the conditions of these techniques and more specifically the preparation of the sample beads, the synthesis of the acceptors, donors, catalysts, racemic references for the HPLC.

1. Materials and General Methods

All the chemicals used during the experiments come from pre-existing reagents in the laboratory. Glassware (i.e. flasks, vials and NMR tubes) was employed for all transformations under ambient atmosphere at room temperature unless specified otherwise. For the purification of the catalysts, reactants and sample for racemic mixture references liquid chromatography system with silica gel columns was used and the separation of the products was followed by TLC Silica gel 60 F_{254}, visualised and analysed by UV-vis lamp at 250 nm and $KMnO_4$. For the purification of the samples with catalysts we used a plug with silica gel, the plug was washed with DCM and Et_2O (3 times) and the solvents evaporated under reduced pressure. NMR spectra were obtained with a 300 MHz or 400 MHz instrument (Figure 3-1) with $CDCl_3$ as solvent. Enantiomeric excesses (ees %) were measured with chiral stationary phase HPLC (Figure 3-2) (the conditions of the HPLC will be précised for each compound). This project is the result of a collaboration with a team of CNRS Montpellier, coordinated by Dr. Nathalie Tanchoux. The PhD student Daniel Aguilera has prepared and characterised the alginate gel beads. Thermogravimetric analyses were measured under air with a 5 °C·min^{-1} rate on a PerkinElmer STA6000 system. Prior to the analyses, the solvogel beads (in ethanol) were filtered and dried by evaporative drying using a rotary evaporator, at 60 °C for 1 h, to obtain xerogels. Initial weight was between 10 and 15 mg. Fourier transform infrared (FT-IR) spectra were recorded at RT using a Perkin Elmer Spectrum Two FT-IR spectrometer equipped with a single reflection ATR (attenuated total reflection) accessory. For the sample preparation, one single bead (aerogel or solvogel) was put over the surface of the sample holder and squeezed slowly until a solid film was produced. Surface areas were measured by the BET method by nitrogen gas adsorption/desorption at -196 °C, using a Micrometrics TriStar apparatus on aerogel samples outgassed at 50 °C for 6 hours.

Figure 3-1 300MHz NMR instrument.

Figure 3-2 HPLC instrument.

2. General Method for preparing the beads

2.1. M^{2+} alginate hydrogel beads (HG-M)

50 mL of a solution of sodium alginate (2% w/V) of the desired type of alginate (Protanal 200S, Protanal 200DL or Protanal 240D) was added dropwise (using a dropping funnel) to 100 mL of a 0.1 mol/L solution of metal chloride ($CaCl_2$, $SrCl_2$, $BaCl_2$, $CoCl_2$, $NiCl_2$, $CuCl_2$, $ZnCl_2$,) kept under magnetic stirring at RT. The amount of metal chlorides corresponds 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 and stored [**HG-Ca**, **HG-Sr**, **HG-Ba, HG-Co, HG-Ni, HG-Cu** and **HG-Zn** samples].

2.2. Solvogel beads (SG)

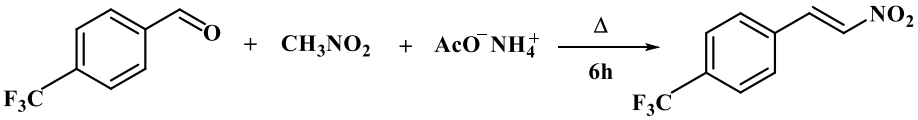
Depending on the reaction medium, alginate hydrogels were transformed into solvogels (**SG**). The desired hydrogel beads were dehydrated by immersion in a series of Ethanol/Water baths, with increasing ethanol content (10, 30, 50, 70, 90 and 100% of solvent), for 15 min each. When using ethanol (EtOH) as a solvent, the resulting solvogels are called alcogels. For other types of solvogels, after the ethanol exchange, a further exchange was done by immersion of the selected alcogels in Solvent/Ethanol baths with increasing solvent content following the protocol described above.

2.3. Aerogel beads (AeG)

Prior to the supercritical drying, the desired alcogel were immersed 15 min in absolute ethanol, were filtered and loaded into a stirred flask containing absolute ethanol and molecular sieves for 24 h, to guarantee the total dehydration of the beads. The wet alcogels were converted into aerogels by low temperature drying under supercritical CO_2 conditions in a Polaron 3100 apparatus. The procedure consists in the replacement of ethanol by washing the alcogels with liquid CO_2 (5 washes, 15 min each). After complete replacement, the supercritical conditions (74 bar, 31.5 °C) were reached and supercritical CO_2 was slowly purged from the system, until the atmospheric pressure was attained, obtaining the desired aerogel (denoted as **AeG**).

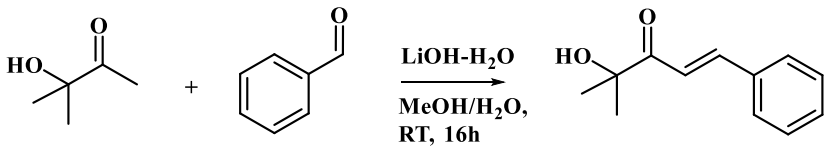
3. Synthesis of the acceptors

3.1. Synthesis of 4-trifluoromethyl-β-nitrostyrene (2a)



In a one neck flask equipped with a reflux condenser and a magnetic stirring bar, 1.36 mL of 4-(trifluoromethyl)benzaldehyde (10 mmol), 16.33 mL of nitromethane (0.3 mol) and 193 mg of ammonium acetate (2.5 mmol) were sequentially added. The resulting mixture was vigorously stirred at 100°C. After 6h, the mixture was allowed to cool to room temperature, and a work up was performed in a separatory funnel with H_2O and CH_2Cl_2 for the separation of the two phases: the organic phase was dried over $MgSO_4$ and filtered through filter paper. The product was dried at the rotary evaporator and purified by chromatographic column with petroleum ether/ethyl ether 9:1 as eluting mixture. The elution was followed by TLC analysis. The fractions were dried at the rotary evaporator. The product is obtained as a yellow-brown solid with an overall mass of 700 mg with a yield of 33%, and can be further purified by crystallisation from EtOH. ^{19}F-NMR (300MHz, $CDCl_3$): δ -63.18 ppm; ^{1}H-NMR (300MHz, $CDCl_3$): δ 8.03 (d, J=13.5 Hz, 1H), 7.74-7.65 (m, J=8.8 Hz, 4H), 7.62 (d, J=13.5 Hz, 1H) ppm.[35]

3.2. Synthesis of 4-hydroxy-1-phenyl-4-menthylpent-1-en-3-one (2c)



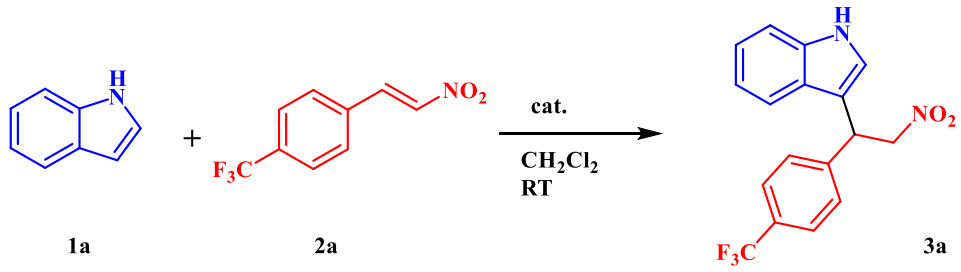
3-Hydroxy-3-methyl-2-butanone (280 µL, 2.5 mmol) was dissolved in a mixture of MeOH (6 mL) and H_2O (2 mL). Benzaldehyde (450 µL, 4.46 mmol) was then added followed by LiOH-H_2O (520 mg, 12.5 mmol). The reaction was stirred at reflux for 3h, and after removal of MeOH under reduced pressure, the aqueous residue was diluted with H_2O (2 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The CH_2Cl_2 extracts were combined, dried over $MgSO_4$ filtered and concentrated. The crude product was flash chromatographed (SiO_2) using DCM as eluant at the beginning and then 2% of diethyl ether in DCM. The elution was followed by TLC analysis. The fractions containing the product were collected and dried at the rotary evaporator. The product is obtained as a pale-yellow oil. ^{1}H-NMR

(300 MHz, $CDCl_3$): δ 7.82 (d, J= 15.4 Hz, 1H); 7.58 (m, 2H); 7.4 (m, 3H); 7.02 (d, J= 15.4 Hz, 1H); 4 (s, 1H); 1.44 (s, 6H) ppm.[36]

4. General Method for catalytic Friedel-Crafts alkylation reactions

(0.075 mmol) of donor **1** and 0.05 mmol of acceptor **2** were added into a vial equipped with a magnetic stirring bar, followed by 150 µL of solvent; finally, 5 aerogel beads of **AeG-M** (ca. 0.01 mmol of M^{2+}) were added. The mixture was gently stirred (200 rpm) at room temperature until the reaction was completed. The reaction conversion was followed by TLC analysis (TLC was performed with TLC Silica gel, n-hexane/diethyl ether as eluting mixture and analysed by UV-vis and $KMnO_4$), or by ^{19}F NMR analysis. If the reaction took place the mixture was filtered on a plug of silica gel, the plug flushed with DCM and Et_2O, the solvents evaporated and the residue analysed by ^1H-NMR and/or ^{19}F-NMR to confirm the formation of the products. The enantiomeric excess of the products **3** was determined by HPLC analysis on a chiral stationary phase, with a UV detector operating at 254nm.

