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Barium based alginates in heterogeneous catalysis for Friedel Crafts enatioselective reaction

Experimental degree thesis

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ABSTRACT:

Alginate is a polysaccharide from brown algae and is available in almost unlimited quantities at very low prices. In the presence of divalent metals, these renewable biopolymers can readily form hydrogels, solvogel, and aerogels. Alginate beads can be used as chiral heterogeneous catalysts for enantioselective reactions.

A representative reaction, the Friedel-Crafts alkylation of nitroolefins with indoles, was tested in this master's thesis. Having prepared previously optimized barium alginate beads prior to the study, this study tested new substrates involving the prevalence of nitroolefins and indoles in different nitroolefins, obtaining moderate yields and good enantiomeric excesses under optimized reaction conditions.

The recyclability studies of barium alginate beads showed good stability and recyclability, with the same catalyst being used at least five times with similar results. As well as the heterogeneity of the catalytic action was also demonstrated by the Sheldon test.

Keywords: heterogeneous catalysis, asymmetric selective catalysis, alginate, biopolymers, polysaccharides. Friedel-crafts alkylation, chirality, enantioselectivity, asymmetric synthesis, organic synthesis.

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1. Introduction

1.1 Green Chemistry

Green chemistry is the use of a set of principles to reduce or eliminate the use or generation of hazardous substances in the design, manufacture, and application of chemical products. Green chemistry aims to maximize the efficiency of reactions, minimize losses, minimize harm to the natural environment, reduce waste generation from the source to the end product, and reduce all kinds of adverse effects such as pollution or impact on the environment. Therefore, it has received a lot of attention. It is well known that there is often a great deal of scope for optimizing the efficiency of chemical reactions themselves and the subsequent separation and purification steps. In fact, many inefficient reaction processes, environmentally unfriendly compounds, catalysts that cannot be recovered and reused, and large amounts of volatile and toxic solvents are routinely used. One of the main directions of optimization in order to reduce the environmental impact is to increase the yield of the reaction and avoid unnecessary products in the reaction.

The concept of "designing chemical products and processes to reduce or eliminate the use and consumption of chemicals", introduced by P.T. Anastas and J.C. Warner, was widely recognized as a platform for green chemistry.([1]) They point out that effective planning of chemical synthesis and molecular design can reduce the negative environmental impact of the corresponding chemical processes. This area has now deeply affected many industries, such as cosmetics, electronics, pesticides, metal smelting, petroleum refining, and pharmaceuticals.([2]) For example, the extraction of botanicals and oils can be achieved using non-toxic solvents and reducing waste. The use of non-toxic and renewable materials, such as plant-based plastics, can reduce the environmental impact of electronics production.

Green chemistry methods can also be used to reduce waste and energy consumption during manufacturing; converting waste biomass into biofuels or developing hybrid systems can help reduce the environmental impact of petroleum use.

Using catalysis and renewable starting materials can reduce waste and energy consumption, while using natural product sources can reduce the environmental impact of drug production.([34])

1.2 Enantioselective synthesis and heterogeneous catalysis

1.2.1 Enantioselective synthesis

Enantioselective synthesis is an important synthetic technique in modern chemistry because it can produce many drugs and other biologically relevant compounds. Enantioselective synthesis describes the reaction that produces stereoisomeric products with high enantiomeric selectivity or enantiospecificity at the end. This is to obtain a specific chiral molecule in the same substance by adopting a specific synthetic method. For example, penicillin is a potent antibiotic drug with few side effects. Penicillin molecules exist in two chiral forms, one of which is effective and the other is not, so enantioselective synthesis is meaningful and necessary for this drug.([3])

The main techniques used for enantioselective synthesis are chiral pool synthesis, chiral auxiliary synthesis, and asymmetric catalytic synthesis. Chiral pool is a group of naturally occurring enantiomerically pure molecules or only one specific isomer, including amino acids or certain sugars. Chiral auxiliary synthesis temporarily combines a chiral molecule with a non-chiral substrate in use to promote other chiral reactions of the substrate. For example, a carboxylic acid group can be converted to an amide or ester through an auxiliary chiral molecule, and the subsequently added chiral group can guide the addition reaction with high enantioselectivity due to its interaction with the chiral center.

Asymmetric catalytic synthesis uses chiral enantiomerically pure catalysts to produce enantioselective products from non-chiral molecules. This asymmetric synthesis method usually has the fewest steps, and our research work also uses this method. For example, the Katsuki-Shapless epoxidation produces highly enantioselective epoxide products using an asymmetric catalyst, as shown in the figure.

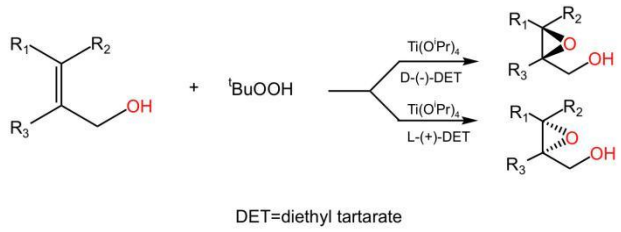


Fig 1 Katsuki-Shapless epoxidation

Currently, the mainstream method for testing enantiomers is the use of chiral stationary phases in chromatography, including gas chromatography (GC), high-performance liquid chromatography (HPLC), supercritical fluid chromatography (SFC), etc. The EE measured in the experimental part of this paper was measured using HPLC. 1.2.3 Discussion of the challenges in achieving high enantioselectivity ([32])

1.2.2 Heterogeneous catalysis

Heterogeneous catalysis, which is the phase of the catalyst, differs from the phase of the reactants or products. ([4]) This process differs from homogeneous catalysis, in which reactants, products, and catalysts are in the same phase. Phase distinguishes not only between solid, liquid, and gaseous component but also between immiscible mixtures such as organic phase and water phase.([5])

Multiphase catalysis usually involves solid-phase catalysts, and a cycle of molecular adsorption, reaction, and desorption takes place on the catalyst surface.

Heterogeneous catalysis is vital due to the fact that it is able to assist both mass manufacturing and the manufacture of selective products. ([6]) Catalysis accounts for about 35% of global GDP.([7]) 90% of chemicals are made with solid catalysts.([5]) The chemical and energy industries are heavily dependent on heterogeneous catalysis. For example, the Haber-Bosch process uses metal catalysts to synthesize ammonia, a key component of fertilizers.

Traditionally, heterogeneous catalysis relied on small molecules leading to enantiopure chiral organic molecules, including amino acids and their derivatives. These molecules can be used as ligands or act as catalysts themselves. Recently, much research on this topic has been devoted to the use of environmentally benign chiral catalysts derived from renewable materials. These particles do not require any special treatment, can be used in large quantities and do not compete with agricultural production.([8])

1.2.3 Heterogeneous catalysis with biopolimers

In 1956, Akabori ([9]) and co-workers demonstrated the first example of asymmetric catalysis using a biopolymer as the source of chirality. Their approach involved the ability of peptides to induce chirality. Reduction of Pd(II) salt on silk cellulose generates a Pd(0) protein-bound catalyst that leads to the hydrogenation of some imine derivatives with moderate enantioselectivity. Although the results obtained were not satisfactory, they were innovative and revolutionary because this is the first example where a biopolymer was used as a chiral heterogenous catalyst. This approach had been developed for many years and led to the development of small molecule organic molecules used in the field of asymmetric catalysis.

Later in another example using DNA([10]) was used as a scaffold for asymmetric catalysis. Today, DNA is used as a chiral scaffold in enantioselective nucleic acid catalysis.([33])

1.3 Friedel Crafts reaction and its limitation in enantioselective versions

The limitations of Friedel-Crafts enantioselective reactions have been the subject of ongoing research and discussion in the scientific community. Despite the development of several effective strategies for achieving enantioselective outcomes in these reactions, there remain several challenges that limit their widespread practical application. One of the main limitations is the difficulty in controlling the reaction selectivity, which can result in poor yields of the desired enantiomer. Additionally, many Friedel-Crafts reactions require the use of highly reactive and potentially dangerous reagents, which can pose significant safety hazards and limit the scope of these reactions.

For example, Friedel-Crafts alkylation (Figure 2) involves the alkylation of an aromatic ring with an alkyl halide using a strong Lewis acid catalyst. With anhydrous aluminum chloride as a catalyst, benzene has been alkylated. However, during the alkylation of the benzene ring, the benzene ring becomes more reactive to electrophilic substitution reactions, leading to the occurrence of polyalkylation. (alkylation with many alkyl groups).