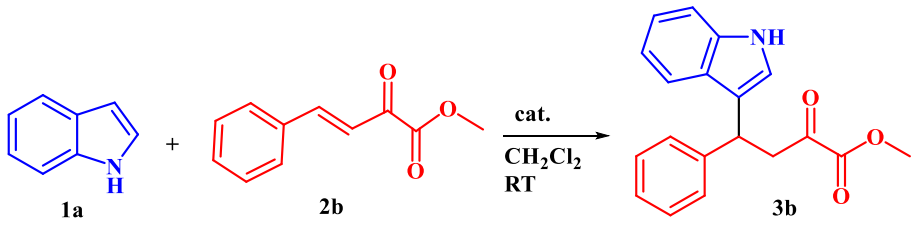
4.1. Reaction with 4-trifluoromethyl-β-nitrostyrene (2a)



1a **2a** **3a**

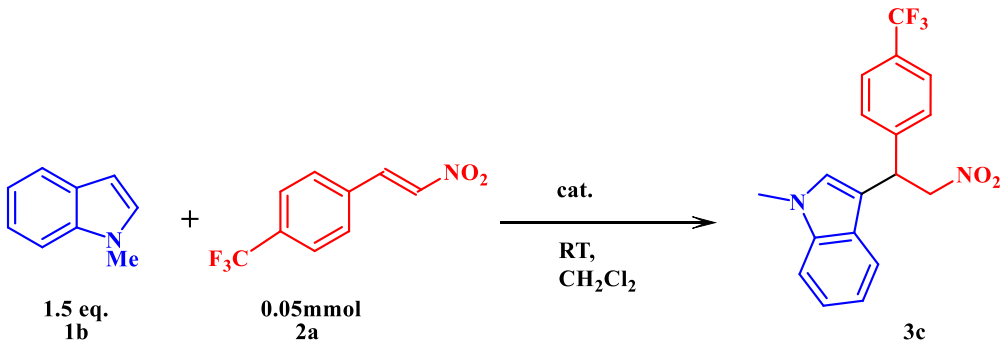
The conditions of the HPLC analysis were the following: AD-H were used as column with a flow of 0.75 mL/min using hexane/isopropanol 90:10 as solvents. The nitroalkene **2a** came out at 17.4 min and indole **1a** at 11.6 min; thus, non-reacted substrates do not interfere with the analysis and the two enantiomers came out at 22.3 min (*R*-enantiomer) and 27.7 min (*S*-enantiomer). The reference racemic sample for the HPLC analysis was done with zinc triflate ($Zn(OTf)_2$) as catalyst. ^{19}F-NMR (300 MHz, $CDCl_3$) peak for the starting material **2a** at -63.18 ppm and peak for the product **3a** at -62.64 ppm. ^1H-NMR (300 MHz, $CDCl_3$): δ 8.15 (s, 1 H), 7.58 (d, *J*= 8.2 Hz, 2 H), 7.48–7.44 (m, 2 H), 7.41–7.36 (m, 2 H), 7.24 (t, *J*= 7.4 Hz, 1 H), 7.14–7.09 (m, 1 H), 7.02 (d, *J*= 2.1 Hz, 1 H), 5.26 (t, *J*= 7.8 Hz, 1 H), 5.12–5.05 (m, 1 H), 4.99–4.92 (m, 1 H) ppm.[37]

4.2. Reaction with the methyl-2-oxo-4-phenylbut-3-enoate (2b)



The conditions of the HPLC analysis were the following: AD-H were used as column with a flow of 0.75 mL/min using hexane/isopropanol 80:20 as solvents. The two enantiomers of the product **3b** came out at 22.9 min (*S*) and 19.4 min (*R*); thus, non-reacted substrates do not interfere with the analysis. The reference racemic sample for the HPLC analysis was done with zinc triflate ($Zn(OTf)_2$) as catalyst (10%mol). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.63 (dd, *J* = 17.1, 7.8 Hz, 1H), 3.72 (dd, *J* = 17.1, 7.2 Hz, 1H), 3.79 (s, 3H), 4.95 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.02-7.08 (m, 2H), 7.15-7.23 (m, 2H), 7.26-7.37 (m, 5H), 7.45 (d, *J* = 7.8 Hz, 1H), 8.03 (br s, 1H).[38]

4.3. Reaction with 1-methylindole (1b)



TLC was performed with n-hexane/diethyl ether 7:3 as eluant. A column with Hexane/diethyl ether 7:3 as solvent and the product was between the fraction 2 and 5. The conditions of the HPLC analysis were the following: AD-H were used as column with a flow of 0.75 mL/min using hexane/isopropanol 95:5 as solvent with a retention times for the two reactants of 14.6min and 17.4 min (**1b** and **2a** respectively) and the two enantiomers product **3c** of 22.3 min (*R*) and 27.7 min (*S*). The reference racemic sample was done with $Zn(OTf)_2$ (10 mol%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.27 (t, J = 7.8 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 5.06-5.11 (m, 1H), 4.95-5.00 (m, 1H), 3.78 (s, 3H); ^{19}F-NMR (300 MHz, $CDCl_3$) δ -62.64 ppm.[39]

5. General Method for the heterogeneity.

Two reactions between the indole **1a** and the nitrostyrene **2a** using 3 beads of **AeG-Cu** as catalyst in dichloromethane were set up simultaneously following the method described previously. The first reaction kept the metal alginate beads until the complete conversion while the metal alginate beads were removed in the second one around 50% of conversion, corresponding at 3h of reaction. The kinetics of both reactions were followed in parallel by ^{19}F-NMR.

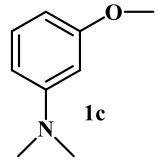
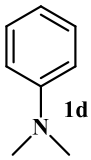
6. General Method for reusing the beads.

The reaction between the indole **1a** and the nitrostyrene **2a** was set up following the general method with 3 beads of **AeG-Cu** as catalyst. Once the reaction finished, the mixture was removed and treated for HPLC analysis, while the beads were kept in the vial to be washed with dichloromethane (5 times at least) and started again a new reaction. The reactions were followed by ^{19}F-NMR. In case of the following reaction could not be directly prepared after the previous one, the beads were conserved in the fridge with a small amount of dichloromethane for the next sample preparation in order to follow correctly the kinetic.

7. Additional data.

HPLC data for additional compound that were prepared but were not discussed in the thesis (Table 3-1).

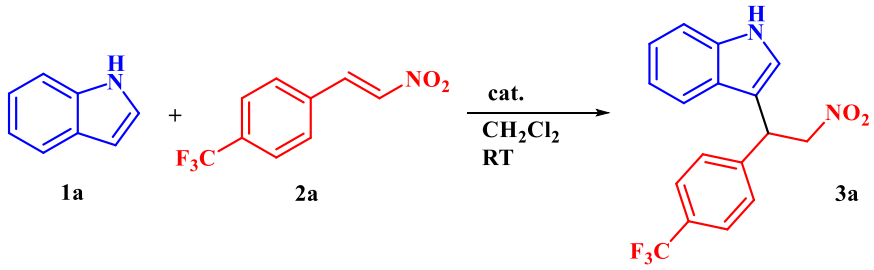
*Table 3-1 HPLC conditions for the reaction between the donors **1c,d** with the nitrostyrene **2a**.*

Donor	HPLC Conditions	Ret. Time (min)
 1c	**Column:** AD-H **Solvents:** Hexane/Isopropanol 90/10 **Flow:** 0.75 mL/min **UV detection:** 254nm	**1c:** 12.6 **2a:** 14.7 **3d:** 22.3; 27.7
 1d		**1d:** 12.2 **2a:** 13.0 **3e:** 22.3; 27.7

4. Results and Discussion

To assess the capability of alginate gels to promote the Friedel–Crafts alkylation of electron-rich N-heterocycles, the reaction between indole **1a** and nitrostyrene **2a** was studied in the presence of various metal alginate aerogels and solvogels (**AeG-M^{2+} and SG-M^{2+}**) (Table 4-1). The reactions were performed in dichloromethane, at RT, and followed by ^{19}F NMR spectroscopy. For these preliminary tests, materials derived from guluronic rich alginate (Protanal 200S, G:M 63/37) were employed, hypothesising that more rigid and ordered material could improve catalytic performances in terms of both activity and perhaps stereoinduction. [34,40,41,42,43]

*Table 4-1 Preliminary assessment of the catalytic activity and stereoselectivity of alginate gels in the Friedel-Crafts reaction of indole **1a** with nitrostyrene **2a**.*[a]



Entry	*Catalyst*	*Time (h)*	*Conv. (%)*[b]	*ee (%)*[c]
1	**AeG-Cu**	17	> 95	21(*R*)
2	**AeG-Ca**	17	> 95	Rac.
3	**SG-Sr**	17	> 95	Rac.
4	**SG-Ba**	17	> 95	24(*S*)
5	**SG-Co**	88	> 67	Rac.
6	**SG-Ni**	88	93	Rac.
7	**SG-Zn**	88	> 95	Rac.
8	**AeG-H**	190	> 53	Rac.

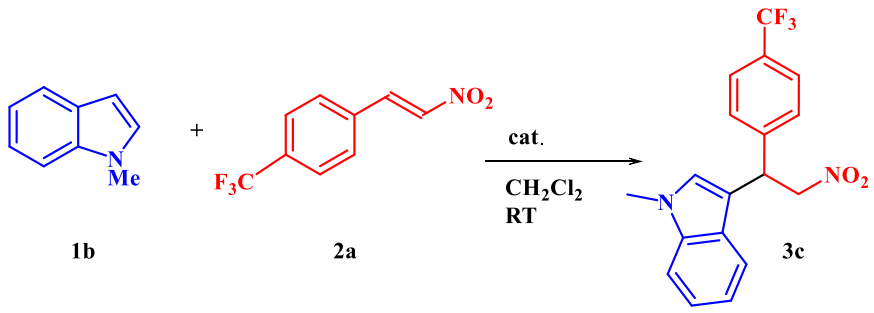
[a] Conditions: 5 aerogel beads of **AeG-M^{2+}** or **SG-M^{2+}** (0.01 mol of M^{2+}), DCM (150 µL), 0.075 mmol of **1a** and 0.05 mmol of **2a**, room temperature. [b] Followed by ^{19}F-NMR. [c] Determined by HPLC, Rac: racemic mixture.

Considering that the reaction without alginates does not proceed to any detectable extent after >48 h, the results collected clearly show the capability of these gels in catalysing this reaction, with the

highest activity displayed by Cu, Ca, Sr and Ba gels (entries 1-4), which reactions were complete in less than 17 h. In contrast, alginic acid (entry 8) was not as efficient as metal alginates, indicating the superior behaviour of Lewis acidic gels over a Brønsted acid counterpart. Excitingly, a small yet measurable degree of enantioinduction was measured in the reactions performed with Cu and Ba gels, which afforded product **3a** with 21 and 24% of enantiomeric excess, respectively (entries 1 and 4). Importantly, the two metals furnished the opposite enantiomers in excess, suggesting the opportunity to access both enantiomers of the product with this catalysis. This is an important aspect, since obviously alginates are only available in one enantiomeric form.

These first results could indicate that the type of cation can select the type of enantiomer. The type of donors could also have an influence on the enantiomeric excesses. This is why, we decided, first, to try different types of donors with **AeG-M^{2+}** (M^{2+}=Cu, Ba which gave the best enantioselectivities, and Ni for comparison) aerogels. We prepared and tested aerogels from now onwards due to their more manageable use. The reaction between three new substrates (**1b-d**) and the nitrostyrene **2a** were evaluated, using **AeG-M^{2+}** gels (Protanal 200S) in dichloromethane at room temperature. (Table 4-2 and Figure 4-1).

*Table 4-2 Catalytic performance using **1b** as donor catalysed by **AeG-M^{2+}** (M^{2+} = Cu, Ba and Ni) gels. [a]*



Entry	*Catalyst*	*Time (h)*	*Conv. (%)[b]*	*ee (%)[c]*
1	**AeG-Cu**	28	91	2(*R*)
2	**AeG-Ba**	23	>95	6(*S*)
3	**AeG-Ni**	28	87	3(*R*)

[a] Conditions: 5 aerogel beads of **AeG-M^{2+}** (0.01 mol of M^{2+}), DCM (150 µL), 0.075 mmol of **1a** and 0.05 mmol of **2a**, room temperature. [b] Followed by ^{19}F-NMR. [c] Determined by HPLC.

The reaction with the indole derivative **1b** (Table 4-2) showed that these gels are able to promote the reaction, however much less efficiently than the corresponding transformation with indole **1a**, in terms of both conversions (>80% conversion only after >20h), and enantiomeric excesses for the Cu and Ba gels.

In contrast, the results obtained show that the reaction did not occur with metal alginate gels **AeG-M^{2+}** (M^{2+}= Cu, Ba and Ni) using the aniline derivatives **1c** and **1d** as donors. No product was observed by TLC and NMR analysis even after five days.

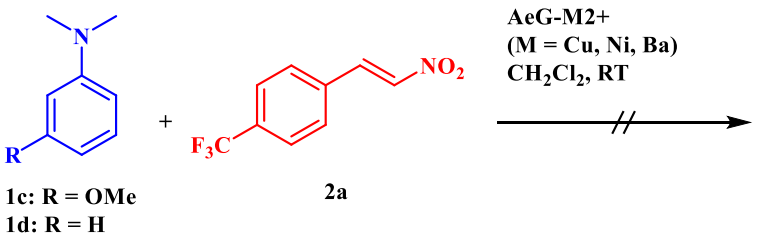


*Figure 4-1 Reaction between aniline donors **1c,d** and the nitroalkene **2a.***

With these results, we can say that indole **1a** offered the highest reactivity and enantiomeric excess in comparison with anilines **1c,d** and N-methylindole **1b**. This is why we decided to continue our studies with indole **1a** as donor for the following tests.

The previous results showed the importance of choosing the right donor for this reaction. So, it could be the same concerning the choice of the acceptors. In this perspective, we decided to study different types of electron withdrawing groups in the Michael acceptor using **AeG-Cu** gel as catalyst, the best performing so far in terms of enantioselectivity. Seven substrates **2b-f** were evaluated using **AeG-Cu** gels (Protanal 200S) in dichloromethane at room temperature. (Figure 4-2)

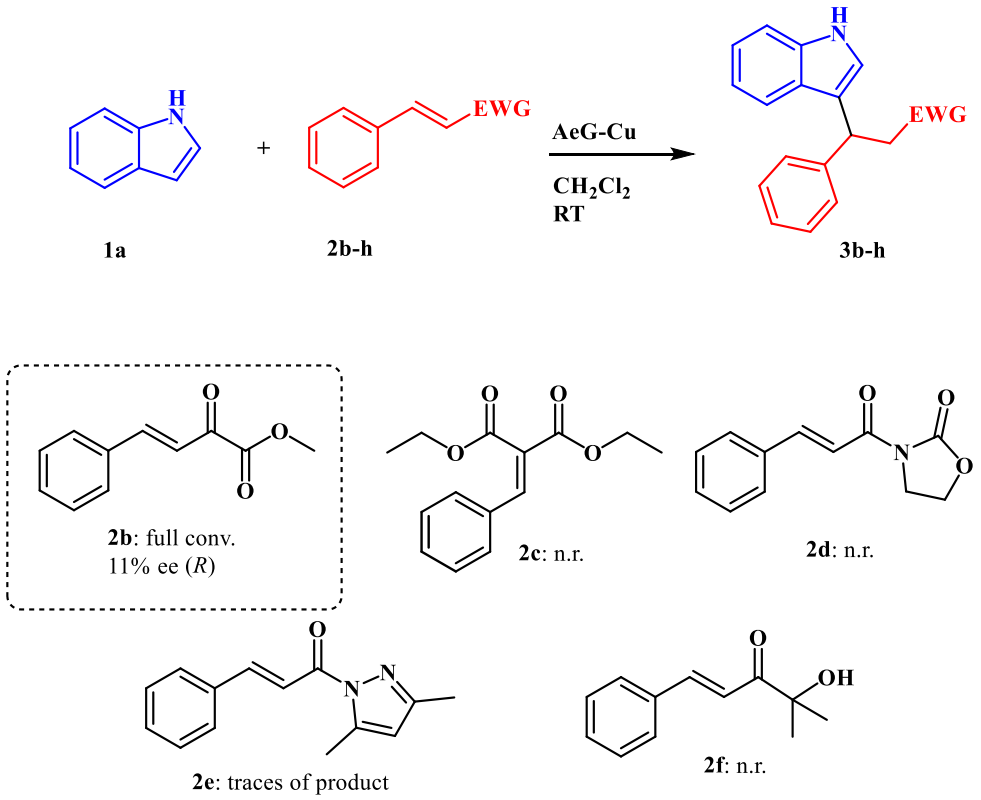
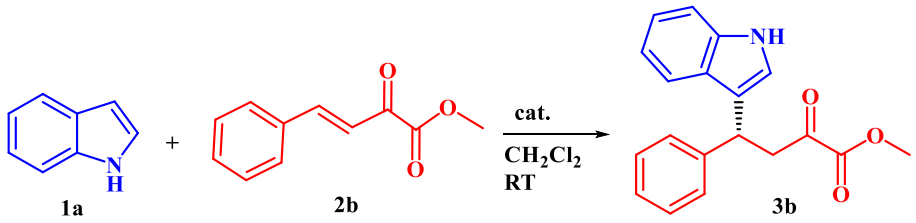


*Figure 4-2 Scheme of the Friedel-Crafts reaction between the indole **1a** with acceptors **2b-f**. n.r.: no reaction.*

These results showed the important role that play the choice of the acceptor in this reaction. Indeed, the reaction with **AeG-Cu** beads as catalyst did not occur for any of the acceptors **2**, with the exception of α-ketoester **2b** which gave full conversion in less than 40h with a low enantioselectivity. Even if the α-keto ester **2b** gave less enantioselectivity and took more time than the reaction with the nitrostyrene **2a** as acceptor, we thought it could be interesting to evaluate the catalytic performance of different metal alginate gels (**AeG-M^{2+}** and **SG-M^{2+}**) in the reaction with **2b**.