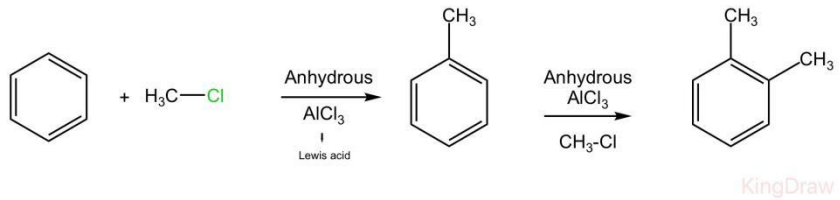


Figure 2 Reaction scheme for Friedel-Crafts polyalkylation

The use of acyl halides or anhydrides as acetylating agents and soluble Lewis acids as catalysts are polluting, expensive and difficult to work with. In normal practice, strong mineral acids, such as H_2S0_4, HF, or supported Lewis acid catalysts like anhydrous $AlCl_3/Si0_2$ and $BF_3/Si0_2$, are used for such reactions. However, these Lewis acids are consumed in more than stoichiometric amounts due to the formation of a 1:1 molar adduct with aromatic ketones and further, the subsequent separation of the product by hydrolysis is cumbersome and generates a large amount of environmentally hazardous and corrosive waste.

The development of more efficient and selective catalysts, as well as alternative reaction conditions that minimize the formation of unwanted by-products, are among the key areas of ongoing research aimed at overcoming these limitations.

1.3.1The need for alternative catalysts to improve enantioselectivity

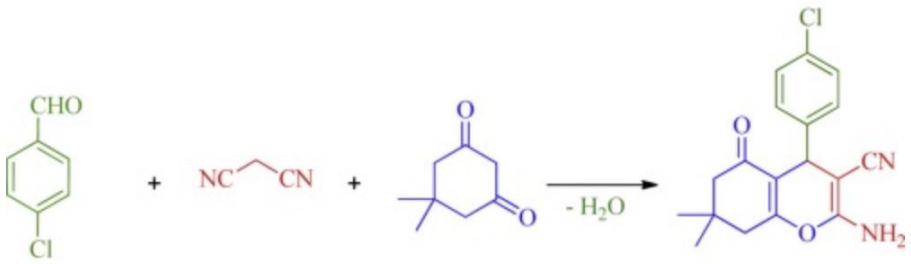
Traditional metal-based catalysts, such as those utilizing transition metals like palladium or platinum, often exhibit inadequate enantioselectivity, in addition to being costly, toxic, and presenting challenges with regard to scalability.

In light of these limitations, alternative catalysts have been developed and extensively researched, including enzymes, organocatalysts, and photo- catalysts, as a means to enhance enantioselectivity.

For example, sodium alginate, a naturally occurring macromolecule, in its granular form and without any post-modification was found to be an efficient and recoverable bifunctional heterogeneous organocatalyst. Each monomeric unit of sodium alginate contains a carboxylate and two hydroxyl groups. Therefore, it can activate the nucleophilic and electrophilic reaction constituents by carboxylate groups and hydrogen bonding as a bifunctional heterogeneous organocatalyst.([37])

To evaluate the catalytic activity of sodium alginate (**1**) for the synthesis of 4H-pyran derivatives, the domino condensation and heteroannulation of 4-chlorobenzaldehyde (**2a**), malononitrile (**3**) and dimedone (**4a**, pKa = 5.23) (1:1:1 mole ratio) was investigated as the model reaction. The results are summarized in Table 1.

Table 1. Optimization of the three-component reaction of 4-chlorobenzaldehyde (**2a**), malononitrile (**3**), and dimedone (**4a**) under various conditions.[a]



2a **3** **4a** **5a**

Entry	Catalyst loading (mol%)	Solvent	Temp. (°C)	Time (min)	Yield[b] (%)
1	–	–	Ambient	120	Trace
2	–	–	100	120	Trace
3	–	EtOH	Ambient	120	10
4	–	EtOH	Reflux	120	17
5	5	EtOH	Ambient	120	28
6	5	EtOH	50	110	38
7	5	EtOH	Reflux	60	84
8	5	MeCN	Reflux	60	52
9	5	*n*-Hexane	Reflux	75	50
10	5	THF	Reflux	60	62
11	15	EtOH	Reflux	50	93
12	10	EtOH	Reflux	50	93
13	2.5	EtOH	Reflux	60	54

a Reaction conditions: 4-chlorobenzaldehyde (**2a**, 1 mmol), malononitrile (**3**, 1 mmol), dimedone (**4a**, 1 mmol), EtOH (2 mL), and required amount of the catalysts.

b Isolated yields.

The obtained results demonstrated that a higher yield in a shorter reaction time can be obtained in EtOH under reflux conditions.

The reusability of sodium alginate (**1**) was also investigated for at least 5 repeated runs. The results are summarized in Fig.3. The obtained results confirmed that sodium alginate (**1**) is reusable for practical applications in the 4H-pyrans synthesis.

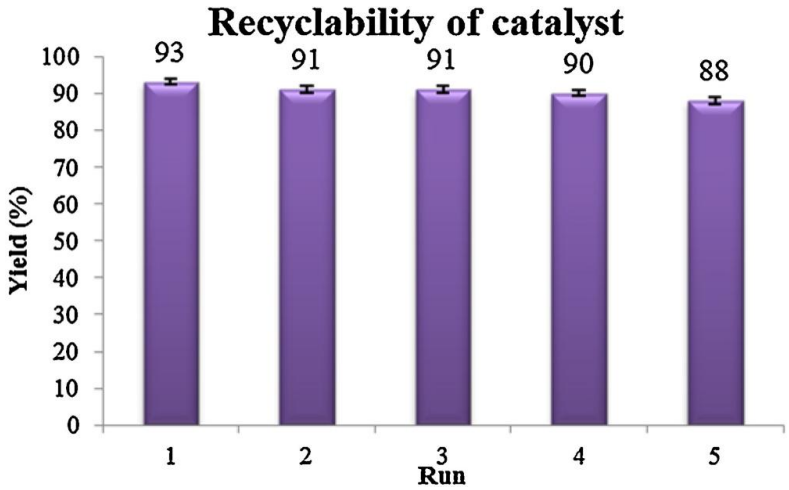


Fig. 3. Reusability of sodium alginate catalyst (1) for the MCR synthesis of 4H-pyran 5a.

This shows that sodium alginate is an alternative method for the production of 4H-pyran as a renewable and easily recyclable biofunctional organocatalyst and the method described in the literature with mild conditions, avoiding the use of any transition metals, high product yields and short reaction times, as well as reusable catalysts and simple post-treatment procedures.([38])

These alternative catalysts exhibit better selectivity and efficiency and often consist of cost-effective and non-toxic materials.

It is evident from the above examples that alginate can be easily obtained from seaweed and that this biopolymer is green and sustainable.

The study and implementation of alternative catalysts in enantioselective reactions has the potential to greatly improve their efficiency and sustainability and continues to be a highly active area of research in the organic synthesis discipline.

With these premises in mind, the utilization of alginate-based catalysts will be the focus of this research. Therefore, a comprehensive explanation of these compounds is presented below.

1.4 Alginates

Alginates are a family of naturally occurring acidic polysaccharides found mainly in the intercellular matrix of brown algae: they are an insoluble mixture of sodium, calcium, magnesium, strontium and barium salts. ([14]) Its colour varies from white to brownish. It is available in filamentous, granular or powdered form.

1.4.1 Structure of alginate

Algal alginates consist of unbranched glycuronans composed of β -D-mannosyluronic acid and α -L-gulosyluronic acid. These two uronic acids adopt different chair conformations, resulting in the bulky carboxyl group being in the energetically favored equatorial position. Therefore, glycosidic bonds at positions 1 and 4 are equatorial in β-D-mannuronate but axial in α-L-guluronate.([11])

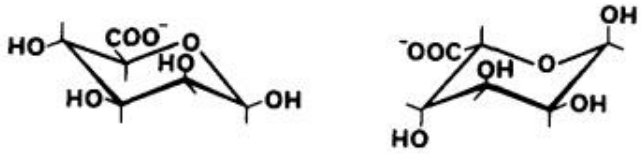


Fig 5 The component monosaccharides of alginate; β-D-mannuronate (left) and α-L-guluronate (right).