We proceeded to evaluate the influence of the cation in this reaction using different metal alginate gels (**AeG-M^{2+}** and **SG-M^{2+}**). All the metal alginate gels were used in the G-rich form (Protanal 200S) in dichloromethane at room temperature (Table 4-3).

*Table 4-3 Catalytic performance of a library of different **AeG-M**$^{2+}$ and **SG-M**$^{2+}$ gels in the reaction with **2b**[a].*



Entry	*Catalyst*	*Time (h)*	*Conv. (%)[b]*	*ee (%)[c]*
1	**AeG-Cu**	40	>95	11
2	**AeG-Ca**	64	>95	19
3	**SG-Sr**	64	>95	14
4	**SG-Ba**	64	>95	Rac.
5	**SG-Co**	64	>95	Rac.
6	**SG-Ni**	64	>95	45
7	**SG-Zn**	64	>95	Rac.
8	**AeG-H**	64	Ca. 50	Rac.

[a] Conditions: 5 aerogel beads of **AeG-M**$^{2+}$ or **SG-M**$^{2+}$ (0.01 mol of M^{2+}), DCM (150 µL), 0.075 mmol of **1a** and 0.05 mmol of **2b**, room temperature, 64 h. [b] Followed by TLC. [c] Determined by HPLC, Rac: racemic mixture.

For all the metal catalysts, the conversion was complete after three days of reaction, even if the kinetics of these reactions was not followed accurately (entries 1 to 7). For the acid catalyst (entry 8) only a partial conversion was observed, which confirm the fact that acid catalyst was not as efficient as metal alginates as showed in the first results (**Erreur ! Source du renvoi introuvable.**). These results showed a different behaviour of the metals with this acceptor **2b**. Indeed, in comparison with the first reaction using nitrostyrene **2a** as acceptor, wherein a racemic mixture was obtained with Ca; Sr; Ni, and 24% of enantiomeric excess was obtained with Ba (entries 2, 3, 6 and 4 respectively in the Table 4-1), with α-keto ester **2b** an enantiomeric excess was obtained for Ca; Sr; Ni and a racemic mixture for Ba (entries 2, 3, 6 and 4 respectively) and the highest enantioselectivity was obtained with **SG-Ni** (entry 6; ee% =45).

Unfortunately, for the reaction with α-keto ester **2b**, it was difficult to obtain a clean product even after column chromatography, making difficult to record of a reliable HPLC chromatogram, which could also be influenced by the presence of the tautomeric form of the product. So, we decided for the further experiments to move back to use nitrostyrene **2a** as acceptor.

After the preliminary tests and confirming the beneficial effect using metal-alginates for the induction of enantioselectivity, we moved to evaluate if the content of guluronate moiety (**G**) in alginates could affect the selectivity in the Friedel-Crafts alkylation. Thus, the most promising materials were selected (**AeG-Cu**, **AeG-Ba** and **AeG-Ni**) and three different alginate formulations were used for the preparation of the gels: Protanal 200S with high quantity of G (**AeG-M^{2+}-200S;** G:M 63/37), Protanal 200 DL with similar quantity of **G** and **M** (**AeG-M^{2+}-200DL**), and Protanal 240 D with lower quantity of **G** (**AeG-M^{2+}-240D;** G:M 33/67) (Figure 4-3). All the materials were prepared by our collaborators in Montpellier and were characterized by surface area and TGA (Figure 4-5).

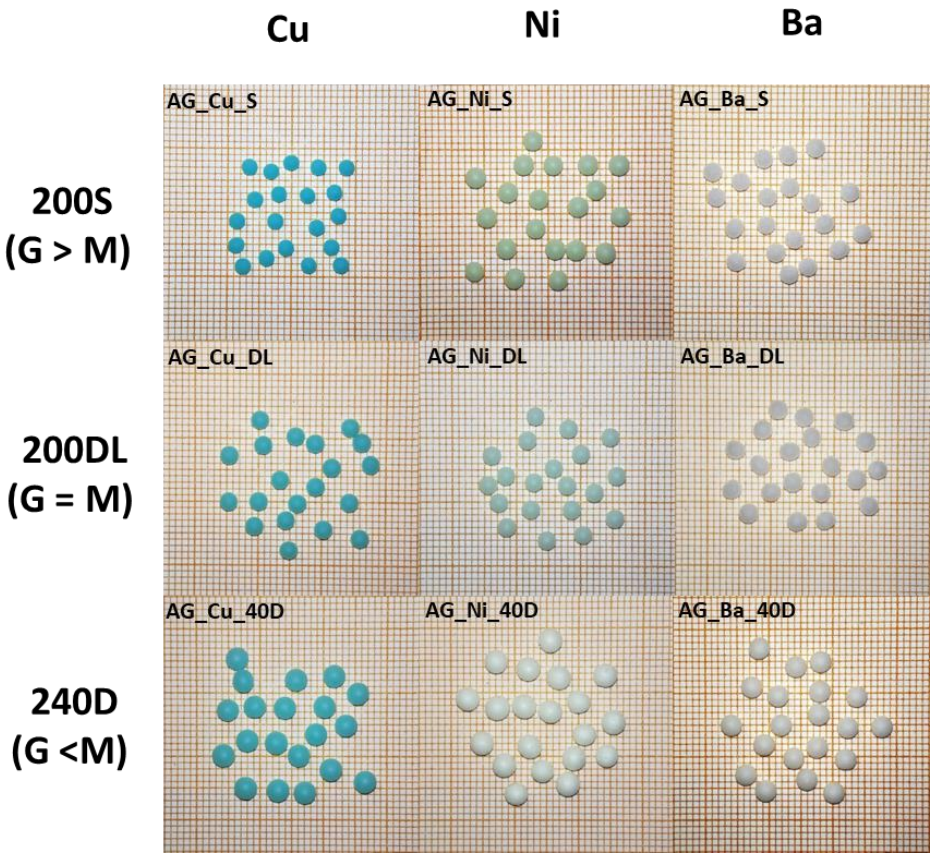


Figure 4-3 ***AeG-M^{2+}*** *beads (M^{2+} = Cu, Ni and Ba) prepared varying the M/G ratio in their structure.*

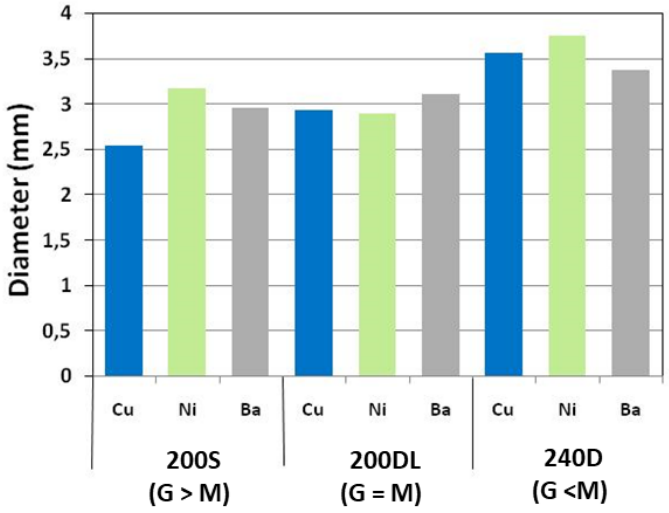


*Figure 4-4 Size distribution of **AeG-M** gels according to the variation of G units. The size determination was done taking the average size of 20 beads in a macroscopic photo. The Fujifilm software was used for the measure of the size.*

Figure 4-4. shows the macroscopic sizes of the gel beads. The use of an alginate solution with less units of **G** in its composition generate materials with higher sizes (**AeG-Cu-240D**, **AeG-Ni-240D** and **AeG-Ba-240D**). The higher size is associated with a decrease in the viscosity of the gels. However, even if the viscosity is lower in Protanal 240D formulation, the possibility of preparing beads with a solution with a low composition of **G** was demonstrated.

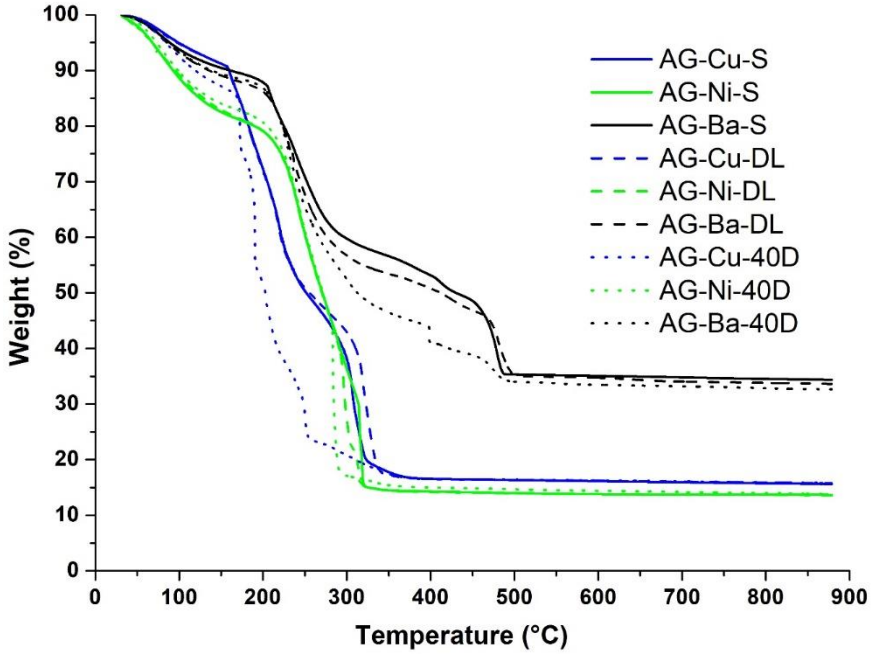


*Figure 4-5 TGA profiles in air at 5°C min-1 for **AeG-M** gels with different G composition.*

The TGA profiles showed the typical behaviour of the thermal degradation of alginates gels. Three main zones were found: the loss of the water, carboxylates degradation in the saccharide moieties and subsequent -OH decomposition. The diminution in the **G** quantity seems to have a detriment on the thermal stability of the gels for the three metals used (Dotted line in **AeG-M-240D** type gels). The materials with barium in their structure (black lines in **AeG-Ba-200S**, **AeG-Ba-200DL** and **AeG-Ba-240D**) requires higher temperatures for their decomposition and the percentage of mass loss was lower associated to the residual phase of $BaCO_3$, in comparison with the metal oxides as residual phases for **AeG-Cu** and **AeG-Ni** gels (Table 4-4).