Alginates consist of monomers arranged in block structures, which can be homopolymeric or heteropolymeric, approximating to an alternating sequence. Depending on the predominance of β -D-mannuronate or α -L-guluronate, different structures may form, such as an extended ribbon structure or a buckled chain, respectively.([12]) Experimental analyses have confirmed these predictions, and solution studies using NMR also provide evidence for the different chair forms adopted by the uronic acids within the alginate chains.

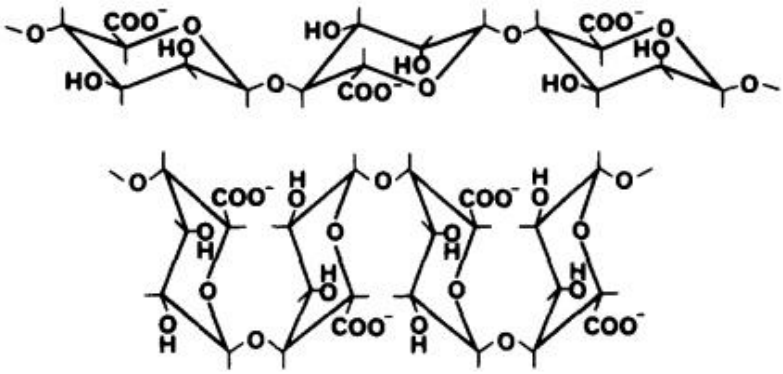


Fig 6 Chain conformations of poly D-mannuronate (top) and poly L-guluronate (bottom).

Alginate has the property of forming gels in the presence of divalent cations, especially Ca^{2+}. The properties of the gel depend on the uronic acid ratio within the polysaccharide chains. Alginates with high L-guluronate content form strong but brittle gels, while those with high D-mannuronate content form weaker but more flexible gels. The M:G ratio can be used as an index to determine the nature of the gel formed in the presence of divalent cations.

Alginate gel strength varies based on the way cations bind to different block structures within the alginate molecule. Polyguluronate blocks have a higher affinity for calcium ions and form stronger interactions, leading to the formation of a classical gel structure. Gel formation is driven by the interactions between G-blocks, which associate to form tightly held junctions in the presence of divalent cations([45]). The divalent cations, such as Ca2+, actas cross-links between the functional groups of alginate chain ([46]),“zipping” the G-blocks inalginate chain, that is, the G-block of one polymer forms junctions with the G-block of adjacent polymer chain through interactions with the carboxylic groups in the sugars, which leads to the formation of a gel network. Because of the structural form of the G-block, the metalchelation-binding chain is called the egg-box model of cross-linking. Figure 7 shows the egg-box model for alginate gel formation.

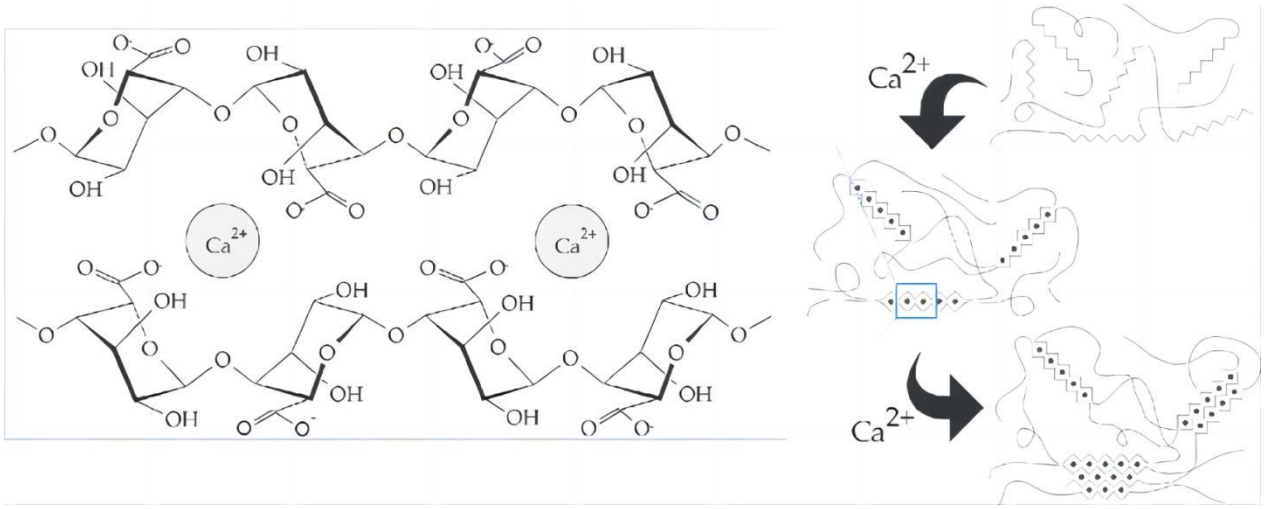


Figure 7 Schematic of “Egg-box” structure in alginate hydrogel crosslinked with calcium ions.

Alginate gels are temperature-dependent and may melt at high temperatures. Bacterial alginates have minor differences in structure, including O-acetylation and occasional di-O-acetylation of D-mannuronate residues. Some bacterial alginates lack polyguluronate blocks found in algal material. Alginate with a significant proportion of polyguluronate blocks is desirable for commercial purposes, and Azotobacter alginate may be a suitable substitute for algal material. The presence of O-acetyl groups can be easily removed, and mutants can be produced to avoid their transfer to the polysaccharide.

1.4.2 Extraction and use of alginate

Alginates are extracted from brown seaweeds. Throughout the world, many species of brown seaweed are harvested for processing and conversion into sodium alginate. Sodium alginate is used in many industries including food, animal feed, fertilizers, textile printing, and pharmaceuticals.([13]) Alginate is used as a gelling agent in dental impression materials. Food-grade alginates are approved for use as an ingredient in processed foods. ([15])

The chemical structure of alginate extracted from different species of brown seaweed varies, resulting in different physical properties of alginate. Some species produce alginate that forms a strong gel, while others produce alginate that forms a weaker gel. Some may produce cream-colored or white alginate, while others may have difficulty gelatinizing, making them more suitable for color-insensitive technical applications.

Commercial-grade alginate is extracted from giant kelp (Macrocystis pyrifera), Ascophyllum nodosum, and various types of kelp. Alginate is also produced by two types of bacteria, Pseudomonas and Azotobacter, which play an important role in elucidating their biosynthesis pathways. Bacterial alginate can be used to produce micro or nanostructures suitable for medical applications.([16])([36])

1.5 Alginate Gel

Upon obtaining the corresponding alginate through the industrial process, one of its potential applications lies in the creation of alginate gels, which can prove useful in catalysis.

Alginates exhibit a tendency to form spontaneously stable gels upon exposure to a dilute aqueous solution of divalent cations or to an acidic solution. This capability arises from the carboxyl groups of the guluronate monomer, which readily coordinate with these metals to produce a stable structure, or through the lowering of pH to favor the production of alginic acid gels.

Alginate gels will be described in this thesis by two distinct categories:

1) the type of counterion of the carboxylic group (ionic alginate gel or alginic acid gel).

2) the type of formulation (hydrogel, solvogel, aerogel, xerogel,criogels).

1.5.1 Colloidal gels

Colloidal gels consist of a permeable particle network in a liquid medium ([17]), which improves mechanical properties ([18]), especially elastic behavior.([19]) Particles can exhibit interesting interactions due to decreased permeability or polymer binding. ([20]) Colloidal gels go through three stages in their life cycle: gelation, aging and collapse. ([21,22]) Gels are initially formed by combining particles in spatially extended arrays, leading to phase arrest. During the aging phase, the molecules slowly rearrange themselves and form thicker filaments, increasing the elasticity of the material. Colloids can also collapse and separate under the influence of external fields such as gravity. ([23]) Colloidal gels show a linear rheological behavior at low amplitudes. ([24])

1.5.2 Hydrogels

Hydrogels are networks of hydrophilic polymer chains, sometimes in the form of colloidal gels, in which water is the dispersing medium.([25]) The structural integrity of the hydrogel network is not broken by high water concentrations due to the natural cross-linking. ([26]) Hydrogels are highly absorbent networks of natural or synthetic polymers (they can contain more than 90% water). Due to their high-water content, hydrogels also have an elasticity very close to that of natural tissue. ([27])As reactive "smart materials", ([28]) hydrogels can encapsulate chemical systems where stimulation by external factors such as pH changes can result in the release of compounds, such as glucose, into the environment, converting the gel-sol to a liquid state in most cases.([29]) Chemomechanical

polymers are also primarily hydrogels that can change volume when excited and act as actuators or sensors.([30])([31])

1.5.3 Solvogel

The synthesis of hydrogels is an intermediate step in obtaining solvogel, which is used as a catalyst in this dissertation. These gels replace water and retain the molecular structure of organic solvents. Alginic acid balls, which are used as catalysts in the laboratory, are actually stored as solvogels, especially in ethanol (in this case, also called alcogels, as the action of organic solvents is exerted by alcohol). Ethanol is one of the most commonly used solvents, as the substitute solvent must have ideal characteristics: it should not dissolve the gel structure, should be miscible with water, should be compatible with the final application of solvogel, and should not promote rapid contraction of the gel. In fact, the latter is one of the phenomena that require a lot of attention, as the release of water involves a decrease in the surface tension of gel pores, which leads to a decrease in capillary pressure and an unfavorable decrease in volume ([39]). Therefore, this protocol is often used to obtain sols, rather than directly immersing hydrogels in new solvents, by using multi-step processes (immersing in new solvent/water mixtures with increasing solvent concentration at each step) and low-frequency solvent exchange, which reduces the diffusion rate of water in the gel and mitigates contraction.

1.5.4 Aerogel

Aerogels are a class of synthetic porous ultralight material derived from a gel, in which the liquid component for the gel has been replaced with a gas, without significant collapse of the gel structure. These types of gels are mainly obtained by using supercritical carbon dioxide ($scCO_2$) to extract alcohol from the spheres: that is why they are not obtained from water gels or sols, because in general, alcohol is more soluble in carbon dioxide than water. The use of carbon dioxide maintains the high porosity and same performance of the initial gel, because the maximum reduction in temperature used in the process minimizes the changes that can occur at the molecular level, thus preserving the conformation and non-covalent interactions between polymer chains ([40]). The advantage of using a supercritical fluid is that there is no intermediate state of liquid-vapor transition, which avoids the collapse of the gel structure ([41]). A less efficient alternative is to use freeze-drying processes from hydrogels, which, however, generally lead to a slightly shrinkage of the structure.

1.5.5 Xerogel

The last type described is xerogel. They are always obtained by removing the solvent from the alginate structure, but in this case, they are obtained by direct evaporation, which leads to the collapse of the porous structure, resulting in a smaller volume product due to material shrinkage. They are obtained using traditional evaporative drying techniques, which cause a meniscus to form inside the pores due to the coexistence of liquid and gas phases. When the solvent is removed, the strong capillary pressure stress generated by the surface tension of the liquid inside the pores causes them to collapse. Due to their low surface area, the use of these dry polysaccharide gels in catalysis is limited by diffusion.

2. Goals

The project is based on the study of barium alginate beads as an heterogeneous catalyst for an enantioselective Friedel-Crafts reaction. The aim is to obtain enantioenriched products.

My internship work started with the achievements made by former colleagues in the project. Their main achievements were based on studying the generality of the Friedel-Crafts reaction and evaluating the recyclability of catalysts. They prepared various nitroalkenes and studied the generality of nitroalkene partners and of indole partners

The specific goals of my experiments involving barium-based alginates in heterogeneous catalysis for Friedel-Crafts enantioselective reactions are to study the following:

1. Shelton tests were performed to verify the specific activity of the heterogeneous catalyst and the possible leaching of it.

2. Kinetic tests were performed to verify the amount of reactants versus the efficiency of the reaction as well as the yield and time.

3. The stability and reusability of the barium-based alginates as catalysts: The experiments will evaluate the stability of the barium-based alginates over multiple reaction cycles, and will determine if the prepared heterogeneous catalyst can be reused without significant loss of activity and enantioselectivity. This information will be useful in determining the feasibility of using these catalysts on a larger scale.

In summary, the experiment involving barium-based alginates in heterogeneous catalysis for Friedel-Crafts enantioselective reactions aims to study the activity, enantioselectivity, stability, and mechanism of these alginates as catalysts in this reaction. The obtained

results may provide valuable information for the development of more efficient and sustainable methods for enantioselective reactions.

3. Results and Discussion

3.1 Preparation of Nitroalkenes

Before studying the main reaction, nitroalkenes were first synthesized through a Henry-type reaction, as shown in Figure 8 and detailed below for substrate **1a**.

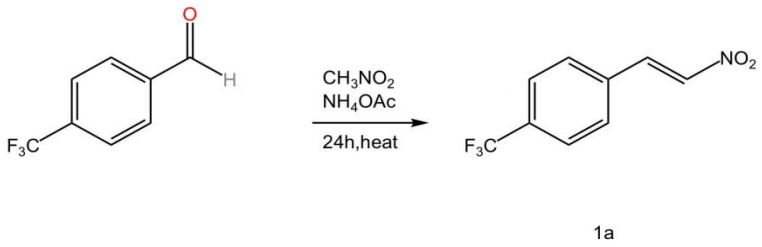
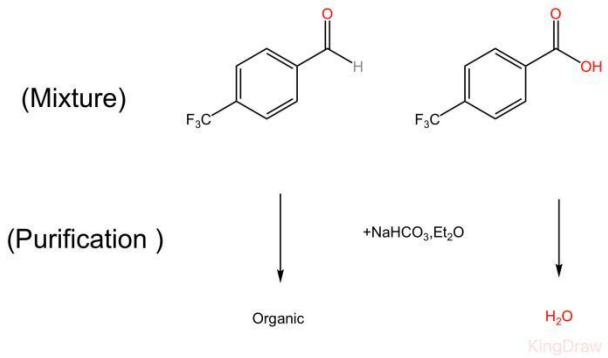


Figure 8: Henry reaction of substrate **1**

As reported in the literature([39]), the reaction was performed in a 100 mL flask with a magnetic stirrer and reflux condenser, wherein nitromethane, 4-(trifluoromethyl)benzaldehyde and ammonium acetate were added. The reaction mixture was heated to 100°C for 24 hours using a hot plate and oil bath. During the course of the reaction, the solution turned to an orange-like color. The reaction was monitored using TLC plates with a hexane/ethyl acetate (9:1) mixture as eluent, and a potassium permanganate solution to visualize the products. Ammonium acetate was removed after careful evaporation of excess nitromethane with by liquid-liquid extraction with water and dichloromethane. The resulting mixture was then dried, concentrated, and the crude product was analyzed by ^{1}H NMR with $CDCl_3$.

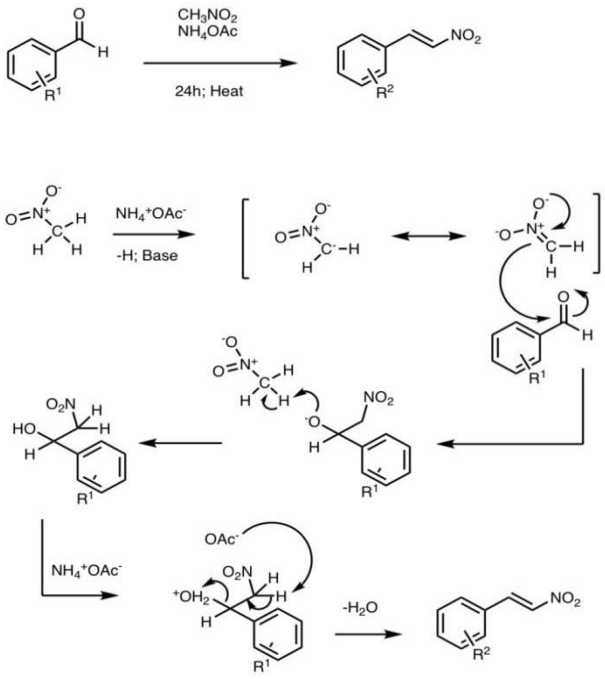
To purify the product, column chromatography was performed using a mixture hexane/ethyl acetate (7:3) as eluent. The chromatography eluent was then evaporated using a rotavapor, and further purification by crystallization of EtOH was performed. The final product was analyzed by ^{1}H NMR and obtained as yellow needles in a yield of 11%. The obtained yield was low compared to that reported in the literature (43%). The reason for this is that the raw material was heavily oxidized to carboxylic acid. We came to this conclusion by analyzing the starting aldehyde by ^{1}H NMR spectroscopy. In order to improve the reaction yield, we removed impurities from the raw material.



A liquid/liquid extraction was performed in order to remove the carboxylic acid. $NaHCO_3$ aqueous solution and Et_2O for the organic phase were used. After this purification process, the reaction was repeated, giving outcomes comparable to those in the literature.