*Table 4-4 Results of the TGA analysis for the metal alginate gels (**AeG-M^{2+}**) with different M/G ratios.*

Entry	***Alginate***	***Catalyst***	***%Loss***	***Residual Phase***	***%wt M^{2+}***
1		**AeG-Cu**	82.7	CuO	13.8
2	**200S**	**AeG-Ni**	83.4	NiO	13.1
3		**AeG-Ba**	61.8	$BaCO_3$	26.6
4		**AeG-Cu**	82.6	CuO	12.1
5	**200DL**	**AeG-Ni**	83.5	NiO	11.5
6		**AeG-Ba**	62.0	$BaCO_3$	26.4
7		**AeG-Cu**	81.7	CuO	12.7
8	**240D**	**AeG-Ni**	83.4	NiO	11.6
9		**AeG-Ba**	63.2	$BaCO_3$	25.6

The isotherms of adsorption and BET area determination are showed from the Figure 4-6 to the Figure 4-8 (isotherms for **AeG-Cu**, **AeG-Ni** and **AeG-Ba** respectively) and Table 4-5, respectively. The alginates gels showed the behaviour of isotherms type IV for mesoporous material. The BET surface areas for the gels were found in the range between 686 and 429 m^2g^{-1}.

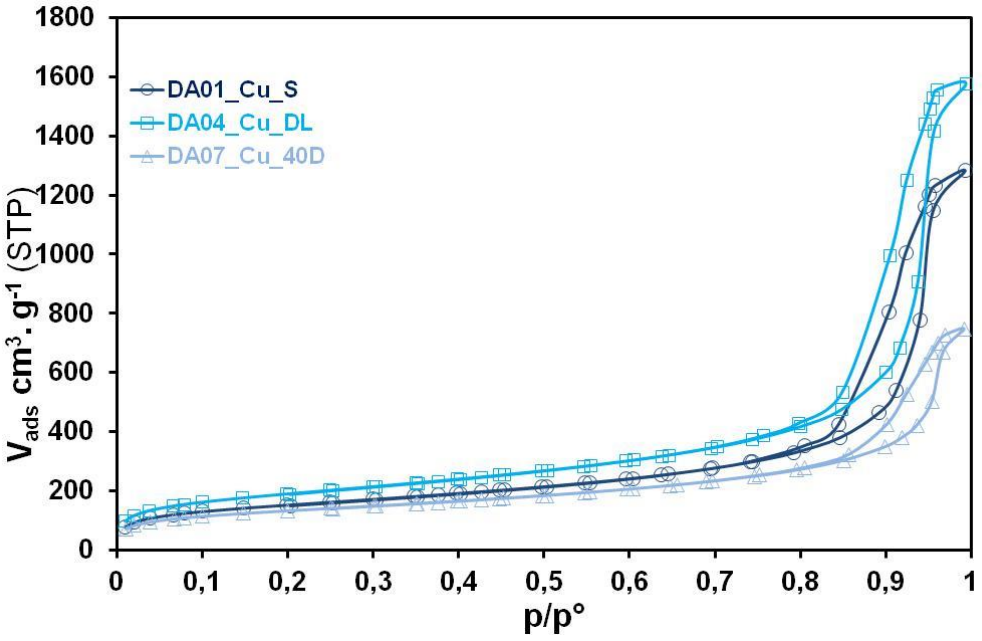


*Figure 4-6 Isotherms of adsorption for **AeG-Cu**.*

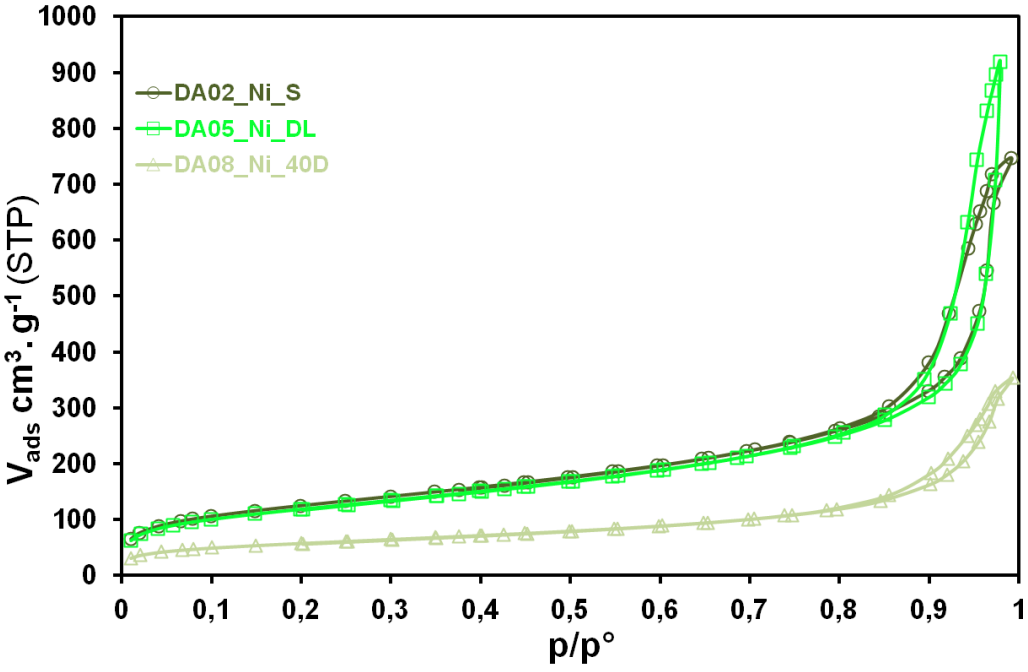


*Figure 4-7 Isotherms of adsorption for **AeG-Ni**.*

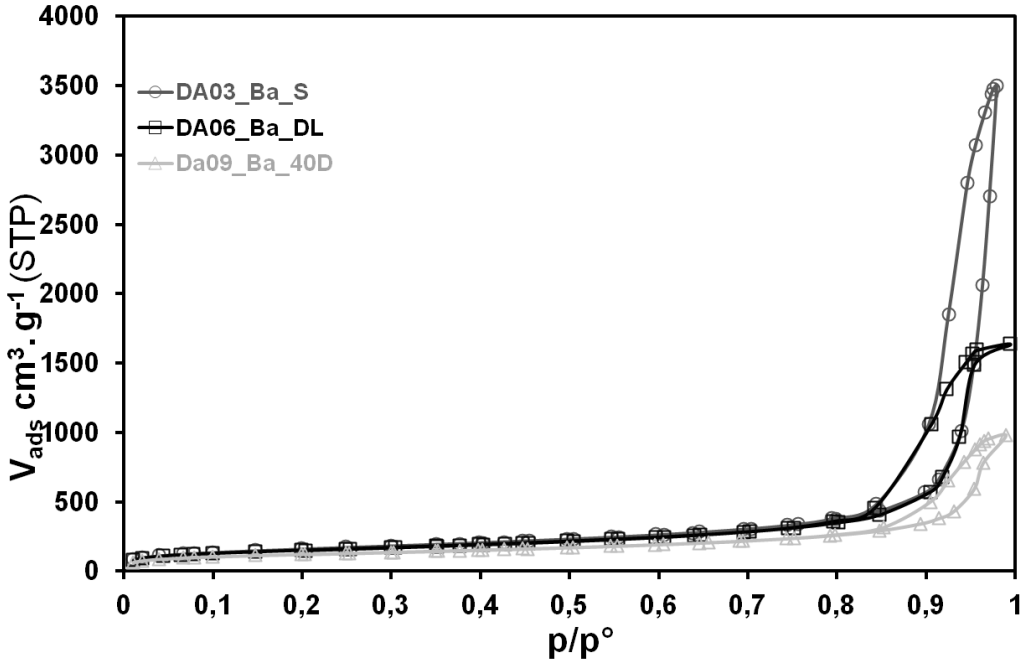


*Figure 4-8 Isotherms of adsorption for **AeG-Ba**.*

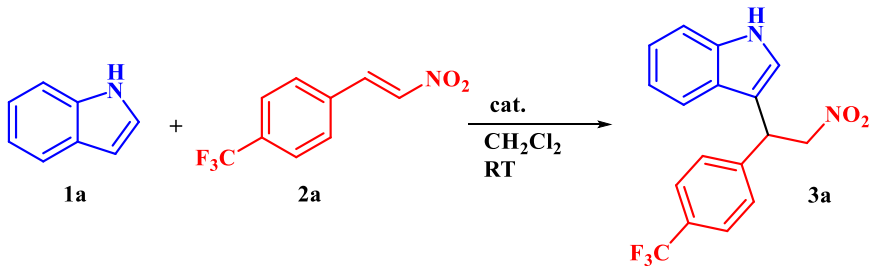
*Table 4-5 Results of the BET surface area for the metal alginate gels (**AeG-M^{2+}**) with different M/G ratios.*