Mechanism of the Henry reaction:

The mechanism of the Henry reaction, as shown in Figure 5, highlights the steps involved in the reaction process. The reaction proceeds by deprotonation of the nitroalkane, forming an intermediate nitronate. This enolate attacks the carbonyl compound. The resulting β-nitro alkoxide is then protonated by the conjugate acid of the base that initially deprotonated the nitroalkane in the first step, leading to the formation of the desired β-nitro alcohol. The final step of the reaction involves the dehydration of the β-nitro alcohol to form the nitroalkene.



3.2 Reaction conditions optimized in previous thesis projects

The reaction conditions involving the standard substrates **1a** and **2a** have been thoroughly studied and optimized by former colleagues during their tenure in the laboratory, as depicted in Figure 9. I continued to use my former colleague's optimized method.

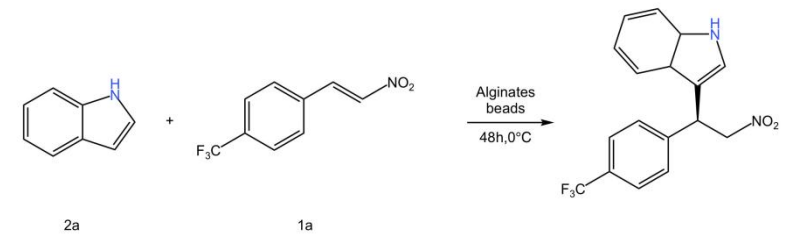


Figure 9: Benchmark Friedel-Crafts addition

They have found that better reproducibility can be obtained if the reaction is performed in a large and deep test tube in which the reactants can be better contained at the bottom and all the beads can be soaked in the reaction solvent. So, I also used the same test tube instead of a classical vial.

Another aspect of optimization discovered in the previous thesis, is the use of molecular sieves. The presence of water in the reaction mixture can cause changes in the catalytic activity of alginate beads or barium coordination spheres, thereby affecting their performance. Therefore, it has been decided to activate a new set of molecular sieves every time a new reaction is conducted, rather than reuse previously activated ones. The activation process involves heating the sieves in a vacuum for a few minutes and subsequently cooling them in the same environment before use.

In addition, the entire reaction process was conducted without mechanical agitation, except during the washing of the beads. At the end, the used test tube was placed in a dewar vessel filled with ice and used as a temperature keeper for two days.

3.3 Study of the generality of the reaction

During my internship, I set out to reproduce the generality of this procedure through reactions between various nitroolefins and indoles.

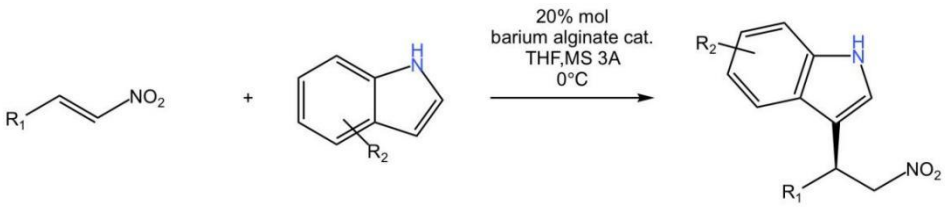


Figure 10: General Friedel-Crafts alkylation synthesis

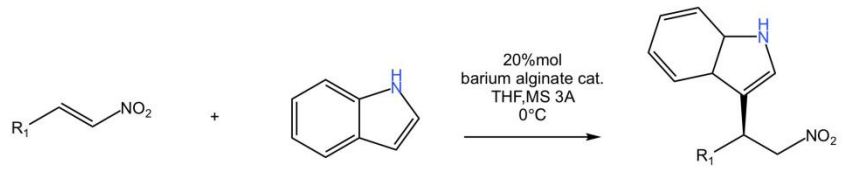
This study supplements a previous work where the generality of the reaction was examined using different nitro-substituted styrenes. The data obtained from the formation of single adducts were categorized into three different tables, as reported in the following sections, based on the analysis of compounds after silica gel chromatography purification. The reaction yield was determined by gravimetric analysis.

In order to verify the conversion and purity of the products, we characterized the synthesized products by ^{19}F NMR and ^{1}H NMR spectroscopy. Moreover, chiral phase high-performance liquid chromatography was used for determining the enantioselectivity obtained.

A. Variation of the nitroalkene

The structure of the nitroalkene was varied first, by using different nitrostyrenes carrying various substituents at the phenyl ring, some hetroaromatic substrates, and even some aliphatic nitroalkenes. The results are collected in Table 1.

Table 1: Result of Friedel-Crafts additions using different nitroalkenes



1a-1f 2a 3aa-3fa

Entry	Substrate 1 (R_1)	Contact time	Yield (%)	ee (%)
1	**1a**: CF_3-C_6H_4	2 days	**3aa**: 79%	89%
2	**1c**: MeO-C_6H_4	5 days	**3ca**:43%	90%
3	**1d**: Cl-C_6H_4	2 days	**3da**:37.4%	87%
4	**1e**: 2-furyl	3 days	**3ea**:33.5%	93%
5	**1f**: 2-thienyl	3 days	**3fa**:43.6%	93%

The obtained results can be summarized according to the following points.

Entry 1: the reaction was performed using purified **1a** and product **3aa** was obtained with a very good yield of 79% and an enantiomeric excess of 89%.

Entry 2: the second substrate is labeled as **1c**; product **3ca** was obtained with a good enantiomeric excess, but the reaction time needed to achieve a reasonable yield was 5 days, probably due to the 4-methoxy group that deactivated the substrate. Methoxy group is indeed an electron donor group that can hinder nucleophilic addition and, in fact, it was necessary to allow the reaction three days longer than the others in order to achieve an acceptable conversion,but still not in line with the results of the standard reaction. In any case, the enantiomeric excess can be quite satisfactory and is consistent with the other results.

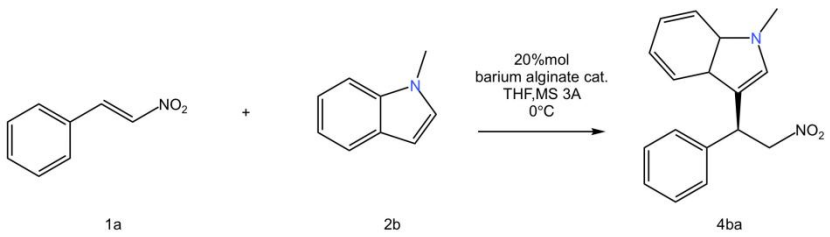
Entry 3: the reaction with 4-chlorine substituted substrate **1d** gave reasonable results in both enantioselectivity and yield.

Next, two heteroaromatic substrates **1** were used, furanyl and thiophenyl, obtaining derivatives **3ea** and **3fa** respectively in satisfactory enantiomeric excess but in moderate yields. When thiophene and furanyl derivatives **1** were used, the yields were lower compared to the ^{1}H NMR calculated conversions, probably because some product was lost during the column chromatography.

B. Variation of the indole

After having analyzed the generality of the reaction with different nitroolefins, the following study evaluates the reaction with *N*-methylindole.

Scheme 1: reaction with different indole



When *N*-methylindole was used instead of indole, the reaction did not work proving the proposed mechanism reported at page 20. Because alginate has many carboxylic moieties. Indole seems to be a perfect nucleophile because its nitrogen interacts with the many carboxylic functions, modifying the trajectory the nucleophilic attack to the nitro styrene. The polysaccharide (alginate) is tridimensionally defined, so the indolic nitrogen has to be free for interact with carboxylic acids and give enantioselection.