Entry	*Alginate*	*Cat.*	$S_{BET}(m^2.g^{-1})$
1		**AeG-Cu**	551
2	**200S**	**AeG-Ni**	450
3		**AeG-Ba**	585
4		**AeG-Cu**	686
5	**200DL**	**AeG-Ni**	429
6		**AeG-Ba**	542
7		**AeG-Cu**	478
8	**240D**	**AeG-Ni**	n.d.[a]
9		**AeG-Ba**	437

[a] n.d.: non determined.

After the characterisation of the metal alginate gels (**AeG-M^{2+}**) with different M/G ratios, we decided to go further and study the effect of the G/M ratio on the reaction between the indole **1a** and nitrostyrene **2a**. The reaction was performed in dichloromethane at room temperature and only with the metal aerogel beads form (**AeG-M^{2+}**). (Table 4-6)

Table 4-6 Catalytic performance using different type of biopolymers. [a]



Entry	*Alginate*	*Cat.*	*Time (h)*	*Conv. (%)[b]*	*ee (%)[c]*
1	**200S**	**AeG-Cu**	4	91	21(*R*)
2	**200DL**	**AeG-Cu**	4	93	21(*R*)
3	**240D**	**AeG-Cu**	19	92	15(*R*)
4	**200S**	**AeG-Ba**	1h45’	>95	24(*S*)
5	**200DL**	**AeG-Ba**	1h45’	>95	18(*S*)
6	**240D**	**AeG-Ba**	1h45’	>95	8(*S*)
7	**200S**	**AeG-Ni**	70	74	8(*R*)
8	**200DL**	**AeG-Ni**	70	95	4(*R*)
9	**240D**	**AeG-Ni**	70	>95	Rac

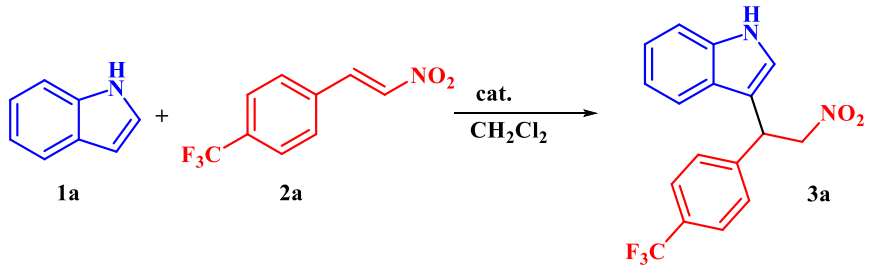
[a] Conditions: 5 aerogel beads of **AeG-M^{2+}** (0.01 mol of M^{2+}), DCM (150 µL), 0.075 mmol of **1a** and 0.05 mmol of **2a**, room temperature, [b] Followed by ^{19}F-NMR. [c] Determined by HPLC, Rac: racemic mixture.

The results show that the ratio **G/M** does not seem to affect the conversion of the reaction for Cu and Ba, only a slight difference of the conversion was observed between the three Protanal forms. We obtained, in contrast, a bigger gap with Ni catalysts and the highest activity corresponds to the form with less **G**-units (Protanal 240D) inside the biopolymer. However, different values of enantiomeric excess were observed according the number of **G**-units. The highest enantiomeric excesses were observed for the Protanal 200S form, (i.e. the form with the highest quantity of **G**), followed by the

very similar values furnished by the Protanal 200DL form (i.e. the form with similar quantity for **M** and **G**). The Protanal 240D was much less efficient in terms of enantioinduction, giving a very low enantiomeric excess, or even a racemic mixture with Ni catalyst. Finally, the **G/M** ratio does not affect the type of enantiomer obtained.

The best results were obtained with the Protanal 200S form, so, for the other studies we decided to use only this form and with the more promising Cu and Ba gel beads, which gave the highest enantiomeric excess and activity. After the effect of the **G** quantity on the reaction, we studied the effects of the temperature on this reaction. The temperature is a parameter which should influence the kinetics of the reaction, and it could be really interesting to see if it could also influence the enantioselectivity. For this experiment, **AeG-Cu** and **AeG-Ba** in the Protanal form 200S were used as catalysts in dichloromethane at different temperatures (-30°C; 0°C; RT) (Table 4-7).

*Table 4-7 Effects of the temperature on the Friedel-Craft alkylation between the indole **1a** and the nitrostyrene **2a**.* [a]



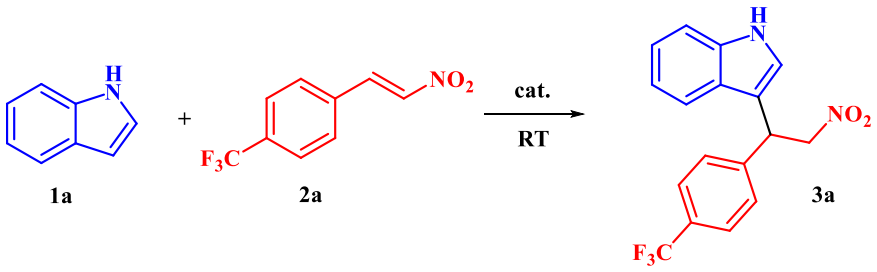
Entry	*Catalyst*	*Temperature (°C)*	*Time (h)*	*Conv. (%)*[b]	*ee (%)*[c]
1		RT	4	91	21(*R*)
2	**AeG-Cu**	0	64	> 95	23(*R*)
3		-30	48	52	26(*R*)
4		RT	1h45’	>95	24(*S*)
5	**AeG-Ba**	0	4h45’	97	28(*S*)
6		-30	51	94	33(*S*)

[a] Conditions: 5 aerogel beads of **AeG-M**$^{2+}$ (0.01 mol of M^{2+}), DCM (150 µL), 0.075 mmol of **1a** and 0.05 mmol of **2a**. [b] Followed by ^{19}F-NMR. [c] Determined by HPLC.

In the case of the temperature, for **AeG-Cu** and **AeG-Ba**, the most obvious effect concerns the time of the reaction, as expected. The decrease of the temperature increases a lot the time of reaction. Concerning the enantiomeric excesses, an increase of the ee% with the decrease of the temperature was observed, especially for the reaction at -30°C (entries 3 and 6) for which the highest ee% were obtained. However, the increase of the enantiomeric excesses was just of 9% for **AeG-Ba** and 5% for **AeG-Cu**, with a reaction time slower. So, even if we could consider the temperature as a parameter influencing the enantioinduction, for the subsequent experiments we decided to continue to work at room temperature, conditions for which a fast reaction was obtained, with a measurable enantioselectivity.

Thus, we moved to study the effect of the solvent on the reaction. In order to do that we screened different solvents with different polarity (Table 4-8).

Table 4-8 Catalytic performance using different type of solvents. [a]



Entry	*Catalyst*	*Solvent (0.33M)*[b]	*Time (h)*	*Conv. (%)*[c]	*ee (%)*[d]
1	**AeG-Cu**	Toluene	19	> 95	17(*R*)
2		DCM	19	> 95	20(*R*)
3		CH_3CN	96	13	ND
4		EtOH	264	73	Rac.
5		THF	64	2	ND
6		MeOH	64	60	ND
7		TBME	64	55	8(*R*)
8		$CHCl_3$	64	82	13(*R*)
10	**AeG-Ba**	DCM	1h45	>95	24(*S*)
11		Toluene	1h20	>95	19(*S*)
12		CH_3CN	51	>95	30(*S*)
13		EtOH	24	>95	50(*S*)
14		THF	48	70%	53(*S*)
15		EtOAc	24	98%	47(*S*)
16		MeOH	52	89%	23(*S*)
17		Isopropanol	24	>95	30(*S*)
18		TBME	1h20’	>95	3(*S*)

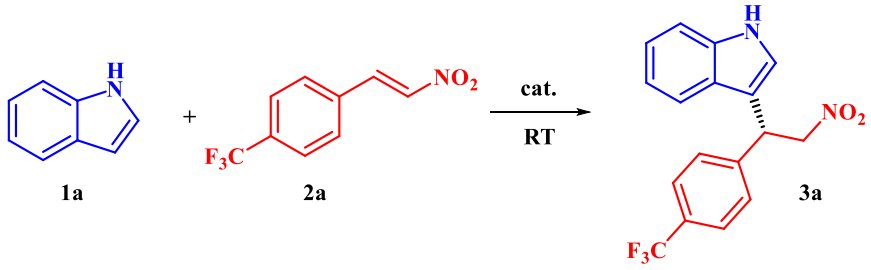
[a] Conditions: 5 aerogel beads of **AeG-M^{2+}** (0.01 mol of M^{2+}), solvents (150 μL), 0.075 mmol of **1a** and 0.05 mmol of **2a**, room temperature, [b] With respect to the acceptor. [c] Followed by ^{19}F-NMR. [d] Determined by HPLC, Rac: racemic mixture and ND: Non determined.