Mechanism of the Friedel-Crafts reaction:

The studied reaction is a nucleophilic addition of indoles to nitroalkenes promoted by Ba-alginate, which catalyses the reaction by acting as Lewis acid. The doublet on nitrogen is delocalized at the double bond, making it electron-rich and favourable for nucleophilic attack with C3 *p*-nitrophenyl ethylene, which acts as an electrophilic and is further activated by Lewis acid, and after the addition, the aromatic indole nucleus is restored due to proton displacement.(Figure 11)

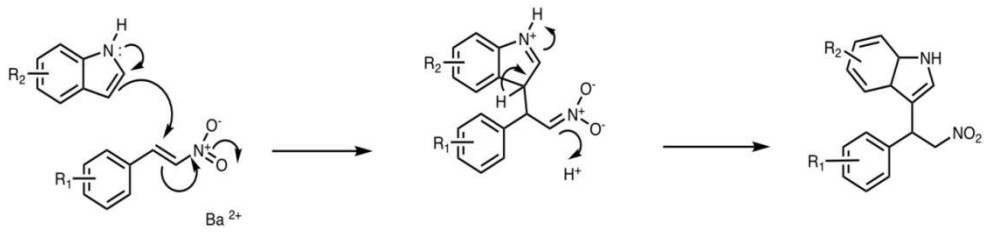
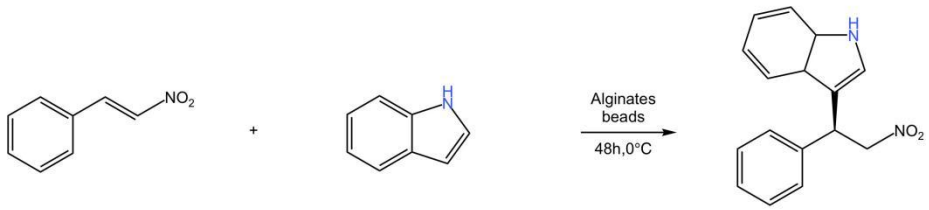


Figure 11: Mechanism of the Friedel-Crafts reaction

3.4 Recyclability test

In the final part of the project, the focus was on a preliminary study of the recyclability of the catalyst. Another essential feature of catalysts, whose primary function is to reduce the activation energy of the reaction and facilitate the formation of the desired product, is their ability to be recovered. One of the advantages of using heterogeneous catalysts is that they are easily separated from the reaction mixture, making subsequent operations simple, however, recovering the catalyst cannot degrade during the reaction. Therefore, this study aims to analyze and the catalytic capacity of Ba-alginates based catalysts that play a role in four subsequent reactions, in addition to understanding more about the factors that influence their activity and selectivity loss.

Table 3: Recyclability study of Ba^{2+} alginate catalyst in Friedel-Crafts addition



1a 2a 3aa

cycle	Reaction time (h)	Storage beads solvent	Reaction solvent	Conversion (%)	ee (%)
1st	<48	EtOH	THF	75	89%
2nd	48	THF	THF	74	87%
3rd	48	THF	THF	100	83%
4th	50	THF	THF	92	81%
5th	<48	THF	THF	65	79%

cycle	Reaction time (h)	Storage beads solvent	Reaction solvent	Conversion (%)	ee (%)
1st	<48	EtOH	THF	100	89%
2nd	48	EtOH	THF	100	89%
3rd	48	EtOH	THF	100	87%
4th	50	EtOH	THF	100	85%
5th	<48	EtOH	THF	100	77%

Table 3 reports the data obtained in catalyst recovery, firstly, we can see that the enantiomeric excess decreases in the first four late stages, but still remains above 80%, indicating a very good stability of the catalyst. However, the reaction time slowly

increases in each cycle, indicating that the catalytic function of the Ba^{2+} alginate gel bead catalyst may be slowly degrading. The enantiomeric excess value decreases to 79% in the fifth cycle, probably due to some degradation of the structure of the beads during the recovery process.

As we can see from the two tables, using ethanol for storing the beads, gives better results.

The best solvent for this reaction, determined in previous studies , is anhydrous THF, even though it is flammable and not an environmentally friendly solvent, while the best solvent for storing the catalysts is EtOH.

The data obtained are not fully reliable due to an experimental mistake in the procedure: since the tests were performed just with THF, we should have used the same solvent also for the extraction. By the way, a misunderstanding occurred and EtOAc was used for this passage. The extraction passage in this way can be considered as a partial reconditioning of the beads used in the test.

So still EtOH is used as the best storage solvent for heterogeneous catalysts.

3.4.1 Shelden test for barium alginate beads

To verify the true heterogeneity of barium alginate beads, the Sheldon test was performed. Thus, the reaction of indole and 4-(trifluromethyl)benzene at 0 degrees C. In agreement with the steps of the reaction procedure for the recoverability test, Table 4 clearly shows that after five hours of reaction when the catalyst was removed from the reaction mixture, the reaction conversion was very little changed and the catalytic activity decreased linearly.

Table 4 Sheldon test for barium alginate beads[a]

Reaction time	1.5h	3h	5h(remove catalyst)	24h	30h
Conversion(^{19}F NMR)	15.75%	29.2%	46.53%	53.74%	53.74%

[a] Reaction conditions:4-(trifluromethyl)benzene(0.14mmol),indole(0.35mmol),barium alginate beads(20%mol),THF(0.5mL) at 0°C.

3.5 Sustainability aspects

Due to the sustainable nature of my Master's degree program, I have decided to explore the feasibility and sustainability of the work I have done in the past few months. In this paragraph, the sustainability of the project will be thoroughly assessed in various aspects.

Firstly, the focus is on the catalyst itself, which is a biopolymer prepared from alginate, extracted from brown algae such as kelp. In China, kelp is extensively cultivated, and the raw material cost is low. The production of brown algae does not compete with agriculture and is considered non-food competition, making it a green chemistry domain. Alginate has a unique property in which its aqueous solution forms a water gel with an "egg-box" structure when it encounters multivalent metal ions, which is simpler and more environmentally friendly than the traditional gel preparation method.

Chloride barium is also used in this thesis, although it is toxic when ingested. However, barium is a very abundant metal on Earth, which ensures that it can be used in large quantities at low cost. Additionally, it can replace many transition metals, slowing down their depletion.

Regarding recyclability testing, we conducted a Sheldon test([35]) and performed three sets of comparative experiments. In the second recycling experiment, two beads were removed, which did not affect the obtained enantiomeric excess value, but prolonged the reaction time. In one control experiment, all beads were removed after the fifth recycling experiment, and the reaction immediately stopped. The other two experiments we did not remove beads and the reaction continued until completed. This indicates that the polymer-supported catalyst can be easily separated from the reaction mixture by simple filtration and does not require a cumbersome purification process, saving many procedures in industrial processes.

In the recyclability testing, we also conducted kinetic testing on the same three sets of comparative experiments, with the first two sets using a catalyst dose of 20% mol and the third set using a dose of 10% mol. We obtained the same enantiomeric excess value, but the third set took longer. This suggests that the catalyst dose has a significant impact on the reaction and indirectly shows that the catalyst has good recycling and circulation capabilities.

Secondly, by analysing the solvents used in the project, from catalyst preparation to the reaction itself, we can prove that this step is almost completely eco-friendly. The development of the catalyst only requires water and ethanol as solvents. However, anhydrous THF is toxic, not environmentally friendly, and highly flammable. Some solutions can be considered to make the entire process more sustainable, such as distillation to recover THF and reduce waste and environmental impact, but energy consumption during distillation must be considered.

The preparation and use of the catalyst can generally be classified as environmentally sustainable. However, from a sustainable perspective, although the catalyst is green and environmentally friendly, not all the materials used in the reaction are green. In fact, evaluating the substrates used in the reaction, the synthesis of nitroalkenes is not environmentally friendly because it involves the use of nitromethane, a toxic and dangerous compound. Additionally, considering the reaction, anhydrous THF is used again in the working steps. The purity of the product must also be considered, and appropriate measures should be taken to reduce waste and ensure the sustainability of the project.

4. Conclusions and Outlook

In conclusion, we can confirm that barium alginate beads can be used as a chiral catalyst for the Friedel-Crafts reaction in the previously explained conditions. The protocol for catalyst preparation is robust, and we have been able to optimize the catalytic reaction protocol further by establishing new reactions to make it more effective. We have also obtained additional data on the catalyst's performance with other substrates, obtaining a wide scope. By following this method, the formation of different compounds with good yield and selectivity can be facilitated.

Certainly, the catalyst can be recycled after several cycles with high recovery yields. However, after each reaction cycle, it needs to be stored in ethanol to maintain its performance.

After the addition of catalyst, the reaction was carried out under low temperature conditions. Future studies can explore optimizing the structure and function of the catalyst, or designing new catalysts to improve their efficiency and reaction rate.

Catalyst stability is a critical factor in determining its service life. My work is conducted at zero degrees Celsius,thus improving their stability is also crucial for practical applications. Future research can explore methods such as modifying the catalyst shell, increasing chemical cross-linking, or changing the spatial structure of the catalytic groups to enhance catalyst stability.

Although zero degrees Celsius is also a mild condition, it is very expensive and costly for industry to maintain zero degrees Celsius to go for production. Future studies can explore applying catalysts to industrial production, such as for the preparation of specific biochemicals or in environmental pollution control, while considering the energy consumed by low-temperature control. Reducing energy consumption can greatly benefit industrial production.