Therefore, for the effects of the solvent we can see that the best solvents using the Cu-aerogel system were toluene and DCM with a high and fast conversion accompanied by moderate enantioselectivity (entries 1 and 2). These solvents gave the best ee% with a really good conversion.

Concerning Ba-aerogel, the trend is different. Indeed, lot of solvents show better ee% than toluene and DCM but for most of them the reaction needs more time to be complete such as CH_3CN; EtOH; THF; EtOAc and TBME (entries 12, 13, 14, 15 and 18 respectively). And also, for those which gave better enantioselectivity than with DCM and toluene the ^{19}F-NMR spectra showed the presence of by-products. Therefore, we thought it could be interesting to mix two solvents together.

The idea was to mix the solvents which gave a good ee% with dichloromethane which gave a faster conversion and a cleaner ^{19}F-NMR spectrum, in order to potentially increase the enantiomeric excess, decrease the time of reaction and obtain a cleaner product **3a**. To do that we choose the highest ee% value (i.e. EtOH, THF and EtOAc and also DMF as representative strong Lewis base) as solvents for the reaction with **AeG-Ba** as catalyst (Table 4-9).

Table 4-9 Catalytic performance using different mixtures of solvents. [a]



Entry	*Catalyst*	*Solvent (0.33M)*[b]	*Time (h)*	*Conv. (%)*[c]	*ee (%)*[d]
1	**AeG-Ba**	DCM + EtOH[e]	23h45’	93	46
2		DCM + THF[e]	6h15’	97	43
3		DCM + EtOAc[e]	4	>95	37
4		DCM + DMF[f]	52	92	19

[a] Conditions: 5 aerogel beads of **AeG-Ba-200S** (0.01 mol), solvents (150 µL), 0.075 mmol of **1a** and 0.05 mmol of **2a**, room temperature, [b] With respect to the acceptor. [c] Followed by ^{19}F-NMR. [d] Determined by HPLC, [e] DCM/EtOH; DCM/THF; DCM/EtOAc 2:1 (100 µL of DCM and 50 µL of the other solvents), [f] DCM/DMF 14:1 (140 µL of DCM and 10 µL of DMF).

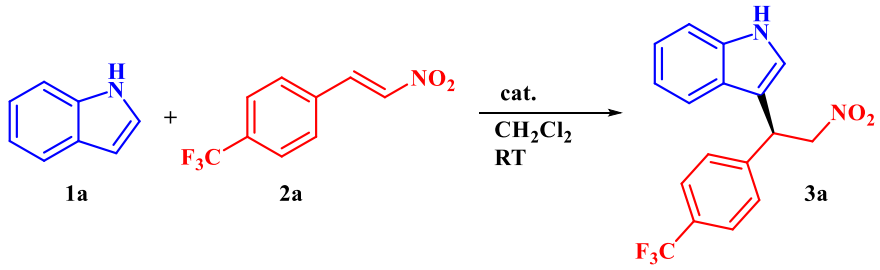
The first thing that could be noticed it is the fact that all the reactions, except the one with EtOH (entry 1), gave a faster and quite high conversion, compared to the corresponding reactions with single solvents, thanks to the addition of dichloromethane. In contrast, the addition of dichloromethane decreased the enantiomeric excesses. However, the values of the ee% stay higher than the ones obtained with only dichloromethane as solvent, except for DMF (entry 4). Finally, it is worth noting that in all cases the ^{19}F-NMR spectra are much cleaner than those obtained without dichloromethane. These results could be interesting and deserve to be studied in the future. Indeed, the fact that high values of ee% were obtained is a good point to think about an optimal ratio DCM/other solvent to improve these results.

These results showed the importance of the solvents in the reaction between the indole **1a** and the nitrostyrene **2a** and how the enantiomeric excesses could be improved by choosing the right solvent or the right ratio DCM/solvents.

Despites this, preliminary results showed that the reaction with **AeG-Ba**, even if faster and potentially more enantioselective, turned out to be poorly reproducible, therefore we proceeded our studies with only the **AeG-Cu** system, postponing a more detailed study on the solvent effect in the **AeG-Ba** catalysis to a future project.

Therefore, the best conditions for the study of an enantioselective Friedel-Crafts alkylation promoted by alginate gels were the reaction between the indole **1a** and nitrostyrene **2a** with **AeG-Cu** as catalyst in the G-rich form (Protanal 200S) in dichloromethane at room temperature. Since the beginning of this study 5 beads of metal aerogels, corresponding to ca. 20 mol% of metal, were used. So, we were interested to know if we could lower the amount of catalyst (Table 4-10).

*Table 4-10 Effects of the amount of catalysts in the Friedel-Craft alkylation between the indole **1a** and the nitrostyrene **2a**.* [a]



Entry	*Catalyst*	*Number of Beads*	*Cu^{2+} Loading (mol%)*	*Time (h)*	*Conv. (%)[b]*	*ee (%)[c]*
1	**AeG-Cu**	5	20	4	91	21
2		3	12	17	>95	22
3		1	4	41	>95	22
4		1/2	2	119	91	23

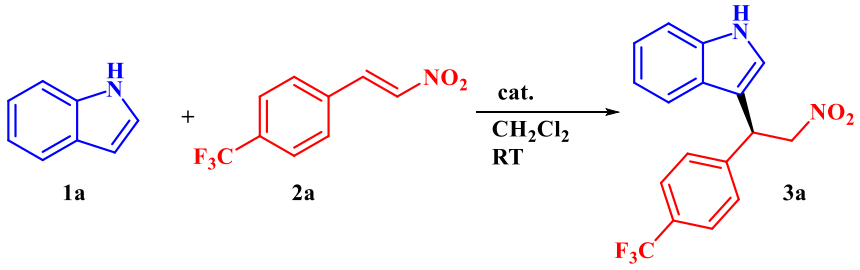
[a] Conditions: DCM (150 µL), 0.075 mmol of **1a** and 0.05 mmol of **2a**, room temperature. [b] Followed by ^{19}F-NMR. [c] Determined by HPLC.

These results showed that the reaction time was affected by the diminution of the metal alginate beads inside the reaction, as we expected due to the kinetic character of the catalysis. Fortunately, only this result changed, the diminution of the beads inside the reaction did not affect the enantioselectivity of the reaction; the same ee% were obtained for all cases. Finally, knowing the fact that the reaction did not occur without any catalyst, these results showed that, even with a small amount of catalyst a full conversion could be obtained (entry 4). However, in this case, the reaction took more time. These

results are promising for the future, and with more experiments, a good balance between the reaction time and the amount of catalyst could be found.

In the same perspective, we were interested to prove the heterogeneous character of these catalysts. In order to do that, two reactions were set up at the same time with **AeG-Cu-200S** as catalyst and the kinetics of both reactions in parallel was followed by ^{19}F-NMR. The beads of one of the reactions were removed when this one was around 50% of the conversion while the other one was kept running. (Table 4-11 and Figure 4-9)

Table 4-11 Heterogeneous test. [a]



Entry	*Time (h)*	*Conv. (%)*[b]	*Notes*
1	1	20	3 Beads of Cu in the vial
2	3	57	
3	5	71	
4	22h30’	>95	
5	1	24	3 Beads of Cu in the vial
6	3	54	
7	3	54	No beads inside the vial
8	5	54	
9	22h30’	54	
10	94	57	

[a] Conditions: DCM (150 µL), 0.075 mmol of **1a** and 0.05 mmol of **2a**, room temperature, [b] Followed by ^{19}F-NMR.