Currently, there is limited research on sodium alginate barium beads, leaving significant room for development. The catalysts under investigation have broad application prospects, and further research will undoubtedly result in more development and progress.

5. Expermental Section

5.1 Materials and methods

The experiment employed commercially available reagents and solvents for laboratory use. To verify the purity of the obtained product and the progress of the reaction, ^{1}H, ^{19}F and ^{13}C nuclear magnetic resonance spectroscopy were performed using a Varian Mercury 400 and 600 spectrometers. The enantiomeric excess (ee%) of the product was determined using a chiral stationary phase high-performance liquid chromatography (HPLC) with a UV detector operating at 254 nm and 210 nm. The reference for the two enantiomers produced by the catalytic reaction was obtained from the previous work of a colleague, who used the achiral N, N'-di[(trifluoromethyl)phenyl] thiourea catalyst to obtain the racemate of the two enantiomers. In this way, the relative retention times were discovered.

5.2 Synthesis of Nitroalkenes

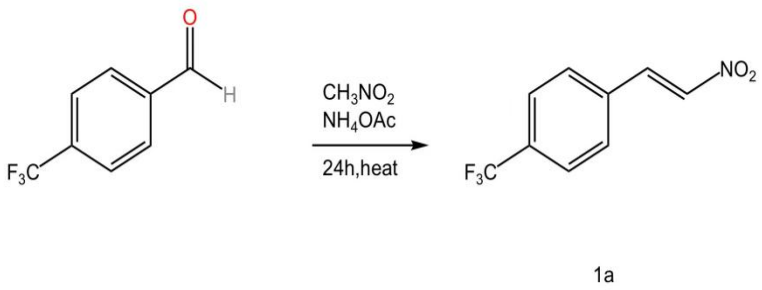


Figure 12: Henry reaction of substrate **1**

The substrate **1a** was synthesized using the following procedure, which I had employed as a method for synthesizing all non-commercial substrates used in my synthetic studies. According to the procedure ([39]), 0.3 moles of nitromethane, 9.1 mmol of functionalized aldehyde, and 2.5 mmol of ammonium acetate (to generate a buffered environment) were placed in a 100 mL round-bottom flask equipped with a magnetic stir bar and reflux condenser. The system was then placed in a 100 °C oil bath for at least 24 hours, and the progress of the reaction was monitored by TLC analysis using a mixture of n-hexane:ethyl acetate=7:3 as the eluent and a potassium permanganate solution to visualize the formation of product **1a**.

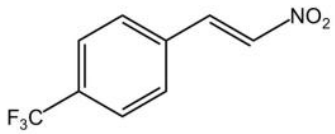
Upon confirmation of the formation of nitroalkene **1a**, the mixture was cooled to room temperature and the ammonium nitrate was separated from the mixture using water. The

organic phase obtained from the extraction was then dried with anhydrous $MgSO_4$ and filtered. The resulting isolated product was then subjected to rotary evaporation to dryness.

The product was then purified using column chromatography (LC) with petroleum ether:ethyl ether=9:1 as the eluent, and the purified fractions containing the product were collected in a round-bottom flask and evaporated using rotary evaporation. Finally, the obtained product was analyzed by ^{1}H NMR spectroscopy to confirm its purity.

1a: (*E*)-1-(2-nitrovinyl)-4-(trifluoromethyl)benzene

Following the general procedure, 1,580 g of 4-(trifluoromethyl)benzaldehyde was reacted with 17.20 mL of nitromethane and 175 mg of ammonium acetate to produce product **1a** as a brown-yellow solution. The purified product was obtained as very pale-yellow chips in solid form.



^{1}H-NMR (400MHz, $CDCl_3$): δ = 8.02 (d, J = 13.7 Hz, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.1Hz, 2H), 7.61 (d, J = 13.7 Hz, 1H).

^{19}F-NMR ($CDCl_3$; 400MHz): d = -63.19 (s, 3F).

5.3 Preparation of racemic samples

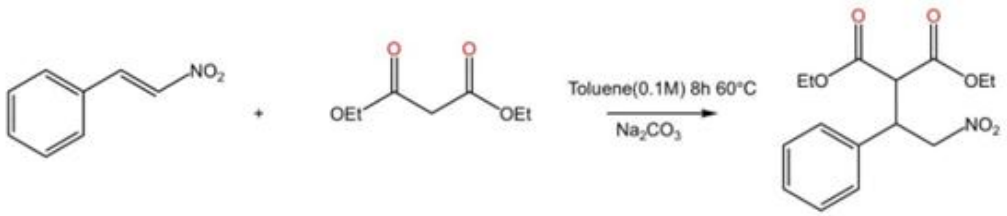
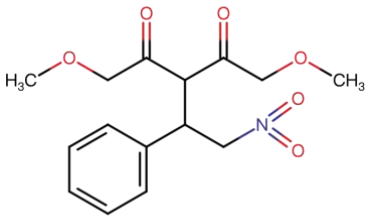


Fig 13 Preparation of racemic samples using Na_2CO_3

Referring to the procedure ([42]), 0.2 moles of trans-β-nitrostyrene, 0.3 mmol of diethyl malonate, 0.3 mmol of Na_2CO_3 and 2ml toluene were placed in a 100 mL round-bottom flask equipped with a magnetic stir bar and reflux condenser. The system was then placed in a 60 °C oil bath for at least 24 hours, and the progress of the reaction was monitored by TLC analysis using a mixture of n-hexane:ethyl acetate=7:3 as the eluent and a potassium permanganate solution to visualize the formation of product.

The resulting isolated product was then subjected to rotary evaporation to dryness. The product was then purified using column chromatography (LC) with petroleum ether:ethyl ether=6:1 as the eluent, and the purified fractions containing the product were collected in a round-bottom flask and evaporated using rotary evaporation. Finally, the obtained product was analyzed by ^{1}H NMR spectroscopy to confirm its purity.



^{1}H NMR (600 MHz, $CDCl_3$): δ =7.38 – 7.33 (m, 2H), 7.30 – 7.23 (m, 3H), 4.71-4.60 (m, 2H), 4.35-4.23 (m, 2H), 2.46 (s, 3H), 2.20-2.04 (m, 1H),1.36 (dt, J = 12.6, 7.2 Hz, 3H),0.78 (t, J=7.2 Hz, 3H).

5.4 Preparation of the alginate barium spheres

The procedure for producing the agarose gel beads (AG-M) ([43,44]) involves preparing a 2% w/V solution of sodium alginate by adding 1 g of 200S proton alginate to 50 mL of deionized water in an Erlenmeyer flask and stirring until a clear and viscous solution is obtained. Then, under magnetic stirring, this mixture is slowly dropped into a beaker containing 100 mL of 0.1 M barium chloride solution at ambient temperature (using a separatory or dropping funnel). The formation of the gel beads is instantaneous and visible, and the resulting beads are slowly stirred overnight to mature. They are then filtered and washed carefully with water, five times for 10 minutes each.

Next, these water gels are converted into the corresponding sol-gels (SG). They are dehydrated by soaking in a series of ethanol/H_2O baths, with increasing solvent content (10, 30, 50, 70, 90, and 100%), for 15 minutes each, followed by three final baths in pure ethanol. To ensure complete conversion from water gel to sol-gel, the beads in ethanol are contacted with activated 3A molecular sieves for 3 days. The sieves are activated by heating under vacuum and then allowed to cool to room temperature under a N_2 inert atmosphere. The beads are then removed and stored as sol-gels in EtOH.

The final task of this procedure is to evaluate and determine the weight of individual beads in order to calculate the amount of barium present in each bead and thus, the number of beads required to achieve a certain loading in a catalytic reaction. To do so, ten sol-gel beads are collected and dried under vacuum using a pump until a constant weight is obtained.

5.5 General procedure for catalytic reactions

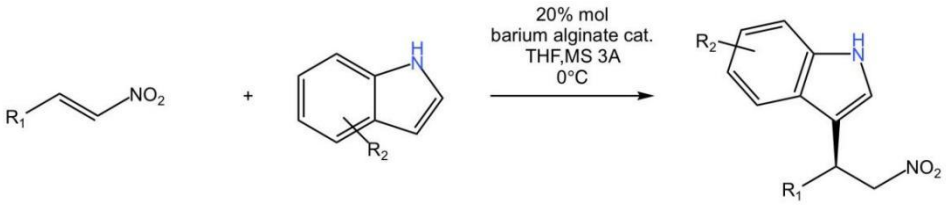


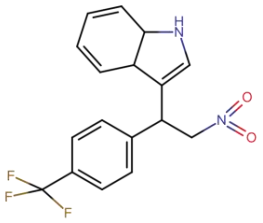
Figure 14: General Friedel-Crafts alkylation synthesis

In a specific test tube, 0.14 mmol of nitroalkene, 0.21 mmol of indole, and 0.5 mL of anhydrous THF previously distilled over sodium, were added and five 3A pore-sized activated molecular sieves. After cooling the system to 0ºCelsius degrees using an ice bath, 8 sodium alginate barium balls, corresponding to 20% barium relative to the base nitroalkene, were added. The sodium alginate salt balls were stored as an ethanol alcohol gel and washed five times with a small amount of anhydrous THF for at least fifteen minutes before use. The reaction had to be carried out for 48 hours at 0ºCelsius degrees, attempting to maintain a constant temperature by fully placing the system in a sustainable low-temperature container (known as a Dewar) and checking the progress using TLC analysis. After confirming the presence of the product and satisfactory conversion of the substrate, the solution was removed from the test tube and filtered through a silica plug. Then, EtOAc was added to the tube, and the mixture was allowed to contact the beads for a few minutes to extract all products, followed by filtration through a plug. The extraction was repeated several times. The solution obtained through plug filtration was subsequently evaporated and purified on a chromatography column. TLC analysis was used to identify the components containing the product, and the same eluent mixture as used in the column was used for developing the plate. Typically, a potassium permanganate solution was used to highlight the product. The fraction containing the product was collected in a flask, followed by drying using rotary evaporation, and then characterized using NMR spectroscopy using $CDCl_3$ as the solvent and chiral stationary phase HPLC (AD-H or OD-H column) to determine enantiomeric excess. After completing all these steps, it is best to store the product in a labelled small vial in a refrigerator.

5.5.1 3-(2-nitro-1-(4-(trifluoromethyl)phenyl)ethyl)-3a,7a-dihydro-1H-indole

Following the general procedure, using 30,4 mg substrate **1a** and reacting it with 24,6 mg of indole (**2a**), product **3aa** is obtained with complete conversion after 48h of reaction time. Chromatography column purification, using a mixture of petroleum ether/ethyl acetate 90:10 as eluent, afforded product **3aa** as a solid with a yield of xx%.

The product was injected into HPLC (AD-H 0.75 ml/min,90:10=n-hexane:isopropanol, λ=254nm, t_{min}=21.28min and t_{maj}=26.33min), so that the enantiomeric excess value can be determined(89%).



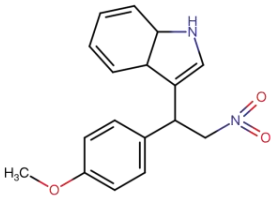
^{1}H-NMR ($CDCl_3$; 400MHz): δ= 8.16 (br s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.22 (t, J = 7.9 Hz, 1H), 7.09 (t, J = 7.9 Hz, 1H), 7.03 (d, J = 2.7 Hz, 1H), 5.26 (t, J = 8.3 Hz, 1H), 5.08 (dd, J = 7.6 Hz, J = 12.9 Hz, 1H), 4.96 (dd, J = 8.7 Hz, J = 12.9 Hz, 1H).

^{19}F-NMR (400 MHz; $CDCl_3$): δ =-62.68.

5.5.2 3-[1-(4-methoxyphenyl)-2-nitroethyl]-1H-indole

Following the general procedure, using 25,1 mg substrate **1c** and reacting it with 24,6 mg of indole (**2a**), product **3ca** is obtained with complete conversion after 5 days of reaction. Chromatography column purification using a mixture of petroleum ether/ethyl acetate 90:10 as eluent afforded product **3ca** as a solid with a yield of 43%.

The product was injected into HPLC (OD-H), so that the enantiomeric excess value can be determined. (90%).

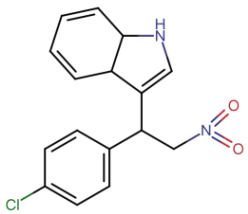


^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.42 (dq, J = 8.0, 0.9 Hz, 1H), 7.34 (dt, J = 8.1, 0.9 Hz, 1H), 7.25 (dd, J = 2.4, 1.9 Hz, 1H), 7.24 – 7.22 (m, 1H), 7.18 (ddd, J = 8.2, 7.0, 1.1 Hz, 1H), 7.06 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H), 7.01 (dd, J = 2.6, 0.9 Hz, 1H), 6.86 – 6.81 (m, 2H), 5.13 (t, J = 8.0 Hz, 1H), 5.04 (dd, J = 12.3, 7.5 Hz, 1H), 4.89 (dd, J = 12.3, 8.4 Hz, 1H), 3.76 (s, 3H).

5.5.3 3-(1-(2-chlorophenyl)-2-nitroethyl)-1H-indole

Following the general procedure, using 25,7mg substrate **1d** and reacting it with 24,6 mg of indole (**2a**), product **3da** is obtained with complete conversion after 48h of reaction. Chromatography column purification, using a mixture of petroleum ether/ethyl acetate 90:10 as eluent, afforded product **3da** as a solid with a yield of 37%.

The product was injected into HPLC (AD-H 0.75 ml/min,90:10=n-hexane:isopropanol, λ=254nm, t_{min}=22.75min and t_{maj}=26.89min),so that the enantionmeric excess value can be determined.(87%).

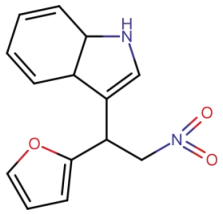


^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.18 (s, 1H), 7.38 (ddt, J = 12.9, 8.2, 0.9 Hz, 2H), 7.33 – 7.25 (m, 5H), 7.21 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.02 (dd, J = 2.5, 0.9 Hz, 1H), 5.20 – 5.12 (m, 1H), 5.05 (dd, J = 12.5, 7.3 Hz, 1H), 4.91 (dd, J = 12.5, 8.6 Hz, 1H).

5.5.5 3-(1-furan-2-yl-2-nitro-ethyl)-indole

Following the general procedure, using 19,48 mg substrate **1e** and reacting it with 41 mg of indole (**2a**), product **3ea** is obtained with complete conversion after 3 days of reaction. Chromatography column purification, using a mixture of petroleum ether/ethyl acetate 90:10 as eluent, afforded product **3ea** as a solid with a yield of 33.5%.

The product was injected into HPLC (OD-H, 0.75mL/min, 80:20=n-hexane:isopropanol,λ=254nm, t_{min}= 32.43min and t_{maj}= 48.03min), so that the enantiomeric excess value can be determined.(93%).

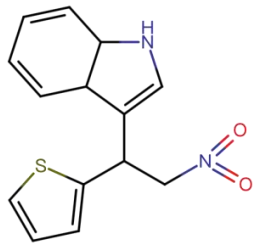


^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (s, 1H), 7.56 (dt, J = 8.0, 1.0 Hz, 1H), 7.41 – 7.34 (m, 2H), 7.22 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.18 – 7.09 (m, 2H), 6.31 (dd, J = 3.3, 1.9 Hz, 1H), 6.16 (dt, J = 3.2, 0.9 Hz, 1H), 5.32 – 5.21 (m, 1H), 5.06 (dd, J = 12.5, 8.1 Hz, 1H), 4.92 (dd, J = 12.5, 7.4 Hz, 1H).

5.5.6 3-(2-nitro-1-thiophen-2-ylethyl)-1H-indole

Following the general procedure, using 21,7 mg substrate **1f** and reacting it with 41 mg of indole (**2a**), product **3fa** is obtained with complete conversion after 3 days of reaction. Chromatography column purification, using a mixture of petroleum ether/ethyl acetate 90:10 as eluent, afforded product **3fa** as a solid with a yield of 44%.

The product was injected into HPLC (OD-H, 1 mL/min, 80:20=n-hexane:isopropanol,λ=254nm, t_{min}= 37.73min and t_{maj}= 41.81min),so that the enantionmeric excess value can be determined.(93%).



^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.58 (s, 1H), 7.49 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.34 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.22 – 7.14 (m, 2H), 7.12 – 7.05 (m, 2H), 6.96 (ddd, *J* = 3.5, 1.2, 0.8 Hz, 1H), 6.92 – 6.88 (m, 1H), 5.44 (tt, *J* = 8.3, 0.8 Hz, 1H), 5.05 – 4.93 (m, 2H).

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