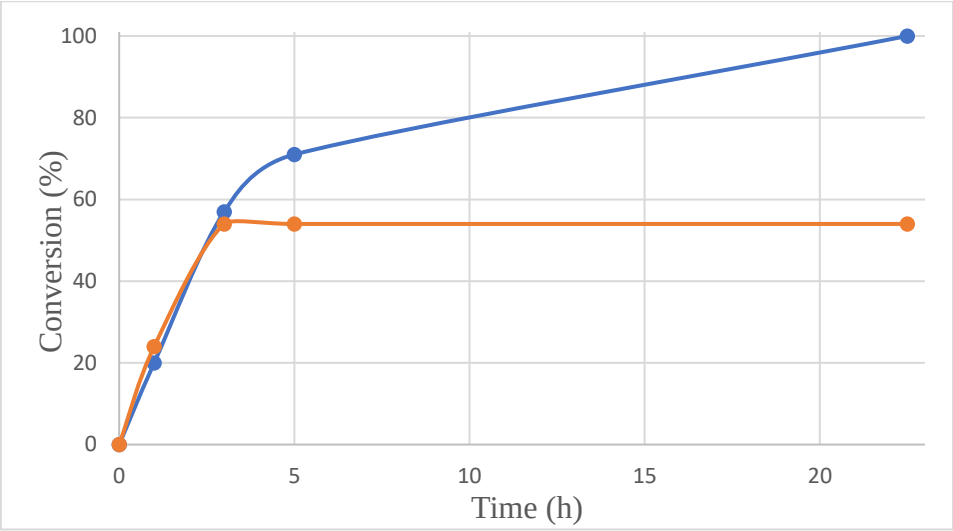


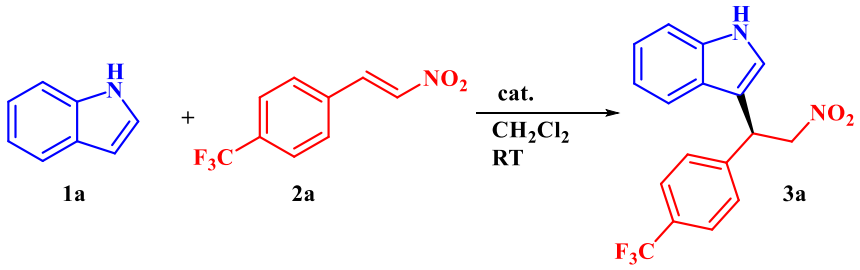
*Figure 4-9 Graph of the kinetic of the reactions. Red curve corresponds to the reaction for which the three **AeG-Cu** beads were removed after 3h of the reaction and Blue curve corresponds to the reaction with the 3 **AeG-Cu** beads.*

The metal alginate beads were removed after 3h of reaction, corresponding to the time of the reaction for which the conversion was around 50% in the reactions (entries 2 and 6). As showed the Table 4-11 and the Figure 4-9, once the beads were removed from the sample the conversion stopped while the reaction with 3 aerogel beads of **AeG-Cu** was still running (entries 1 to 4) until the complete conversion after less than 22h 30 minutes. These results proved that the catalyst stays inside the beads and are not spread in the solution during the reaction. So, thanks to these results, the heterogeneous character of the catalysts was confirmed.

Finally, after the results obtained for the heterogeneous character of the metal alginate gels **AeG-Cu**, a last parameter was studied. Indeed, the fact that the heterogeneity of the catalysts was proved allowed us to ask if the beads could be reused. And, if yes, how many times could we reuse the same beads?

The same reaction was set up 6 times using the same beads of **AeG-Cu** in the condition previously considered as the best conditions for this reaction; the following results were obtained. (Table 4-12 and Figure 4-10)

*Table 4-12 Effects of reusing the metal aerogel beads **AeG-Cu-200S** on the Friedel-Craft alkylation between the indole **1a** and the nytrostyrene **2a**.* [a]



Entry	*Time (h)*	*Conv. (%)[b]*	*ee (%)[c]*
1	22h30’	>95	21
2	23h40’	95	23
3	40	90	20
4	45	>95	21
5	47h35’	92	19
6	60	>95	14

[a] Conditions: 3 aerogel beads of **AeG-Cu-200S** (0.01 mol of Cu), DCM (150 µL), 0.075 mmol of **1a** and 0.05 mmol of **2a**, room temperature, [b] Followed by ^{19}F-NMR. [c] Determined by HPLC.

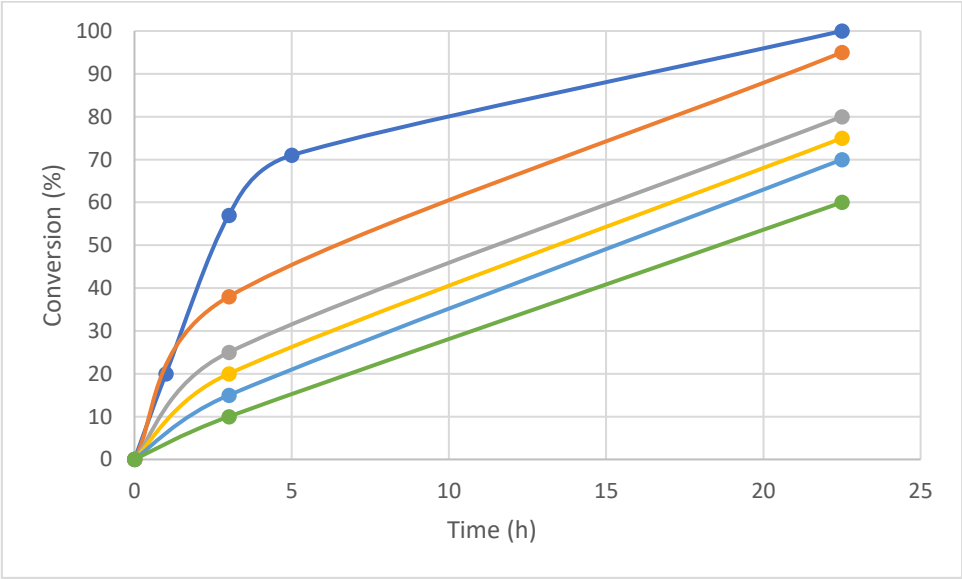


*Figure 4-10 Representation of the evolution of the kinetic of the reaction after 22h30 of reaction between indole **1a** and nitrostyrene **2a** with 3 beads of **AeG-Cu** reused for 6 experiments. Blue, red, grey, orange, pale blue and green curves correspond to the run 1, 2, 3, 4, 5 and 6 respectively.*

The Table 4-12 and the Figure 4-10 showed that the reaction time increases slightly with the number of times the same aerogel beads were used, indicating a decrease of activity with the number of times this one was used. Concerning the conversion of the reaction, any influence from the number of times the catalyst has been used, in all cases a complete or almost complete conversion was reached, provided that a sufficient reaction time was applied. Finally, for the enantiomeric excesses did not show any significant change with the number of times the beads were used, at least for five times (entries 1 to 5). At the 6^{th} time of running the reaction a consequent drop of ee% appeared. These results showed that the metal aerogel beads could be reused for at least 5 times without changing the enantioselectivity and the conversion of the reaction. Only the time of the reaction was affected by the fact to reuse the same aerogel beads. In the perspective of green chemistry, these results could be helpful for future reaction.

5. Conclusion and outlook

In order to answer to the fundamental question: can we use the intrinsic chirality of these biopolymeric materials to induce asymmetry in a chemical transformation? Some preliminary tests have been done on the Friedel-Crafts alkylation reaction.

The results obtained clearly show the capability of the metal alginate gels to promote the Friedel-Crafts alkylation in the reaction between the indole **1a** and the nitrostyrene **2a** to form the product **3a** with a complete conversion. The highest activity and enantioselectivity were given by two Lewis acidic gels: Cu and Ba (21 and 24% ee, respectively), while a Brønsted acid counterpart was not useful. Furthermore, with these metal alginate gels the opposite enantiomers were obtained (*R*- for Cu and *S*- for Ba) suggesting that the type of cation could selected the type of enantiomer.

Different donors and acceptors were tested to see if these promising metal alginate gels could promote also these reactions, and the results showed that the best results were obtained for the reaction between the indole **1a** and the nitroalkene **2a**. Indeed, we can say that the indole **1a** offered the highest activity and enantiomeric excess in comparison with anilines **1c,d** and N-methylindole **1b** and the reaction with **AeG-Cu** beads as catalyst did not occur for any acceptor **2**, with the exception of α-ketoester **2b** which gave full conversion but with a difficult-to-measure enantioselectivity.

The G-rich form (i.e. Protanal 200S, G:M 63/37) of the biopolymer was determined to be the most efficient form, suggesting that more rigid and ordered material improves catalytic performances in terms of enantioinduction. In contrast, the **G/M** ratio did not affect the conversion and the type of enantiomer obtained.

Concerning the conditions of the reaction (i.e. temperature and solvent used), for **AeG-Cu** the results showed clearly that the best conditions for this reaction were to work at room temperature in dichloromethane or toluene. For the **AeG-Ba**, instead, other solvents at room temperature showed a better ee% than the one obtained in dichloromethane and toluene but needed more time to be complete. However, the mix between these solvents and dichloromethane gave interesting results and deserves to be studied in the future. Indeed, the fact that high values of ee% were obtained is a good point to think about a perfect ratio DCM/other solvent to improve these results.

Finally, this study confirmed the heterogeneity of the metal alginate **AeG-Cu** gels, showed that only a small amount of catalyst (2mol%) could be used and that the beads can be used at least five time,

in both cases without changing the enantiomeric excesses. In the perspective of the green chemistry these results are really interesting.

Even if more studies need to be performed to improve the conditions of this reaction and the enantiomeric excesses, indeed for now a moderate ee% were obtained for our best metal alginate (**AeG-Cu** and **AeG-Ba**), these preliminary results are a good starting point for the future optimisation.

In the future, this work will continue in the following directions:

-investigate the reaction scope with the simple **AeG-Cu** system which has been assessed as optimal so far; variations in both indole and nitrostyrene reaction partners will be considered.

-in depth study of the **AeG-Ba** system: the preliminary results collected showed a greater potential displayed by this catalyst compared to **AeG-Cu**, in terms of both activity and, more importantly, enantioselectivity. The reasons for the poor reproducibility should be investigated, followed by a broader screening of solvents, additives, and solvent mixtures.

-reinvestigation of the reaction with the α-ketoester **2b**, which gave a very promising result with the **AeG-Ni** catalyst but requires a considerable work for the development of a reliable analytical method.

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